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November 18, 2021

Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
5001 Campus Drive
College Park, MD 20740

Re: Generally Recognized as Safe (GRAS) Notice for MENAQUINONE-7

Dear Sir/Madam:

Pursuant to 21 C.F.R. part 170, subpart E, GF Fermentech, Inc., hereby submits the enclosed notice, that use of its MENAQUINONE-7 (MK-7) at a maximum level of 10 µg MK-7 per serving in conventional foods is excluded from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because the notifier has determined that such use is generally recognized as safe (GRAS).

Sincerely,

Ashish Talati
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EVALUATION OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF

MENAQUINONE-7

AS A FOOD INGREDIENT

Prepared for:
GF Fermentech, Inc.
(30077) 74-12,
Geumhoseonmal-gil,
Bugang-myeon, Sejong-si,
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October 31, 2021

EVALUATION OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF MENAQUINONE-7 AS A FOOD INGREDIENT

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1. PART I- SIGNED STATEMENTS AND CERTIFICATION

In accordance with 21 CFR § 170 Subpart E consisting of § 170.203 through § 170.285, GF Fermentech, Inc. (GF Fermentech) hereby informs the FDA that Menaquinone-7, derived from *Bacillus subtilis natto*, is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on GF Fermentech's view that the notified substance is Generally Recognized as Safe (GRAS) under the conditions of its intended use described below.

1.1. Basis of Conclusion:

This GRAS conclusion for the use of Menaquinone-7 (MK-7) has been reached in accordance with requirements in 21 CFR 170.220.

1.3. Name and address of organization:

GF Fermentech, Inc.
(30077) 74-12, Geumhoseonmal-gil,
Bugang-myeon, Sejong-si,
Republic of Korea

1.4. Name of substance:

The name of the substance of this GRAS assessment is Menaquinone-7. The substance is also known as MK-7; Vitamin K2-7; Vitamin MK-7. It will be marketed under the trade name: MediQ7.

1.5. Intended conditions of use:

Menaquinone-7 (MK-7) is intended to be used as a food ingredient and as a nutrient [21 CFR § 170.3(o)(20)][1] in selected food categories such as Beverages and Beverage Bases, Breakfast Cereals, Cheeses, Fats and Oils, Frozen Dairy, Desserts, Grain products and pastas, Milk, Milk Products, Processed Fruits and Fruit Juices, and Processed Vegetables and Vegetables Juices at a maximum level of 10 µg MK-7 per serving of food (Reference Amounts Customarily Consumed Per Eating Occasion; 21 CFR § 101.12). It is recognized that there are Standard of Identity requirements for some of these specified foods and these foods will not be referred by their commonly recognized names. The MK-7, subject of this GRAS assessment, is not proposed for uses in foods that are intended for infants, such as infant formulas.

1.6. Statutory Basis for GRAS conclusion:

This GRAS conclusion is based on scientific procedures in accordance with 21 CFR 170.30(a) and 170.30(b).

[1] "Nutrient supplements": Substances which are necessary for the body's nutritional and metabolic processes.

1.7. Exemption from Premarket approval requirements:

GF Fermentech has concluded that MK-7 is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on our conclusion that MK-7, meeting the specifications cited herein, and when used as a nutrient and as a food ingredient in selected conventional food products, is GRAS and is therefore exempt from the premarket approval requirements.

It is also our opinion that other qualified and competent scientists reviewing the same publicly available toxicological and safety information would reach the same conclusion. Therefore, we have also concluded that MK-7, when used as described in this dossier, is GRAS based on scientific procedures.

1.8. Availability of data and information:

The data and information that are the basis for this GRAS conclusion will be made available to FDA upon request by contacting

Dr. Jeong Jun Han
CEO
GF Fermentech, Inc.
(30077) 74-12, Geumhoseonmal-gil,
Bugang-myeon, Sejong-si,
Republic of Korea

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Email: gftinfo@genofocus.com

Or

Amin Talati Upadhye, LLP
100 S. Wacker Dr., Suite 2000
Chicago, IL 60606

Phone: 312.327.3381
Email: Ashish@aminatalati.com

The data and information will be made available to FDA in a form in accordance with that requested under 21 CFR 170.225(c)(7)(ii)(A) or 21 CFR 170.225(c)(7)(ii)(B).

1.9. Data exempt from Disclosure:

Parts II through VII of this GRAS notification does not contain data or information that is exempt from disclosure under the Freedom of Information Act. There is no privileged or confidential information such as trade secrets and/or commercial or financial information in this document. Therefore the information contained in this dossier can be made publicly available.

1.10. Certification:

GF Fermentech certifies that, to the best of its knowledge, this GRAS conclusion is based on a complete, representative, and balanced dossier that includes all relevant information, available and obtainable by GF Fermentech, including any favorable or unfavorable information, and pertinent to the evaluation of the safety and GRAS status of the use of MK-7. GF Fermentech accepts responsibility for the GRAS determination that has been made for MK-7 as described in this dossier.

1.11. Name, position/title of responsible person who signs dossier and signature:

Dr. Jeong Jun Han
CEO
GF Fermentech, Inc.
(30077) 74-12, Geumhoseonmal-gil,
Bugang-myeon, Sejong-si,
Republic of Korea

Signature: 

1.12. FSIS/USDA – Use in Meat and/or Poultry:

GF Fermentech does not intend to add MK-7 to any meat and/or poultry products that come under USDA jurisdiction. Therefore, 21 CFR 170.270 does not apply.

2. PART II- IDENTITY AND TECHNICAL INFORMATION

2.1. Description

The subject of this GRAS assessment, Menaquinone-7 (MK-7; MediQ7), is a standardized powder or oil preparation derived from a specific strain of *Bacillus subtilis natto* by a fermentation and extraction process. MK-7 is a long chain menaquinone, part of vitamin K2 derivatives. The extract is mixed with food grade material to a desired concentration in the final product. General descriptive characteristics of MK-7 are summarized in Table 1.

Table 1. General Descriptive Characteristics of Menaquinone-7

Parameter	Description *
Source	*Bacillus subtilis natto*
Synonyms	Vitamin K2-MK7; Vitamin K2; Menaquinone-7(USP grade)
Trade name	MediQ7
Systematic name	(all-E)-2-(3,7,11,15,19,23,27-Heptamethyl-2,6,10,14,18,22,26-octacosaheptaenyl)-3-methyl-1,4-naphthalenedione
CAS No.	2124-57-4
Chemical formula	$C_{46}H_{64}O_2$
Molecular weight	649 g/mol
Appearance	Yellowish white powder; yellowish oil
Color	Yellowish
Odor	Characteristic
Taste	Characteristic
Storage	In cool temperature in a dry and dark place, and away from high heat, humidity, and light
Shelf life	24 months

*Based on information provided GF Fermentech

Vitamin K is known to occur in two forms, one as vitamin K1 (phylloquinone) and other as vitamin K2 (menaquinones). Both forms share a common 2-methyl-1,4-naphthoquinone ring, also known as menadione. Phylloquinone contains a phytyl side chain which comprises four prenyl units (Shearer and Newman, 2008), while menaquinones contain an unsaturated aliphatic side chain with a variable number of prenyl units. The number of prenyl units decides the type of menaquinone that can be short-chain (i.e., menaquinone-4; MK-4) and long-chain (i.e., MK-7, MK-8, and MK-9). The chemical structure of MK-7 is presented in Figure 1.

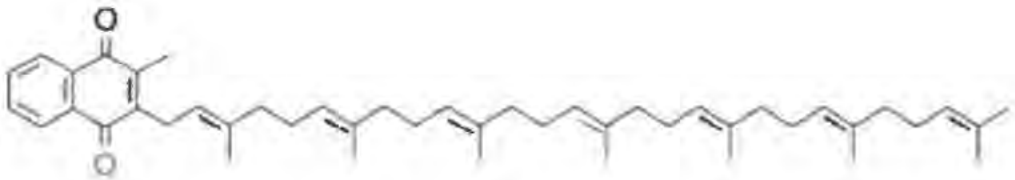

Figure 1. Chemical Structure of Menaquinone-7 (MK-7).

2.2. Specifications and Identity

GF Fermentech has established food grade specifications for both the powder and oil form of MK-7 (MediQ7) (Table 2). Analytical results from three non-consecutive lots of powder form (Appendix I-A) and oil form (Appendix I-B) demonstrate that MK-7 is consistently manufactured and meets the standard specifications. The analytical methods used in establishing the specification are validated and fit for purpose. It meets the MK-7 specification of USP41 (US Pharmacopeia) and EU novel food.

Table 2. Specifications of Menaquinone-7 for Powder and Oil Forms

Parameters	Specification		Analysis method
	Powder form	Oil form	
Appearance	Yellowish white	Yellowish oily	Internal method
Identification			
VitaminK2 (MK-7) assay (HPLC) Content (Menaquinone-7)	≥ 2,000 ppm	≥ 50,000 ppm	USP NF, Menaquinone-7 preparation
Isomeric Purity	≤ 1.0 %	≤ 1.0 %	
Acid Value	NA	≤ 1.0 mg/g	USP <401>
Moisture	≤ 5.0 %	NA	USP <921>
Heavy metals			
Arsenic(As)	≤ 0.5 ppm	≤ 0.5 ppm	USP <233>
Cadmium(Cd)	≤ 0.5 ppm	≤ 0.5 ppm	
Lead(Pb)	≤ 0.5 ppm	≤ 0.5 ppm	
Mercury(Hg)	≤ 0.1 ppm	≤ 0.1 ppm	
Microbial limits			
Total Bacterial Count	$\leq 10^3$ cfu/g	$\leq 10^3$ cfu/g	USP <2021>
Total Yeasts & Molds Count	$\leq 10^2$ cfu/g	$\leq 10^2$ cfu/g	
Salmonella	Negative	Negative	USP <2022>
E. coli	Negative	Negative	
Staphylococcus aureus	Negative	Negative	
Carrier	Maltodextrin	Vegetable oil (MCT oil, etc.)	Internal method

NA= not applicable

2.3. Manufacturing Process

Menaquinone-7 (MK-7; MediQ7) from GF Fermentech is manufactured according to Korea Good Manufacturing Practices for health functional food at (30077) 74-12, Geumhoseonmal-gil, Bugang-myeon, Sejong-si, Republic of Korea. MK-7 is produced by

fermentation using a *Bacillus subtilis natto* strain isolated from a traditional Korean fermented soybean food (Cheonggukjang). This strain has a significantly higher production capacity of MK-7 compared to conventional strain. It has a trans-type content of more than 99%, a MK-6 content less than 2% and can efficiently produce MK-7.

The GF Fermentech manufacturing facility is ISO9001, ISO22000 and Korea good manufacturing practice for health functional food certified. The manufacturing process flow diagram for MK-7 powder form and oil is presented in Figure 2. MK-7 is produced by submerged fermentation using *Bacillus subtilis natto*, a non-toxicogenic and non-pathogenic strain, as the production strain.

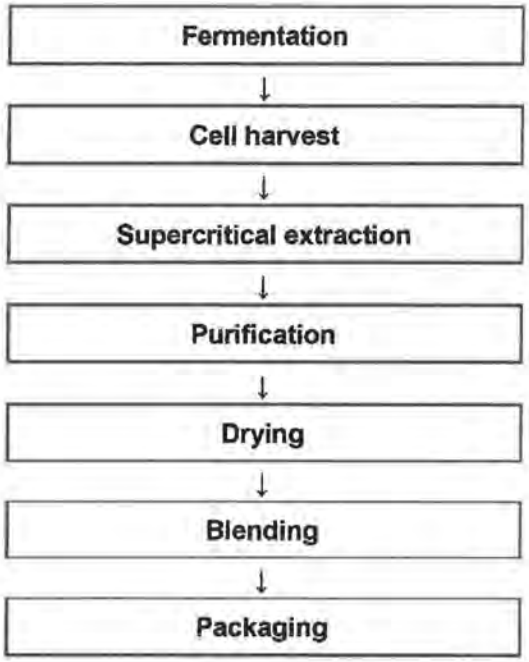

Figure 2. Manufacturing Flow Chart for Menaquinone-7 (MediQ7) from *Bacillus subtilis natto*

The identification of the *B. subtilis natto* strain is determined by the sequence of 16S rRNA bases and the sequence of base and amino acids corresponding to aprN, and the 298th amino acid was confirmed to be Valine. The analysis of the strains of *B. subtilis natto* of GF Fermentech, Inc. confirmed that it was *B. subtilis natto*. The *B. subtilis natto* strain has been fully characterized and deposited with Korean Collection for Type Cultures.

As indicated above MK-7 is produced by fermentation using *B. subtilis natto*. The concentrated culture medium is extracted with supercritical CO_2 and ethanol. MK-7 extracts are purified by using micro filters. The purified MK-7 is dried. MK-7 powder products are manufactured by blending and pulverization with maltodextrin, while the oil products are manufactured by blending with vegetable oil. The oil is filtered and the product is packaged according to specifications.

In the manufacturing of MK-7, high quality food grade materials are used. The manufacturing process assures a consistent and high quality MK-7 product. The production

process ensures that the potential for contamination or the introduction of impurities is minimized. Processing aids, ethanol that are removed by evaporation, and additives used as carrier in the manufacturing process are all food-grade quality and comply with specifications described in the current Edition of the Food Chemicals Codex.

2.4. Biological Activity

Vitamin K is a fat-soluble vitamin. The letter "K" is derived from the German word 'koagulation.' For over 70 years the essential role of vitamin K in the functioning of several proteins involved in blood clotting has been well documented. In 1930, Danish scientist, Henrik Dam discovered vitamin K. In a quest to understand cholesterol metabolism in chicken by feeding them a diet free of sterols and low in fat, Henrik Dam discovered vitamin K (Shampo and Kyle, 1998). In these studies, the diet reduced the intake of fat-soluble vitamin K leading to subcutaneous and intramuscular hemorrhages in chickens. This led to isolation, identification and characterization of the vitamin K structure and its importance as an anti-hemorrhagic agent. Among the several vitamin K deficiency metabolic processes, bleeding still remains the potentially most serious generally known consequence. However, in recent years the role of vitamin K on osteoporosis and its inhibitory role in arterial calcification and vascular biology in general populations has been recognized.

It is unquestionable that the metabolic activities mentioned above require vitamin K for γ-carboxylation, a step essential to their proper functioning. Additionally, several other functions of vitamin K have been discovered that appears to be independent of its classical co-factor function. Furthermore, metabolic effects of vitamin K such as ameliorating effect on peripheral neuropathy, cramps, autonomic nervous system, improving perfusion, etc., remain unexplained. Vitamin K also acts as a ligand for the receptor SXR, the steroid and xenobiotic sensing nuclear receptor (SXR), which is a transcriptional regulator of the cytochrome P450 gene CYP3A4.

The understanding of the vitamin K family has significantly evolved over the years. It is well recognized that there are two primary forms of vitamin K, commonly known as vitamin K1 (phylloquinone) and vitamin K2 (menaquinones). All K-vitamins have the same function; however, they differ in bioavailability and bioactivity. Vitamin K2 (menaquinones), the main storage form in animals, has several subtypes or homologues that differ in isoprenoid sidechain length. Menaquinones are generally abbreviated MK-n, where M stands for menaquinone, the K stands for vitamin K, and the n represents the number of isoprenoid side chain residues. Among different menaquinones, the two prominent in human nutrition are MK-4 and MK-7. In animal products, MK-4 is the most common type, as it is normally synthesized from all types of vitamin K in certain animal tissues. The available information indicate that MK-7 and other long-chain menaquinones are different from MK-4 in that they are not produced by human tissue, but are generated by gut bacteria. A range of vitamin K2 analogues are present as a mixture in several foods, such as sauerkraut, hard cheese, soft cheese and curd cheese (Schurgers and Vermeer, 2000). These foods have a long history of human consumption by humans as basic foods.

3. PART III- DIETARY EXPOSURE

3.1. Intended Uses and Food Categories

GF Fermentech intends to use menaquinone-7 (MK-7) in selected conventional food categories such as beverages and beverage bases; cereal and cereal products; dairy products; fats and oils; and pasta, rice and other miscellaneous grains at a maximum level of 10 µg MK-7 per serving of food. The details of food categories to which MK-7 is proposed for use are summarized in Table 3, along with descriptions of the types of foods within the category that was included in the assessment, the serving size associated with each food type, and the maximum use level of MK-7. The intake analysis was conducted by Intertek Group PLC and the complete report is attached as Appendix II. The subject of this GRAS, MK-7, will not be used in any foods for which food standards would preclude its use. Foods that are intended for infants, such as infant formulas and meat and poultry products that come under USDA jurisdiction are excluded from the list of intended food uses of MK-7.

3.2. Background and Methods Used for Estimated Daily Intake

As vitamin K is a nutrient that is naturally present in the diet and is also added to foods and dietary supplements for fortification purposes, intakes of MK-7, as well as other vitamin K isomers, from all dietary sources were estimated to evaluate the nutritional impact of the proposed food uses of MK-7 in the diet of the U.S. population. Overall, three intake assessments were conducted: (A) Estimated daily intake of menaquinone-4 (MK-4), MK-7, vitamin K2, vitamin K1, and total vitamin K from the background diet, *i.e.*, current sources of vitamin K, including its natural occurrence in food and current fortification uses in foods and dietary supplements; (B) Estimated daily intake of MK-7 from proposed food uses only; and (C) Cumulative estimated daily intake of MK-7, vitamin K2, and total vitamin K from proposed food uses and background diet (food and supplements)[2].

The intake estimates of the vitamin K isoforms (MK-4, MK-7, vitamin K1, vitamin K2, and total vitamin K) were based on the current and/or proposed levels of the nutrient in food in conjunction with food consumption data included in the U.S. National Center for Health Statistics' National Health and Nutrition Examination Surveys (NHANES) 2017-2018. Additionally, exposure estimates for vitamin K isomers from dietary supplement products were based on the supplement composition and consumption data included in the same NHANES survey (CDC, 2021a,b; USDA, 2021). Calculations for the mean and 90th percentile *per capita* and consumer-only intakes were carried out for all 3 assessments, and the percentage of consumers were determined. Similar calculations were used to estimate the intake of MK-7 resulting from each individual source (*i.e.*, current food sources, dietary supplements, proposed food uses). The impact of the proposed food uses of MK-7 in food and beverage categories was evaluated by calculating the absolute change in MK-7 intakes from the proposed uses relative to the background diet. As indicated above, all this analysis is provided in Appendix II. In this section only intake estimates of MK-7 from the proposed uses and the cumulative intake of MK-7 from all sources is summarized.

[2] Intakes of MK-4 and vitamin K1 were not included in the cumulative intakes assessment, as they are not part of the proposed uses.

Table 3. Summary of the Individual Proposed Food Uses and Use Levels for MK-7 in the U.S.

Food Category (21 CFR §170.3) (FDA, 2020a)	Food Uses	Proposed MK-7 Use Level (µg/serving)	RACC[a] (g or mL)	Proposed MK-7 Use Levels (µg/100 mL or 100 g)
Beverages and Beverage Bases	Soft drinks	10	360 mL	2.8
Breakfast Cereals	Breakfast cereals			
	Puffed cereals	10	15 g	66.7
	High-fiber cereals	10	40 g	25.0
	Biscuit-type cereals	10	60 g	16.7
Cheeses	Cottage cheese	10	110 g	9.1
	Low-fat cheese	10	30 g	33.3
Fats and Oils	Low fat margarine	10	15 mL	66.7
	Low fat mayonnaise	10	15 g	66.7
	Olive oil	10	15 mL	66.7
Frozen Dairy Desserts	Frozen yogurt	10	90 g	11.1
	Ice cream	10	130 g	7.7
Grain Products and Pastas	Cereal bars	10	40 g	25.0
	Pasta	10	140 g	7.1
	Pizza crust	10	55 g	18.2
Milk	Milk	10	240 mL	4.2
Milk Products	Other milks	10	240 mL	4.2
	Creams	10	15 mL	66.7
	Yogurt	10	170 g	5.9
	Yogurt drinks	10	90 to 207 g	11.1
	Fromage frais[b]	10	110 g	9.1
Processed Fruits and Fruit Juices	Fruit juices	10	240 mL	4.2
Processed Vegetables and Vegetables Juices	Vegetable juices	10	240 mL	4.2

CFR = *Code of Federal Regulations*; MK-7 = menaquinone-7; RACC = Reference Amounts Customarily Consumed per Eating Occasion; U.S. = United States.

[a] RACC based on values established in 21 CFR §101.12 (FDA, 2020b).

[b] No food codes were identified; however, consumption is expected to be similar to yogurts; therefore, no change is expected versus the intakes calculated amongst consumers.

[c] Lowest RACC value was used to determine the use level per 100 mL or 100 g.

Values are rounded as relevant.

3.2.1. Estimated Daily Intake of MK-7 from Proposed Uses

The estimated total intake of MK-7 (µg/person/day) from all proposed food uses is presented in Table 4, while this data on a per kilogram body weight basis (µg/kg body weight/day) is provided in Table 5. The percentage of consumers was high among all age groups evaluated in the current intake assessment [with the exception of infants ages 0 to 6 months (3.1% consumers)], whereby more than 65.9% of the population groups consisted of consumers of food products in which MK-7 is currently proposed for use (Table 4). Children (ages 1 to 3 years old) and females (ages 9 to 13 years old) had the greatest proportion of consumers at 98.8%. Among the total population (ages 1 and older), the mean and 90th percentile consumer-only intakes of MK-7 were determined to be 24.7 and 47.8 µg/person/day, respectively (Table 4). Of the individual population groups, males (ages 14 to 18 years old) were determined to have the greatest mean and 90th percentile consumer-only intakes of MK-7 on an absolute basis, at 32.6 and 63.2 µg/person/day, respectively, while infants (ages 7 to 11 months) had the lowest statistically reliable estimates of 11.1 and 34.9 µg/person/day (intakes by infants were not statistically reliable due to the low number of consumers).

Table 4. Summary of the Estimated Daily Intake of MK-7 from Proposed Food Uses in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/day)		Consumer-Only Intake (µg/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
Infants						
0 to 6 months	<0.1*	na	3.1	9	1.2*	2.7*
7 to 11 months	7.3	27.5	65.	81	11.1	34.9
Children						
1 to 3 years	25.9	42.4	98.8	408	26.2	42.6
4 to 8 years	25.9	46.8	97.9	522	26.5	46.8
Females						
9 to 13 years	26.9	52.6	98.8	301	27.2	52.6
14 to 18 years	19.5	45.3	94.9	265	20.6	45.3
19 years and older	19.8	42.4	92.6	2,026	21.4	43.4
Males						
9 to 13 years	27.7	48.2	97.7	274	28.4	48.2
14 to 18 years	30.8	58.2	94.5	264	32.6	63.2
19 years and older	24.7	51.7	92.2	1,831	26.8	53.3
Total Population						
All ages (≥1 year)	23.1	46.8	93.5	5,891	24.7	47.8

MK-7 = menaquinone-7; n = sample size; na = not available; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.
* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements (mean n<30; 90th percentile n<80).

On a body weight basis, the total population (ages 1 and older) mean and 90th percentile consumer-only intakes of MK-7 were determined to be 0.4 and 1.0 µg/kg

body weight/day, respectively. Among the individual population groups, children (ages 1 to 3 years old) were identified as having the highest mean and 90th percentile consumer-only intakes of any population group, of 1.9 and 3.3 µg/kg body weight/day, respectively. Females and males (ages 19 years and older) had the lowest mean and 90th percentile consumer-only intakes of 0.3 and 0.6 µg/kg body weight/day, respectively (Table 5).

Table 5. Summary of the Estimated Daily Per Kilogram Body Weight Intake of MK-7 from Proposed Food Uses in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/kg bw/day)		Consumer-Only Intake (µg/kg bw/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
Infants						
0 to 6 months	<0.1*	na	3.1	9	0.2*	0.4*
7 to 11 months	0.8	3.0	65.9	81	1.2	4.4
Children						
1 to 3 years	1.9	3.3	98.8	398	1.9	3.3
4 to 8 years	1.1	1.9	97.9	521	1.1	1.9
Females						
9 to 13 years	0.6	1.2	98.8	300	0.6	1.2
14 to 18 years	0.3	0.6	94.8	263	0.3	0.6
19 years and older	0.3	0.6	92.7	2,006	0.3	0.6
Males						
9 to 13 years	0.7	1.4	97.7	272	0.7	1.4
14 to 18 years	0.5	1.0	94.5	263	0.5	1.0
19 years and older	0.3	0.6	92.3	1,819	0.3	0.6
Total Population						
All ages (≥1 year)	0.4	0.9	93.6	5,842	0.4	1.0

bw = body weight; MK-7 = menaquinone-7; n = sample size; na = not available; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.
* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements (mean n<30; 90th percentile n<80).

3.2.2. Cumulative Estimated Daily Intake of MK-7 from All Sources

The cumulative estimated daily intakes of MK-7 from the background diet (please see Appendix II) and proposed food uses (as above section 3.2.1.). These estimates are on an absolute basis (µg/person/day) are presented in Table 6, while this information on a body weight basis (µg/kg body weight/day) is given in Table 7. In the total population (ages 1 and older), the cumulative mean and 90th percentile consumer-only estimated daily intakes of MK-7 from the background diet and proposed food uses were determined to be 24.3 and 47.6 µg/person/day. Among individual population groups, males (ages 14 to 18 years) were identified as having the highest mean and 90th percentile consumer-only intake of MK-7, at 31.6 and 60.6 µg/person/day. Infants (7 to 11 months old) had the lowest statistically reliable mean and 90th percentile consumer-only intakes of 10.8 and 34.9 µg/person/day, respectively (Table 6).

Table 6. Cumulative Estimated Daily Intake of MK-7 from the Background Diet and Proposed Use in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/day)		Consumer-Only Intake (µg/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
Infants						
0 to 6 months	<0.1*	na	3.1	9	1.2*	2.7*
7 to 11 months	7.3	27.5	68.2	83	10.8	34.9
Children						
1 to 3 years	25.9	42.4	99.0	410	26.2	42.6
4 to 8 years	26.0	46.9	99.1	526	26.2	46.9
Females						
9 to 13 years	27.0	52.7	99.6	306	27.1	52.7
14 to 18 years	19.6	45.5	97.9	275	20.0	45.5
19 years and older	21.2	43.3	97.5	2,127	21.7	43.3
Males						
9 to 13 years	27.8	48.3	99.3	279	28.0	48.3
14 to 18 years	30.9	58.3	97.8	273	31.6	60.6
19 years and older	25.2	52.5	97.7	1,932	25.7	53.3
Total Population						
All ages (≥1 year)	23.8	47.2	97.9	6,128	24.3	47.6

MK-7 = menaquinone-7; n = sample size; na = not available; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.

* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements (mean n<30; 90th percentile n<80).

On a body weight basis, the total population (ages 1 and older) mean and 90th percentile consumer-only intakes of MK-7 were determined to be 0.4 and 1.0 µg/kg body weight/day, respectively (Table 7). Among the individual population groups, children (ages 1 to 3 years old) and infants (ages 7-11 months) were identified as having the highest mean and 90th percentile consumer-only intakes of any population group, of 1.9 and 4.4 µg/kg body weight/day, respectively. Females ages 14 years and over and adults (females and males) ages 19 years and over had the lowest mean and 90th percentile consumer-only intakes of 0.3 and 0.6 µg/kg body weight/day, respectively (Table 7).

Table 7. Cumulative Estimated Daily Per Kilogram Body Weight Intake of MK-7 from the Background Diet and Proposed Use in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/kg bw/day)		Consumer-Only Intake (µg/kg bw/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
Infants						
0 to 6 months	<0.1*	na	3.1	9	0.2*	0.4*
7 to 11 months	0.8	3.0	68.2	83	1.2	4.4
Children						
1 to 3 years	1.9	3.3	98.9	400	1.9	3.3
4 to 8 years	1.1	1.9	99.1	525	1.1	1.9
Females						
9 to 13 years	0.6	1.2	99.6	305	0.6	1.2
14 to 18 years	0.3	0.6	97.9	273	0.3	0.6
19 years and older	0.3	0.6	97.5	2,105	0.3	0.6
Males						
9 to 13 years	0.7	1.4	99.3	277	0.7	1.4
14 to 18 years	0.5	1.0	97.8	272	0.5	1.0
19 years and older	0.3	0.6	97.7	1,916	0.3	0.6
Total Population						
All ages (≥1 year)	0.4	0.9	97.9	6,073	0.4	1.0

bw = body weight; MK-7 = menaquinone-7; n = sample size; na = not available; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.
* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements (mean n<30; 90th percentile n<80).

3.2.3. Summary of Intake Analysis

In summary, consumption data and information pertaining to the occurrence and levels of vitamin K isomers from current sources in the background diet and from the proposed food uses of MK-7 were used to estimate the *per capita* and consumer-only intakes of MK-7 and related vitamin K isomers for the U.S. population. Dietary intakes were evaluated for (i) the background diet, considering naturally occurring sources and fortification uses in food and dietary supplements of MK-4, MK-7, vitamin K1, vitamin K2, and total vitamin K; (ii) the proposed food uses of MK-7 in specific food and beverage categories; and (iii) the cumulative intake from current sources of MK-7, vitamin K2, and total vitamin K from the background diet and the proposed food uses.

The intakes of MK-4 and vitamin K1 were assessed only from background diet, as the estimated daily intakes of these vitamin K isomers are unlikely to change with proposed uses of MK-7. The mean and 90th percentile estimate of MK-4 among the total population (ages 1 year and older) were 17 and 33 µg/person/day, respectively. The highest mean and 90th percentile consumer-only intakes of MK-4 from current sources were determined to be 22 and 40 µg/person/day, respectively, as identified in males (ages 19 years and older). For vitamin K1, the mean and 90th percentile estimates among the total population (ages 1 year

and older) of 115 and 229 µg/person/day, respectively. The highest mean and 90th percentile consumer-only intakes of vitamin K1 from current sources were determined to be 130 and 237 µg/person/day, respectively, as identified in males (ages 19 years and older). The intakes of vitamin K isomers such as VK1 and MK-4, along with MK-7 are further summarized in Appendix II.

The proposed uses of MK-7 at levels of 10 µg/serving were estimated to result in consumer only intakes of 24.7 µg/person/day (0.4 µg/kg bw/day) and 47.8 µg/person/day (1.0 µg/kg bw/day) at the mean and 90th percentile respectively, among the total U.S. population over 1 year of age. Among the individual population groups, the highest mean and 90th percentile consumer-only intakes of MK-7 were determined to be 32.6 µg/person/day (0.5 µg/kg bw/day) and 63.2 µg/person/day (1.0 µg/kg bw/day), respectively, as identified among males (ages 14 to 18 years old).

For safety assessment purposes, the highest intake of 63.2 µg/person/day for male ages 14-18 years (Table 4) is considered. It should be noted that the cumulative maximum intake of MK-7 on a body weight basis (1.00 µg/kg bw/day) from the proposed uses is similar as compared to that described in GRN 887 for children (0.99 µg/kg bw/day).

4. PART IV- SELF LIMITING LEVELS OF USE

Menaquinone-7 (MK-7) does not have any self-limiting intake levels under the conditions of use described in this GRAS notification. GF Fermentech does not intend to add MK-7 at any level beyond what is described in this GRAS document.

5. PART V- EXPERIENCE BASED ON COMMON USE IN FOODS BEFORE 1958

The statutory basis for the conclusion of GRAS status of Menaquinone-7 (MK-7) in this document is not based on common use in food before 1958. As described in this document, MK-7 is found in dairy and fermented food products that have been routinely consumed orally prior to 1958. Notwithstanding this, it is reasonable to conclude that, since MK-7 has been used traditionally across the world, it was present in food prior to 1958. This GRAS assessment for use of MK-7 as a food ingredient is based on scientific procedures.

6. PART VI- NARRATIVE

6.1. Natural Occurrence and Uses

6.1.1. Historical Uses

Naturally occurring forms of vitamin K include phylloquinone (vitamin K1; VK1) and a family of molecules called menaquinones (vitamin K2; VK2 or MKs). Menaquinone-7 (MK-7) is found in certain food products including fermented foods, especially the Japanese traditional dish Natto, and certain cheeses, pork, steak, buckwheat bread and eel. All of these foods have been consumed for a long time. As a widely consumed food for centuries in Japan, Natto is considered a rich source of dietary menaquinones, particularly MK-7. In other Oriental countries, such as China, Korea, Thailand, Indonesia, as well as parts of India and Nepal, soybean fermented foods, rich sources of dietary menaquinones, are commonly consumed. These traditional foods have a long history of consumption in these countries (Shurtleff and Aoyagi, 2007). In Japan, fermented soybeans were prepared as common food sometime prior to the 11th century. During the late 18th century, the Natto preparation has been changed by the science of microbiology. Subsequently, the microbial species used in the production of Natto have been identified as *Bacillus subtilis natto* and *B. mesentericus vulgatus*.

In addition to Natto, MK-7 is also consumed from other dietary sources, as it is found in commonly consumed ordinary food. In Western countries, common dietary sources of menaquinones and MK-7 include cheese, e.g., American cheese, Kraft, Land O'Lakes, Cheddar, Mozzarella, Muenster, Jarslberg, Pecorino Romano, Goat milk cheese and Provolone cheese), pork, fish (e.g., eel, plaice) and buckwheat bread. Several studies from Germany suggest a dietary intake of menaquinone (primarily MK-7). Compared to various cheeses that are also sources of MK-7, Natto has been found to contain >100 times more MK-7 (Katsuyama et al., 2002).

6.1.2. Natural Occurrence in Foods and Exposure

Several publications, particularly from Japan, reports the presence of MK-7 in foods, particularly Natto. For centuries, peoples have consumed MK-7 from food, primarily from Natto and to some extent from cheese. Depending on the method of preparation, Natto may provide between 775 to 1750 μg of MK-7/100 g of Natto (Tsukamoto et al., 2000). The available information suggests that the average MK-7 content of Natto products is 1100 μg/100 g. Since there is regular consumption of Natto by Japanese consumers, they are exposed to MK-7 on a regular basis. Several other countries have been reported to produce similar traditional soybean foods fermented with *Bacillus subtilis*. Natto is also marketed in Western countries, including the USA. A list of common foods containing VK2 is provided in Table 8.

In a study from Japan, Kamao et al. (2007) analyzed 58 different food items for the presence of vitamin K1 and vitamin K2. On average, the daily consumption of vitamin K for women aged 18-29 years old living in eastern Japan was estimated to be 230 μg per person. The contributions of K1, MK-4, and MK-7 to total vitamin K intake were reported as 67.7, 7.3, and 24.9%, respectively. Based on this information, the daily background average intake of MK-7 is estimated as 57 μg per person. For Natto eaters, the average daily intake is estimated at 133.2 μg/person. The presence of MK-7 in three preparations

was reported as follows: fermented soybean Natto- 939±753 μg/100 g; Hikiwari (chopped) Natto- 827±194 μg/100 g; and black-bean Natto- 796±93 μg/100 g. These observations are also supported by another study, in which Isobe et al. (1995) reported that the MK-7 content in 19 different Natto products ranged from 780 to 2100 μg/100 g. As the average daily Natto serving is 40 - 50 g, this equates to an exposure of about 300 to 800 μg MK-7 per 40 g/meal.

In a recent publication, Kojima et al. (2020) investigated whether habitual Natto consumption is associated with a risk of osteoporotic fractures. In this prospective cohort study, intake of Natto, tofu, and other soybean products was surveyed with use of a food frequency questionnaire (FFQ) at baseline in 1417 postmenopausal Japanese women (aged ≥45 years). Fractures were ascertained in follow-up surveys conducted in 1999, 2002, 2006, and 2011/2012. The findings from this study revealed that habitual Natto intake may be associated with a reduced risk of osteoporotic fractures independent of confounding factors, including BMD, in Japanese postmenopausal women. In this study, of the 1417 participants, 531 (37.5%) consumed less than 1 pack Natto/week (40 g/pack), 697 (49.2%) consumed 1 to 6 packs, and 189 (13.3%) consumed >7 packs/week. One portion size of Natto is usually 1 pack (approximately 40 g), which contains 350 μg of MK-7. It is reported that over 13% of postmenopausal Japanese women are daily exposed to 350 μg or more of MK-7.

Table 8. Primary Food Sources of VK2 with Amounts

Food Category	Food Source	VK2 *
Fermented foods	Natto Sauerkraut	850–1000 (90% MK-7, 8% MK-8) 5.5 (31% MK-6, 23% MK-9, 17% MK-5 and -8)
Hard cheeses		50–80 (15–67% MK-9, 6–22% MK-4, 6–22% MK-8)
Soft cheeses		30–60 (20–70% MK-9, 6–20% MK-4, 6–20% MK-8)
Eggs	Yolk	15–30 (MK-4)
Meats	Pork, beef, chicken	1.4–10 (MK-4)

*μg/100 g food sample; MK-n (menaquinone); Adapted from Popa et al. (2021)

Marles et al. (2017) summarized the available quantitative data from different sources on levels of MK-7, other menaquinones, and vitamin K1 in foods. These reviewers also noted that the richest dietary sources of long-chain menaquinones are foods fermented by bacteria (not by molds or yeasts), typically represented in Western diets by dairy products such as cheeses (MK-8, MK-9) and in the Japanese diet by Natto (MK-7). Apart from animal livers, meat and fish products generally are low in long-chain menaquinones and are of little importance as dietary sources of vitamin K2. The most commonly consumed menaquinones in the human diet have a side chain with 4, 6, 7, 8, 9, or 10 isoprene residues. The evidence available suggests that dairy products are likely the predominant dietary sources of long-chain MKs. Cheese and milk products were estimated to contribute to 54% and 22% of total MK intake, respectively, in a cohort of Dutch women in whom long-chain MKs were estimated to account for 9% of the total vitamin K intake.

Several studies from Germany reported the dietary intake of menaquinones (including MK-7) from several sources including cheese. As compared to various cheeses that also contains MK-7, Natto has been reported to contain >100 times more MK-7

(Katsuyama et al., 2002). Depending on the type of cheese, menaquinones, such as MK-6, MK-7, MK-8 and MK-9 are found in varying ratios. It has been further observed that long-chain menaquinones, MK-7, MK-8 and MK-9 found in Natto are also present in several other foods (Schurgers et al., 1999; Schurgers et al., 2007). The available information indicate that menaquinone intake comprised 10% of the total vitamin K intake (Geleijnse et al., 2004). In a review article, Beulens et al. (2013) reported that dietary intake of menaquinones accounts for up to 25% of total vitamin K intake and contributes to the biological functions of vitamin K.

6.1.3. Current Approved and other Uses

In several countries, the use of MK-7 and related products has been recognized by regulatory and other agencies. Vitamin K, (including MK-7) and other products containing vitamin K, are available as dietary supplements in the US. MK-7 is also available as a single ingredient dietary supplement with dosage form usually 100 μg/capsule. The Dietary Supplement Label Database[3] lists 821 products which contain the term menaquinone anywhere on the label. These products are regulated under the Dietary Supplement Health and Education Act (DSHEA, 1994). Additionally, as discussed below, recently FDA reviewed a GRAS Notice (GRN 887) for the use of MK-7 as an ingredient and as a nutrient according to 21 CFR 170.3(o)(20) in nutritional beverage products intended for consumers ages 1-13 years at a use level of 4 μg/serving. The agency did not question this proposed use of MK-7.

In Japan, Natto has received certification for health claims for both bone health and gut health under the regulation - Food for Specified Health Uses (FOSHU). In the European Union, use of MK-7 is permitted as a source of vitamin K for nutritional purposes in foodstuffs. The European Food Safety Authority (EFSA, 2008) reported that approved uses of MK-7 are estimated to result in a mean daily intake that ranged from 36 μg (female adults) to 54 μg (male teenagers), while high intakes ranged from 75 μg/day (children) to 115 μg/day (male teenagers). The EFSA Panel concluded that the use of menaquinone-rich edible oil in foods for the general population including food supplements and in foods for particular nutritional uses, other than baby foods and infant formula, at the use levels of 10 μg/serving was not a safety concern. Food supplements marketed in the UK may contain up to 45 μg vitamin K (either as K1 or K2) for general consumption and 200 μg in supplements intended for women from pre-conception to nursing.

In summary, the available information demonstrates that MK-7 is regularly consumed from dietary sources. Food regulations in Japan permit the use of health claims for MK-7 rich Natto food. In Oriental countries, MK-7 is commonly consumed from Natto, while in the Western diet, cheese is a good source of MK-7. In European countries, the use of MK-7 in food is permitted for nutritional purposes. In the US, MK-7 is marketed as a dietary supplement and as discussed below it has received GRAS status as a nutrient in nutritional beverage products for children at use level of 4 μg/serving.

6.2. Data Pertaining to Safety

The available information suggests that the main function of vitamin K is to activate proteins that play important roles in blood clotting, heart health and bone health. However,

[3] Available at: https://www.dsld.nlm.nih.gov/dsld/rptQSearch.jsp?item=MK-7&db=adsld.

as discussed below differences in absorption and transport of different types of vitamin K (K1 and K2) can result in significantly different effects. The available studies also suggest that among the members of the K2 family, the bioavailability and bioactivity differs depending on the chain length. Long chain menaquinones, such as MK-7, has superior bioavailability over other short chain homologs (MK-4) and vitamin K1. Thus, from a safety point of view, it is important to differentiate the potential effects of vitamin K family members, including MK-4 and MK-7. These effects are important in patients on anti-coagulant therapy. Hence, an attempt has been made to present the differences in bioavailability of MK-4 and MK-7 and its implications.

For the present GRAS assessment, the safety determination of MK-7 is based on the totality of the available evidence, including human clinical observations/trials, animal experimental studies and *in vitro* studies. Efforts have been made to present both the data supporting MK-7 safety as well as any data on potential adverse effects. As vitamin K, including MK-7 plays a role in coagulation, an attempt has been made to interpret the findings from relevant studies as it relates to the present GRAS assessment. The assessment of efficacy studies is limited to a review of the results related to safety and tolerability. In the following sections, relevant biological and toxicological studies on MK-7 and structurally related substances are described that provide support for the conclusions reached in this determination.

The published literature contains several studies related to the safety of vitamin K, including MK-7. In several human clinical studies, Natto food with known amounts of natural MK-7 has been investigated for its health benefits. As vitamin K (K1 and K2) plays an important role in blood coagulation, there has been a significant effort to elucidate the mechanism of action of MK-7. Given the natural occurrence of menaquinones (particularly MK-7) in foods such as Natto and cheeses, and consumption, the need for systematic toxicity studies of MK-7 has been diminished. However, in a series of well-designed unpublished pre-clinical toxicity studies, conducted as per current accepted guidelines, GF Fermentech investigated the effects of MK-7 (subject of current GRAS) in animals and *in vitro* experimental systems. These unpublished specific studies of MK-7 are used to corroborate the safety of MK-7.

6.2.1. Absorption, Distribution, Metabolism and Excretion

The available bioavailability related information of different forms of vitamin K is limited. Among the different forms of Vitamin K such as VK1, VK2- MK-4, MK-7, etc., the absorption rate of VK1 (phylloquinone) in its free form is approximately 80%, but its absorption rate from foods is significantly lower. VK1 in plant foods is tightly bound to chloroplasts, so it is less bioavailable than that from oils or dietary supplements. The body absorbs only 4 to 17% as much VK1 from spinach as from a tablet. Consuming vegetables at the same time as some fat improves VK-1 absorption from the vegetables, but the amount absorbed is still lower than that from oils. The available research suggests that long-chain MKs may have higher absorption rates than VK1 from green vegetables.

In a recent review article, Akbulut et al. (2020) noted that recent discoveries suggest the role of vitamin K-dependent proteins in processes beyond coagulation. VK2 differs from VK1, as the latter only has one unsaturated sidechain unit (Figure 3). Various isoforms of vitamin K have been identified, and long chain VK2 (such as MK-7)

specifically has been highlighted for its long half-life and extrahepatic activity, whereas the dietary form VK1 has a shorter half-life (Figure 3).

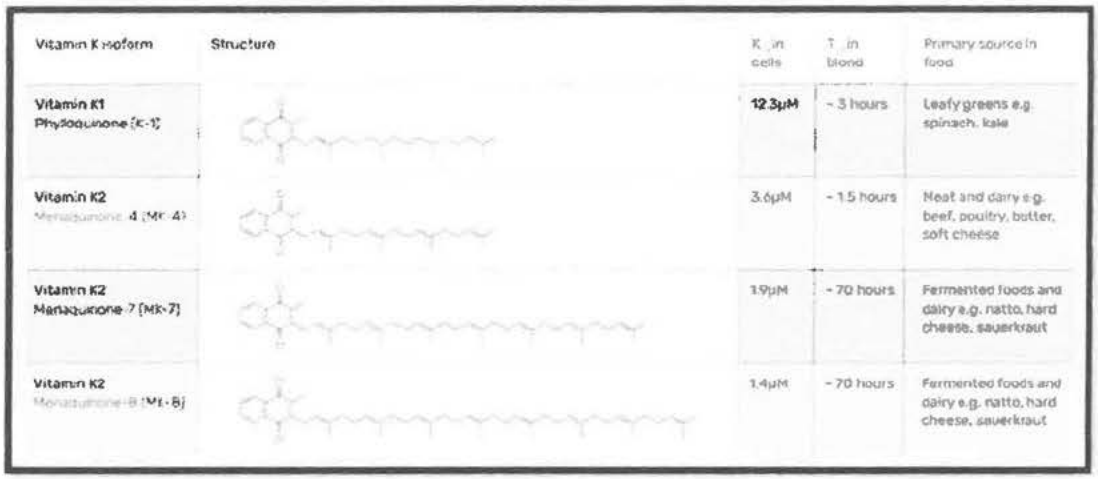

Figure 3. Name, Structure, Half Saturation Concentration ($K_{1/2}$), $T_{1/2}$ (half-life), and Primary Sources of VK1 and Major VK2 Isoforms (adapted from Akbulut et al., 2020)

The intestinal absorption of vitamin K follows a well-established pathway that applies to most dietary lipids. Following absorption in the small intestines, K vitamins enter the circulation via the lymphatic system and are transported in the blood by binding to chylomicrons (Wildman and Medeiros, 2000). VK1 in blood appears to be derived exclusively from the diet, while as regards circulating VK2 (menaquinones, including MK-7), it is not clear whether it is derived from the diet, intestinal flora, or a combination of these sources. The translocation of VK1 and VK2, their entry into target tissues, and their excretion are known to be affected by the structural differences in the isoprene side chain between these vitamins. The transport of VK1 takes place by triglyceride-rich lipoproteins, whereas long-chain VK2 are transported mainly by low-density lipoproteins (Kohlmeier, 1996).

In humans, liver stores of K vitamins generally comprise about 90% VK2 and 10% VK1 (Conly and Stein, 1992; Ichihashi et al., 1992). The predominant vitamin K in human cortical and trabecular bone has been reported as VK1, and, unlike liver, no VK2 higher than MK-8 were detected (Shearer, 1988; Usui, 1990). The major circulating form of vitamin K is primarily VK1. The VK2 such as MK-7, and possibly MK-8 are also found in blood. However, the common hepatic forms such as MKs 9-13 are not detected in the blood (Shearer, 1988; Shearer et al., 1996; Hodges, 1993; Suttie, 1995; Shearer, 1992).

Bioavailability of VK1 and MK-7 has been extensively investigated by Schurgers et al. (2007). These studies revealed that maximum serum concentrations of both VK1 and MK-7 are reached at approximately 4 hours after intake; followed by a steep decline in serum concentrations and then a second phase at 8-96 hours in which VK1 declined to baseline but MK-7 remained stable for up to 4 days or more. In this study, the half-life of MK-7 was estimated as 68 hours for the latter phase of elimination. Using the area under the curve at 24 hours, the ratio of bioavailability of MK-7: VK1 was 2.5. Using the area under the curve at 96 hours, the ratio of bioavailability of MK-7: VK1 was 6. These

investigators concluded that as compared to VK1 (1-2 hours), MK-7 has a significantly longer half-life (68 hours).

In these investigations by Schurgers et al. (2007), both VK1 and MK-7 revealed linear dose-response curves at 4 hours post treatment, from 0 to 500 μg, while at 24 hours, there was no effect of VK1 at up to 200 μg, but MK-7 at 100 μg gave an upper limit of normal range for total serum vitamin K (1.5 nM or 1 μg/L). MK-7 accumulated during the first 2 weeks until it reached a plateau level of approximately 10 nM (6 μg/L), and VK1 remained slightly above the placebo values during the entire study period. Both VK1 and MK-7 induced a statistically significant increase in osteocalcin carboxylation within 3 days, but only with MK-7 did the ratio of circulating carboxylated osteocalcin to uncarboxylated osteocalcin continue to increase during the entire study period, suggesting that, if taken on a daily basis, MK-7 at 25 μg/day is more efficacious than VK1 at 100 μg/day.

In the same study, Schurgers et al. (2007) also reported that MK-7 is 3 to 4 times more potent on a molar basis at interfering with the action of oral anticoagulant drugs, and by weight the effect of MK-7 is approximately 2.5 times that of VK1. Schurgers et al. (2007) reported that MK-7 at daily dose level of 50 μg or higher may interfere with anticoagulant treatment in a clinically relevant way. Based on these findings of the potency of MK-7 compared with that of VK1 and extrapolation of findings from a previous study in which supplements containing no more than 100 μg/day of VK1 were not likely to result in clinically relevant adverse effects of oral anticoagulant therapy in healthy individuals. Marles et al. (2017) reported that the studies conducted by Schurgers et al. (2007) were not designed or powered to assess safety.

Shearer et al. (2012) reviewed and described available studies related to absorption, distribution, metabolism, and excretion of VK1 and MK-7. These researchers noted that MK-7 is absorbed rapidly and unchanged from the small intestine following incorporation into mixed micelles. In the enterocytes, the mixed micelles are packaged into chylomicrons and secreted by exocytosis from the intestinal villi into the lymphatic capillaries, ultimately reaching the systemic circulation via the larger lymphatic vessels. Circulating MK-7 containing chylomicrons undergo changes in their apoprotein content that facilitate their uptake by receptor-mediated endocytosis in the liver and in bone osteoblasts, involving interactions between surface apoproteins and low-density lipoprotein receptor-related proteins.

In human subjects, absorption of MK-7 following oral ingestion of Natto and Natto-derived MK-7 by human subjects has been studied. These studies suggests that MK-7 is absorbed and can be detected in plasma (Sumi, 1999: Kaneki et al., 2001; Tsukamoto et al., 2000; Schurgers et al., 2007). Kaneki et al. (2001) reported that, MK-7 levels were higher in women from Japan as compared to women in Britain. Kaneki et al. (2001) analyzed serum MK-7 from blood of eight postmenopausal women consuming 80 g of Natto containing approximately 1100 μg of MK-7 just before eating Natto and on Days 1, 3, 7, and 14 after Natto consumption. The findings from this study, along with other studies, suggest good bioavailability of MK-7 derived from Natto or with Natto food (Vermeer, 2003; Schurgers et al., 2007). These studies reported higher and more stable blood levels of MK-7 as compared to VK1.

Moller et al. (2016) studied the bioavailability of a synthetic MK-7. In this randomized single-blinded two-way cross-over study, healthy subjects (20-66 years of age) took a single 180 µg dose of synthetic MK-7 (n=8) or fermentation-derived MK-7 (n=9), and serum MK-7 concentrations were monitored for 72 hours to calculate AUC (0-72 hours) and Cmax. The 90% confidence interval for the ratio of the AUC (0-72 hours) values for synthetic and fermentation-derived MK-7 was 83-111, indicating bioequivalence. The 90% confidence interval for the Cmax ratio was 83-131.

In another study, Knapen et al. (2016) compared the fasting plasma concentrations of MK-7 in healthy men and postmenopausal women (45-65 years) following consumption different foods such as: yogurt Kplus [yogurt enriched with MK-7, vitamins D3 and C, magnesium, n-3 poly unsaturated fatty acids (n-3 PUFA) and fish oil]; yogurt K (yogurt fortified with MK-7 only); and soft gel capsules containing only MK-7, daily for 42 days. The MK-7 content of yogurt was 71.2 µg/day while that of capsule was 58.3 µg/day. The increase in plasma MK-7 of subjects consuming the yogurt Kplus product was more pronounced as compared to the increase in MK-7 from the capsules. These investigators concluded that dairy matrix and nutrient composition may affect MK-7 delivery and improvement of vitamin K status. Yogurt fortified with MK-7 is a suitable matrix to improve the nutritional status of the fat-soluble vitamins.

Halder et al. (2019) described differences between isoforms VK1 and VK2 by means of source, function, and extrahepatic activity. These investigators reported that the difference in structure between VK1 and VK2 is seen in different absorption rates, tissue distribution, and bioavailability. In spite of differences in structure, both VK1 and VK2 act as cofactor for the enzyme gamma-glutamylcarboxylase, surrounding both hepatic and extrahepatic activity. Only carboxylated proteins are active and promote a health profile like hemostasis. These investigators noted that MK-7 has been shown to be a bioactive compound in regulating osteoporosis, atherosclerosis, cancer and inflammatory diseases without risk of negative side effects or overdosing.

Sato et al. (2012) compared the bioavailability of MK-4 and MK-7 in healthy women. In this study, 10 female volunteers (age: 20-21 years) were randomized into two groups (n=5/group) and treated with a single dose of MK-4 (420 µg; 945 nmol) or MK-7 (420 µg; 647 nmol) within 10 minutes after ingesting a breakfast containing 13-17 g of fat. Serum MK-4 and MK-7 levels were analyzed at different time points up to 72 hours. MK-7 was well absorbed and reached maximal serum level at 6 hours after intake and was detected up to 48 hours after intake. MK-4 was not detectable in the serum in any of the subjects at any time point. Consecutive administration of MK-4 (60 µg; 135 nmol) or MK-7 (60 µg; 92 nmol) for 7 days demonstrated that MK-4 supplementation did not increase serum MK-4 levels. However, consecutive administration of MK-7 increased serum MK-7 levels significantly in all subjects. These investigators concluded that MK-4 present in food did not contribute to the vitamin K status as measured by serum vitamin K levels, whereas MK-7 significantly increased serum MK-7 levels.

The comparison of published bioavailability studies indicates a 6-10 times better serum/plasma bioavailability of MK-7 compared to MK-4 or to that of VK1 (Schurgers et al., 2007, Schurgers et al. 2002). Ingestion of MK-4 at a dose level of 45 mg/day in osteoporotic patients (n=120; placebo=121) resulted in blood levels of 65 ng/ml (0.15 nM (Shiraki et al. 2000). In the published bioavailability studies, MK-4 is consumed daily as a

therapeutic agent at very high doses (3x15 mg/day) - a dose which is significantly higher as compared proposed use of MK-7 as a food supplement in Europe.

In an extensive review article, Akbulut et al. (2020) reported that VK2 differs from VK1, as the latter only has one unsaturated sidechain unit (Figure 1). Various isoforms of vitamin K have been identified, and long chain menaquinones (such as MK-7) specifically has been highlighted for its long half-life and extrahepatic activity, whereas the dietary form VK1 has a shorter half-life (Figure 1).

In summary, intestinal absorption of vitamin K follows a well-established pathway that applies to most dietary lipids. VK2 (menaquinones), including MK-7, appear to be absorbed unchanged from the gastrointestinal tract. Following absorption, VK2 are carried in the lymph in mixed micelles composed of bile salts, and subsequently released into circulation. VK2 from circulation are primarily distributed to the liver, in which MK-6 through MK-13 comprise 90% of the total vitamin K composition. Only 10% of the hepatic vitamin K stores consist of VK1. VK1 metabolism primarily takes place in the liver, and involves oxidative degradation of the side-chain resulting in subsequent elimination via the bile or urine. The available studies indicate a 6-10 times better serum/plasma bioavailability of MK-7 compared to MK-4 or to that of VK1. It has been suggested that short half-life of MK-4 will result in fluctuating serum levels. Given the short half-life, VK1 will be eliminated quickly, while MK-7 with its relatively longer half-life is likely to build up more stable serum levels. Thus, bioavailability among the various forms of VK2 appears to be related in part to the length of the side chain, as menaquinones with long side chains (e.g., MK-7, MK-8, and MK-9) are better absorbed from food compared with MK-4, which has a short side chain.

6.2.2. Human Clinical Evidence Related to Safety of MK-7

In the published literature, numerous studies investigating the effects of MK-7, as regards its efficacy and safety in human subjects, have appeared. Additionally, the available literature on MK-7 and other vitamin K has been extensively reviewed and summarized in multiple review articles and in meta-analysis. In GRN 887, several studies of MK-7, from a safety point of view, have been critically evaluated and extensively described. Some of the available published clinical studies of MK-7 are presented in Table 9, while more recent studies are described below. The available safety related evidence from individuals undergoing anti-coagulation therapy and from the review articles is also described below.

6.2.2.1. Recent Meta-analysis and Review Articles

As part of a US Pharmacopeial Convention safety evaluation of MK-7, Marles et al. (2017) extensively reviewed the published clinical studies of MK-7 from a safety point of view, excluding the trials that made no mention of whether adverse events occurred or of any other aspects of safety. In this special review article, the chemistry, nomenclature, dietary sources, intake levels, and pharmacokinetics of menaquinones, along with the nonclinical toxicity data available and the data on clinical outcomes related to safety (adverse events) has been described. Based on the comprehensive search and review of the peer-reviewed scientific literature published up to July 2016, these investigators concluded that the evidence indicate that MK-7, when ingested as a dietary supplement, is not associated with any serious risk to health or with other public health concerns. The US

Pharmacopeia monographs have been developed to establish quality standards for MK-7 as a dietary ingredient and as a dietary supplement in various dosage forms. Some of the studies mentioned in this monograph are also summarized in Table 9.

In a recent review article, Akbulut et al. (2020) reported that, given the role of vitamin K-dependent proteins in processes beyond coagulation, there is a need for a recommended daily intake (RDI) for VK2, separate from that of VK1. These investigators extensively evaluated the current knowledge and studies, either performed or still ongoing, to assess whether VK2 meet the nine criteria to be considered for a specific dietary recommendation intake. These criteria include (1) an accepted definition; (2) a reliable analysis method; (3) a food database with known amounts of the bioactive; (4) cohort studies; (5) clinical trials on metabolic processes; (6) clinical trials for dose-response and efficacy; (7) safety data; (8) systematic reviews and/or meta-analyses; and lastly, (9) a plausible biological rationale. These investigators highlighted the specific activity of VK2 based upon the proposed frameworks necessary for a bioactive substance to be recommended for an RDI. VK2 was found to meet all these criteria and should be considered for a specific dietary recommendation intake. These researchers noted that VK2 specifically has been highlighted for its long half-life and extrahepatic activity, whereas the dietary VK1 has a shorter half-life (Figure 3). These investigators stated that based upon basic and clinical sciences (including safety), there is need to establish an RDI for VK2.

Based on the relative activities of VK molecules, Sato et al. (2020) also suggested a need for establishing distinct RDIs for VK1, MK-4, and MK-7. In yet another review article, Simes et al. (2020) also reported that both VK1 and VK2 can play an important role in the pathogenesis and progression of many diseases. Nevertheless, the vitamin K2 (MK-7) has been shown to have advantages given its superior bioavailability and higher half-life in circulation when compared with other K vitamers. In an earlier review article and based on extensive evaluation of published literature, Simes et al. (2019) mentioned that an important conclusion can be drawn relatively to the safe use of VK health benefit, since no adverse effect or documented toxicity for VK1 or MK-4 and MK-7 has ever been reported for individuals consuming higher amounts of VK. Even when doses above the RDA of 75 μ VK (Commission Directive 2008/100/EC) were used, no hypercoagulable state was observed. Based on this, a Tolerable Upper Intake Level is not available (Simes et al., 2019). This review article indicates safety in use of MK-7.

Vlasschaert et al. (2020) reviewed controlled trials on VK supplementation for the prevention of CVD, including adverse effects described in these trials. This publication also included findings from some recent trials (Oikonomaki et al., 2019; Zwakenberg et al., 2019; De Vriese et al., 2020). Of the nine clinical trials included in this review, five earlier published studies reported the frequency and types of adverse events experienced by the trial participants. In three trials that were published in 2019, no adverse events were experienced in either the treatment or control arm. There was a high prevalence of adverse events reported in the trial of elderly individuals. There were more reported falls and gastrointestinal side effects observed in the VK treatment group but no differences related to serious adverse events or death. In the De Vriese et al. (2020) trial, 132 hemodialysis patients were randomized to warfarin, rivaroxaban, or rivaroxaban plus VK2 three times per week, over a period of eighteen months. In this study, subjective and objective tolerability was evaluated; no adverse events related to the intake of MK-7 (2000 μg) thrice

weekly after dialysis were reported. However, there were 36 major or life-threatening bleeding events reported in this trial of high risk participants receiving some form of anticoagulation treatment. There was no report of thrombosis in any of the clinical trials. Overall, these studies indicate that MK-7 is unlikely to cause adverse effects at levels up to 180 µg/day or 2000 µg thrice weekly.

6.2.2.2. Human Clinical Studies of MK-7

As indicated above some of the available human studies of MK-7 are summarized in Table 9. In a recent study, Ronn et al. (2021a) investigated the effect of MK-7 on serum ucOC, bone mass, and insulin sensitivity in postmenopausal women. In this randomized placebo-controlled trial, 148 postmenopausal women participated and received either MK-7 (375 µg/day) or placebo, as an add-on to calcium (800 mg) and vitamin D (38 µg) for 12 months. The findings revealed that administration of MK-7 for 12 months decreased plasma ucOC, increased plasma adiponectin, but did not change insulin sensitivity suggesting that ucOC does not affect insulin sensitivity in healthy postmenopausal women. No adverse effects were reported. This study is an extension of the previous study (Ronn et al., 2016) that is described below.

In another similar study, Ronn et al. (2021b) reported the results of 3 years of exposure to the same treatment in 142 postmenopausal women with osteopenia. In this study, bone turnover markers in serum and bone mineral density and microarchitecture was measured. Treatment with MK-7 at levels of 375 µg/day as an add-on to calcium and vitamin D increased carboxylation of osteocalcin. However, treatment of postmenopausal women with osteopenia for 3 years did not affect biochemical markers of bone turnover, bone mineral density, or bone microarchitecture. In this study, safety biochemistry was obtained after 3 and 6 months, and there after every 6 months. Additional details of the biochemistry parameters investigated were not provided. The treatment was well tolerated with few women developing adverse events. Four women were excluded from the MK-7 group (3 due to cancer, 1 due to arteritis temporalis), 4 women were excluded from the placebo group (2 due to cancer, 2 due to hip fracture). Furthermore, serious adverse events occurred in 4 women in the MK-7 group (1 traumatic subdural hematoma, 2 infections with hospitalization (pneumonia and uterine infection), 1 wrist fracture), and in 2 women in the placebo group (2 wrist fractures), but all continued in the study. Nine women in the MK-7 group and 16 in the placebo group discontinued the study before completion for personal reasons. Therefore, 119 women of the 148 women included completed the 3-year study.

In a randomized, double-blind, placebo-controlled clinical trial, Tarkesh et al. (2020) studied the effect of oral MK-7 on clinical and biochemical parameters in polycystic ovary syndrome (PCOS) patients. In this study, 84 PCOS patients (18-40 years old) were assigned to receive MK-7 (90 µg MK-7/day) and placebo for 8 weeks. Of the 84 patients, two in the MK-7 group were withdrawn from the study due to lack of follow-up, and three patients in the placebo group did not complete the study; one patient, due to lack of follow-up, and, the other two became pregnant. The patients' compliance rate was more than 90% in both groups of the study. No significant effect of MK-7 supplementation was observed on fasting serum glucose, endocrine parameters, and other components of serum lipid profile. There was no significant difference between the groups at baseline and end-of-trial in dietary macro- and micronutrient intake (Energy, protein, fat, carbohydrate,

fiber, vitamin K, and vitamin D). No adverse effects of MK-7 treatment at dose level of 90 µg/day for 8 weeks were reported during the course of study.

In a study with type 2 diabetes mellitus (T2DM) subjects, Karamzad et al. (2020) investigated the effects of MK-7 supplementation on glycemic indices, anthropometric indices and lipid profile. In this double-blind, placebo-controlled, randomized clinical trial, 60 men and women (aged 20-55 years) with T2DM were allocated equally to received either the MK-7 (200 µg/day) or the placebo group for 12 weeks. Anthropometric measures, blood pressure, glycemic indices and lipid profile including fasting blood sugar (FBS), hemoglobin A1c (HBA1C), fasting insulin (FI), homeostatic model assessment insulin resistance index (HOMA-IR), triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL-C) and low-density lipoprotein (LDL-C) were measured at baseline and after twelve weeks. Forty-five participants (MK-7 group n=23; placebo group n=22) completed the trial. There were no significant differences between the treated and placebo as regards calorie intake, macronutrient intake, physical activity level or anthropometric measures at baseline and at the end of the study. IN MK-7 treated group, a significant decrease in FBS, HbA1c, fasting insulin and HOMA-IR was noted. Lipid profile did reveal any significant change between the groups. No adverse effects of MK-7 were reported by any of the participants, retained or lost, at any stage of the trial. The findings from this study support the safety of MK-7 at use levels of 200 µg/day for 12 weeks.

In another study, Sakak et al. (2020) investigated the same parameters as described in the above study (Karamzad et al., 2020), except that effects of higher levels of MK-7 (360 µg/day) were studied for 12 weeks. In this randomized controlled trial, 68 insulin-independent, diabetic subjects participated. At the end of the study, the T2D patients in the MK-7 group had significantly lower levels of fasting plasma glucose and HbA1c compared with the placebo group, while again, no significant changes were noticed in the lipid profiles. Fasting insulin and HOMA-IR significantly decreased in the MK-7 group compared to baseline, suggesting a decrease in insulin resistance. No adverse effects were reported.

In a recent study, Zwakenberg et al. (2019) assessed if MK-7 supplementation, compared to placebo, decreases vascular calcification in people with type 2 diabetes and known CVD. In this double-blind, randomized, placebo-controlled trial, men and women with type 2 diabetes and CVD were randomly assigned to 360 µg/day MK-7 or placebo for 6 months. Thirty-five patients were assigned to the MK-7 group (33 completed follow-up) and 33 to the placebo group (27 completed follow-up). At baseline and after 3 and 6 months, anthropometric parameters, blood pressure were measured. Non-fasting blood samples were drawn, and glycated hemoglobin, creatinine, and lipid levels were measured. After the 6-month of intervention, target-to-background ratios tended to increase in the MK-7 group compared with placebo, although this was not significant. Log-transformed computed tomography calcification mass did not increase in the intervention group compared with placebo. MK-7 supplementation significantly reduced dp-ucMGP compared with placebo. No adverse events were reported.

McFarlin et al. (2017) studied the effects of dietary supplementation of MK-7 on cardiovascular responses to a graded cycle ergometer test. In this randomized controlled trial, aerobically trained young (average age 21 years) males and female athletes (n=26) were randomly assigned either to a control group that received a rice flour placebo or to an

intervention group that received MK-7. In this study, during weeks 1 to 4, participants received 320 μg MK-7/day; for weeks 5 to 8, they received 160 μg MK-7/day. MK-7 supplementation was associated with a 12% increase in maximal cardiac output, with a trend toward an increase in heart-rate AUC. No significant changes occurred in stroke volume. The investigators stated that at no time during the study did any participant report an adverse effect to taking either the supplement or the placebo.

In a double blind, placebo controlled, trial in 148 postmenopausal women (average age 67 years), Ronn et al. (2016) studied the effects of MK-7 in prevention of age-related deterioration of trabecular bone microarchitecture at the tibia. In this study, the dose of MK-7 used was 375 μg/day for one year and the effect on under-carboxylated osteocalcin (ucOC), bone mass and quality were investigated. After three months of the administration of MK-7, ucOC was found to be decreased in the MK-7 group as compared with placebo group. High resolution peripheral quantitative computed tomography (HRpQCT) after 12 months demonstrated that tibial trabecular number and trabecular spacing was decreased in placebo group and unchanged in treatment group. It was also observed that trabecular thickness was unchanged in the MK-7 group and increased in the placebo group. Compliance was 97.2% and 97.8% in the MK-7 and placebo groups respectively and all but one participant were more than 80% compliant. There were no differences between the groups regarding adverse events or serious adverse events ($p>0.05$ for both, data not shown). The findings revealed that administration of MK-7 (375 μg/day) for 12 months decreased serum ucOC, indicating an increased carboxylation of osteocalcin, and an increase in serum bone-specific alkaline phosphatase (s-BAP).

In a randomized, double-blind, parallel study, Moller et al. (2016) investigated the effects of fermentation-derived MK-7 (90 μg) and 3 doses of synthetic MK-7 (45, 90 and 180 μg). In this study, healthy adult subjects (n=43; 20-60 years of age) took one of the supplements daily for 43 days, and the fraction of serum carboxylated osteocalcin (OC) was compared between day 1 and day 43 as a marker for vitamin K activity. Following daily administration of 180 μg of synthetic MK-7 for 43 days, the serum concentrations of carboxylated OC (cOC) increased, while that of unOC reduced, indicating increased vitamin K activity. In this study, 27 subjects reported a total of 40 adverse events; 32 of these were judged unlikely to be related to the study supplement. In two cases, the adverse events were judged possibly to be related to the study supplement: dry mouth from day 4 to the end of the study (180 μg synthetic MK-7 group) and diarrhea (fermentation- derived MK-7 group). Another case of diarrhea in the fermentation-derived MK-7 group was judged probably to be due to the study supplement. The investigators concluded that the synthetic form of MK-7 is bioequivalent to fermentation-derived MK-7 and is well tolerated in healthy subjects.

In a series of studies, Knapen et al. (2012, 2013, 2015a, 2015b, 2016) investigated the effects of MK-7. These studies are summarized in Table 9. In a more recent report, based on an analysis from 214 postmenopausal women (55-65 years of age), Knapen et al. (2018) reported the effects of high levels of MK-7 (180 μg/day) or placebo for 3 years on body fat and weight. These investigators reported that MK-7 intake may support reducing body weight, abdominal and visceral fat, notably in subjects showing a strong increase in cOC. A causal relationship between the changes in cOC and body fat or distribution cannot be concluded from these data. The study appears to be an extension of others studies by

these investigators. The investigators did not mention any adverse effects in this publication.

Dalmeijer et al. (2012) investigated the effects of MK-7 supplementation on carboxylation of matrix Gla-protein (MGP). In this randomized, double-blind, placebo-controlled trial, 60 subjects (age 40-65 years) received MK-7 supplementation at dose levels of 180 and 360 µg/day or placebo for 12 weeks. At the end of 12 weeks, a significant and dose-dependent decrease in desphospho-uncarboxylated MGP (Dp-ucMGP) was noted in groups treated with 180 µg and 360 µg MK-7 (31% and 46%, respectively), while dp-ucMGP levels remained unchanged after placebo treatment. The osteocalcin ratio also decreased significantly after 12-week supplementation with 180 µg (60%) and 360 µg (74%) MK-7, while levels remained unchanged after placebo treatment. These results indicate improved vitamin K levels and good compliance to the study treatment. Changes over time of dp-cMGP and t-ucMGP levels did not differ between treatment arms. Other cardiovascular risk factors did not differ between treatments arms. No adverse effects were reported.

In summary, MK-7 has been extensively studied for its safety and efficacy in over 25 clinical trials, involving over 2500 participants. These clinical studies also include several double-blind, placebo-controlled trials that are least likely to result in bias, will capture the adverse effects, and provide an opportunity to assess the safety and 'tolerability' of MK-7 in a diverse population. The findings from long-term high dose trials in which treatment with MK-7 at levels up to 180 µg/day for 3 years, or up to 360 µg/day for 12 weeks, or up to 1080 µg thrice weekly for 8 weeks did not reveal any significant adverse effects compared with placebo. Adverse effects specifically attributed to MK-7 were limited to gastrointestinal upset associated with the product's smell. The available information from multiple clinical trials suggest that MK-7 is unlikely to cause any adverse effects at the intended use levels in healthy subjects. In some individuals, MK-7 supplementation at doses as low as 10 µg significantly influenced anticoagulation sensitivity. The findings related to effects of MK-7 and anti-coagulation are separately described.

Table 9. Summary of Clinical Trials with MK-7 and Adverse Event Reports

Reference	Clinical study design	No. of subjects	Demographic characteristics	Dose	Length of treatment	Endpoint(s)	Adverse events
McFarlin et al., 2017	Randomized controlled trial; conducted in two phases of 4 weeks each	N=26 (18 women); 13/group	Healthy athletes; average age 21 years	Phase I- 320 µg/day; Phase II- 160 µg/day for 4 weeks	Total 8 weeks; Phase I 4 weeks and Phase II 4 weeks	Effects of supplemental MK-7 on heart rate, stroke volume, cardiac output, oxygen consumption, blood lactate, and ventilation	No adverse events reported by subjects
Ronn et al., 2016	Randomized, double-blind, placebo controlled trial	N= 148 (71 each group)	Postmenopausal women with osteopenia; average age 67 years	375 µg/day	For 12 months	Effects of supplemental MK-7 on mineral density (BMD), bone microarchitecture and biochemical bone turnover markers	No differences between the groups regarding adverse events or serious adverse events
Knapen et al., 2016	Randomized, partly single-blind, partly open-label bioavailability	N=43 men, 64 women	Healthy men and postmenopausal women, 45-65 y	MK-7 at 71.2 µg /d (in yogurt) or 58.3 µg (in capsule)	42 day	Effect of supplemental MK-7 in yogurts or capsules on fasting plasma MK-7 concentrations	In yogurt-treated groups, 7 cases of satiated feeling, heartburn, stomach ache, abdominal cramps, diarrhea, and nausea attributed to increased yogurt intake
Inaba et al., 2015	Randomized, double-blind, placebo-controlled	N=60 women N=120 men and women	Healthy postmenopausal women, 50-69 y Healthy men and women, 20-69 y	MK-7 at 0, 50, 100 or 200 µg /d MK-7 at 0 or 100 µg /d	4 weeks 12 weeks	Dose finding and efficacy of low dose daily MK-7 supplementation to improve osteocalcin γ-carboxylation	No adverse effects associated with study products were observed
Knapen et al., 2015	Randomized, double-blind, placebo-controlled parallel	N=120 treated women, N=124 nontreated women	Healthy postmenopausal women, 55-65 y	MK-7 at 180 µg /d	3 years	Effect of MK-7 on arterial stiffness in healthy postmenopausal women	No effect on fasting glucose, acute-phase markers (hs-CRP, IL-6, TNF-α) or markers of endothelial dysfunction (VCAM, E-selectin, and

							AGE)
Caluwe et al., 2014	Randomized, single-blind, dose-finding intervention	N=200	Chronic hemodialysis patients in stable medical condition; men and women, ≥ 18 y	MK-7 at 360, 720, or 1080 µg, 3 times weekly	8 week	Determination of optimum dose of MK-7 for activation of vitamin K-dependent MGP by measuring reduction of inactive dp-uc-MGP	Gastrointestinal upset due to smell of MK-7 tablets in 9 subjects who withdrew
Knapen et al., 2013	Randomized, double-blind, placebo-controlled, parallel	N=120 treated women, N=124 nontreated women	Healthy postmenopausal women, 55-65 y	MK-7 at 180 µg /d	3 years	Effect on MK-7 on serum uc-OC and c-OC concentrations and efficacy to decrease bone loss	Dropout rate of 8.6%. 12 dropouts in placebo group (hair loss, brittle nails, hot flashes, knee pain, numbness in limbs, fatigue, weight gain); 9 dropouts in MK-7 (bone pain, hot flashes, rash around eyes and ears, smelly capsules, weight gain)
Ozdemir et al., 2013	Nonrandomized prospective pilot study	N=12 girls; N = 8 boys	Pediatric thalassemic osteopathy patients, 3-18 y	MK-7 at 50 µg + calcitriol at 5 µg /d	12 months	Efficacy of MK-7 and calcitriol combination to reduce thalassemic osteopathy by improving bone mineral density and z score of lumbar spine	No noncompliance or side effects observed
Theuwissen et al., 2013	Randomized, double-blind, placebo-controlled	N=42 children N=68 adults	Healthy children, 6-19 y, healthy adults, 20-80 y, divided into age groups of 10 y increments; selected for supplementation if circulating values of uc-OC or dp-uc-MGP were significantly higher than those of young	Children: MK-7 at 0 or 45 µg /d Adults: MK-7 at 0 or 90 µg /d Linseed oil, casein, or gum Arabic used as carrier	Children: 8 week Adults: 7 week	Effect of MK-7 supplementation on serum uc-OC and dp-uc-MGP	1 dropout due to unrelated reasons (broken leg)- no adverse effects noted

			healthy adults, 20-29 y				
Theuwissen et al., 2012	Randomized, double-blind, placebo-controlled exploratory pilot	N=20 men, 22 women	Healthy men and women, 18-45 y	MK-7 at 0, 10, 20, 45, 90, 180, or 360 µg /d	12 week	Estimation of dose-response effects of MK-7 supplementation on (a) carboxylation of osteocalcin and MGP (b) thrombin generation as an indicator of safety	No dropouts, no adverse effects on thrombin generation observed
Dalmeijer et al., 2012	Randomized, double-blind, placebo-controlled	N=60	Healthy men and healthy postmenopausal women, 40-60 y	MK-7 at 0, 180, and 360 µg /d	12 week	Effect of MK-7 on circulating dp-uc-MGP and dp-c-MGP and on total uc-MGP, uc-OC, and c-OC	1 dropout after enrollment but prior to treatment; no adverse events, no changes over time of prothrombin time (P = 0.92). Other CVD risk factors such as blood lipid profile or blood pressure did not differ between treatments
Knapen et al., 2012	a. Cross-sectional analysis b. Randomized, double-blind, placebo-controlled, dose-response c. Randomized, double-blind, placebo-controlled	a. N=244 untreated women b. N=22 women, N=20 men, randomized into 7 groups of 6 individuals c. N=124 untreated women, N=133 treated women	a. Healthy postmenopausal women, 55-65 y b. Healthy postmenopausal women and healthy men, 25-45 y c. Healthy postmenopausal women, 55-75 y	a. Untreated b. MK-7 at 0, 10, 20, 45, 90, 180, or 360 µg /d c. MK-4 at 0 or 45 mg/d	a. Not applicable b. 12 week c. 3 years	a. Vitamin K status with circulating adiponectin and body composition b. Minimal effective dose for effect on circulating osteocalcin and adiponectin c. Effect of MK-4 on bone loss, bone geometry, body weight, and body composition	c. 2 dropped out of placebo group for weight gain; no other adverse effects reported
Brugè et al., 2011	Non-randomized, non-blinded,	N=4 males; N=8 females	Healthy adults, mean age 37 y (SD	MK-7 at 0, 45, and 90 µg /d	2 week for each	Bioavailability of MK-7 in olive oil (MK-7	No dropouts or adverse events reported

	bioavailability		= 3)		treatment, separated by 2 week washout period	plasma levels) and effect on osteocalcin and its carboxylation status	
Emaus et al., 2010	Randomized, double-blind, placebo-controlled	N=334	Healthy women, 50-60 y; 1-5 y after menopause	MK-7 at 0 and 360 µg /d	12 months	Effect of MK-7 supplementation on rate of bone loss among healthy postmenopausal women	5 participants in each group sustained a fracture; 2 in treatment groups had increased nocturnal hot flushes and abdominal pain, 1 in treatment had increased palpitations that ceased at study end; in placebo group, 4 reports of muscular pain and general unwell feeling, 2 reports of itching
Forli et al., 2010	Randomized, double-blind, placebo-controlled, prospective, longitudinal	N=35 lung transplant patients, N=59 heart transplant patients	Transplant patients at risk for osteoporosis; stratified by heart vs. lung transplant, men and women ≤ 50 y vs. > 50 y, and sex	MK-7 at 0 or 180 µg /d	12 months	Effect of MK-7 on bone mass in the 1st year after lung or heart transplant	10 heart patients did not complete 12 mo follow-up; 1 in MK-7 treatment arm died from causes not connected to study. Other adverse effects not related to treatment and not different between treatment and placebo groups
Schurgers et al., 2007	a. Single-dose oral bioavailability b. Escalating dose-response c. Randomized crossover d. Nonrandomized drug interaction study	a. N=15 b. N=10 c. N=18 d. N=12	Healthy men and women 25-35 y; in trial 4, subjects were treated with individualized dose of acenocoumarol to reach target INR value of 2.0 within 3 week, then maintained at stabilizing dose of	a. MK-7 and K_1 at 2000 µg each b. MK-7 and K_1 at 50, 100, 150, 200, 250, 300, and 500 µg each c. MK-7 at 143 µg /d, K_1 at 99 µg /d	a. Once b. Once; 2 week washout between doses c. 6 week d. 1 week at each dose level	Comparison of absorption and efficacy (osteocalcin carboxylation) of synthetic vitamin K_1 and natto-derived MK-7	No adverse reactions in trials a, b, and c; in the interaction trial, doses of K_1 at 315 µg /d and of MK-7 at 130 µg /d caused significant decrease in INR from 2.0 to 1.5 (i.e., MK-7 was much more potent)

			acenocoumarol while treated with escalating doses of MK-7 or K_1	d. MK-7 at 97.4 µg /d with weekly increment of 97.4 µg and K_1 at 49.6 µg /d with weekly increment of 49.6 µg			

AGE: advanced glycation end products; c-OC: carboxylated osteocalcin; CVD: cardiovascular disease; dc-uc-MGP: desphospho-uncarboxylated matrix Gla protein; hs-CRP: high-sensitivity C-reactive protein; IL-6: interleukin 6; INR: international normalized ratio; MGP: matrix Gla protein; SD: standard deviation; TNF-α: tumor necrosis factor α; uc-OC: uncarboxylated osteocalcin; VCAM: vascular cell adhesion molecule
Adapted from Marles et al. (2017) with inclusion of new studies

6.2.2.3. Coagulation Related Studies and Review of Vitamin K

Vitamin K plays a major role in coagulation pathways because it is a cofactor required for the activity of several key proteins containing carboxyglutamic acid residues. Vitamin K antagonists (VKA) are a class of drugs used for therapeutic anticoagulation. Oral anticoagulation therapy with VKA has been used for over 60 years to prevent frequent and serious thromboembolic complications associated with pathological conditions such as cardiac valve replacement, atrial fibrillation, and venous thromboembolic disease. Anticoagulants are the cornerstone therapy for thrombosis prevention and treatment. As mentioned earlier, both VK1 and VK2 contain a 2-methyl-1,4- naphthoquinone nucleus with a lipophilic side chain and this structure is similar to warfarin and other coumarin-like anticoagulants that function as VKA. Given this, it is important to understand the potential interference of increased dietary vitamin K intake in patients on anticoagulant therapy. These VKA, such as warfarin, inhibit coagulation through antagonizing the action of vitamin K and can thereby interfere with the coagulation cascade. The uncarboxylated, inactive vitamin K-dependent coagulation proteins synthesized in the presence of warfarin result in reduced blood clot formation. The available information and studies related to the effects of vitamin K, including MK-7 have been extensively summarized and discussed in GRAS No. 887.

In a recent study, Ren et al. (2021) investigated the effects of MK-7 administration on carboxylation and coagulation activity of vitamin K dependent coagulation factors, and to clarify the plausible concern for the procoagulant effect of MK-7 in healthy individuals. In this study, 40 healthy volunteers (18 male/22 female; age 25 - 40 years; body weight 57.33±7.92 g; BMI 20.82±1.54 kg/m^2) were recruited. The subjects were given 90 μg/day of MK-7 for 30days. Blood samples were withdrawn on Days 0, 7 and 30 after the intake of MK-7 supplement. Blood samples were collected on Days 0, 7 and 30 after the intake of the MK-7 supplement. Common coagulation related parameters such as prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and blood coagulation factors II, VII, IX, and X activities and Protein induced by vitamin K absence or antagonist-II (PIVKA-II) were measured. Compared with baseline, no significant differences in PT, APTT, and TT were noted on day 30 following administration of MK-7. Similarly, the activities of coagulation factors II, VII, IX, and X on day 30 showed no significant differences with those at baseline. Furthermore, PIVKA-II levels were unchanged after 30 days of MK-7 supplementation. The investigators concluded that MK-7 supplementation at doses of 90μg/day does not affect vitamin K-dependent coagulation factors' coagulation activity, and does not enhance the carboxylation of prothrombin in healthy individuals. This indicated that MK-7 administration does not alter hemostatic balance in healthy populations without anticoagulation treatment. In this study, no volunteer complained of gastrointestinal discomfort, such as vomiting, diarrhea and abdominal pain. Swelling or pain in muscles did not occur in any individual, and no other adverse effects were observed. This study revealed a steady coagulation profile in healthy individuals taking MK-7. The possible explanation for the steady coagulation profile after taking MK-7 is that all Gla-containing coagulation factors are fully carboxylated at recommended dietary allowance levels, and excess MK-7 intake might not induce over carboxylation (Marles et al., 2017).

The available evidence suggest that different vitamin K homologs differ in their mode or extent of action in disturbing VKA induced anticoagulation. Over the years, Schurgers and his colleagues have extensively investigated the effects of vitamin K, including MK-7, during

anticoagulant therapy. As described earlier in the metabolism section, Schurgers et al. (2007) reported that, on a molar basis and as compared to VK1, MK-7 is 3 to 4 times more potent at interfering with the action of oral anticoagulant drugs, while by weight the effect of MK-7 is approximately 2.5 times that of VK1. These investigators reported that at daily dose level of 50 μg or higher, of MK-7 may interfere with anticoagulant treatment in a clinically relevant way.

In a study on patients undergoing anticoagulant therapy after valve replacement operations. Kudo (1990) reported significantly elevated thrombi-test (used in controlling the amount of anticoagulant used in preventing thrombosis) values following intake of Natto. In this study, 10 patients (age 25-45 years; 5/sex) undergoing anticoagulant therapy after valve replacement operations were studied. A good correlation between the amount of Natto consumed and thrombo-test value was noted. Serum levels of VK1, MK-4 and MK-7 were measured at 0, 24 and 48 hours. No changes in VK1 and MK-4 levels were noted, while a significant increase in MK-7 was noted at 24 and 48 hours. These investigators suggested that the antagonistic effects of Natto to warfarin may be attributable to the massive production of vitamin K in the intestine by *B. subtilis* that is present in Natto. Subsequent studies have shown that MK-7 is particularly active in disturbing the anticoagulation and this has been suggested to be due to long half-life of MK-7. As mentioned earlier, 100 g of Natto contains up to 1000 μg MK-7 and will certainly disturb the VKA treatment. These levels are quite high as compared to the proposed use of 10 μg/serving.

van Summeren et al. (2009) investigated the effects of 45 μg of MK-7/day for eight weeks on different biomarkers and coagulation-related parameters, including serum levels of MK-7. In this double-blind, randomized, placebo-controlled trial, 55 healthy pre-pubertal children were divided into placebo group (27 male children; age 6-10 years) and MK-7 receiving group (28 male children; age 6-10 years). Over the course of the study in both the placebo and treatment group, bone markers and coagulation parameters remained constant. The findings from this study suggest that oral administration of 45 μg MK-7/day for 8 weeks to children increased serum levels of MK-7 and osteocalcin carboxylation without affecting blood coagulation. Periodically, following the study, the subjects were checked for the occurrence of adverse events of treatment and none were reported.

Given the increasing availability of MK-7 and its promotion for bone and cardiovascular health, Theuwissen et al. (2013) investigated the posology (dosage) for the interference of supplemental MK-7 with VKA therapy. These investigators carried out a dose-escalation study to measure the antidotal potency of lower doses (10, 20 and 45 μg/day) of MK-7 supplements in healthy volunteers stabilized on acenocoumarol. In this study, in addition to conventional INR measurements, response on thrombin generation and the γ-carboxylation status of specific Gla-proteins with coagulation and noncoagulation functions were studied. For these investigations, healthy men and women (n=18; age 18-45 years) were anticoagulated for four weeks with acenocoumarol. Of the 18 participants, 15 subjects (8 men, 7 women) attained a target INR of 2.0. In the six successive weeks, subjects were supplemented with increasing doses of MK-7 (10, 20, 45 μg/day) while continuing acenocoumarol treatment at established individual doses. Apart from the INR, acenocoumarol treatment significantly increased under-carboxylated forms of prothrombin (ucFII), osteocalcin (ucOC) and matrix Gla-protein (dp-ucMGP), and decreased endogenous thrombin generation (ETP).

Theuwissen et al. (2013) reported that a daily intake of 45 μg MK-7 significantly decreased the group mean values of both the INR and ucFII by about 40%, while daily intakes of 10 and 20 μg MK-7 were independently judged by two hematologists to cause a clinically relevant lowering of the INR in at least 40% and 60% of the subjects, respectively, and to significantly increase ETP by about 20 and about 30%, respectively. Intake of MK-7 did not affect circulating ucOC and dp-ucMGP. These investigators concluded that MK-7 supplementation at doses as low as 10 μg (lower than commonly recommended dose of 45 μg) significantly influenced anticoagulation sensitivity in some individuals. Based on these observations, these investigators recommended to avoid use of MK-7 supplements in patients undergoing VKA therapy.

In an extensive recent review article, Camelo-Castillo et al. (2021) summarized published data on the potential impact of the gut microbiota on the quality of anticoagulation of patients receiving VKA therapy. The available information suggests that efficacy and safety of VKAs as oral anticoagulants depend on the quality of anticoagulation control, as reflected by the mean time in therapeutic range (TTR). Several factors such as comorbidities, high inter-individual variability, interacting drugs, and non-adherence may be associated to poor TTR. Recent studies suggest that gut microbiota plays an important role in the pathogenesis of cardiovascular diseases, but the effect of the gut microbiota (GM) on anticoagulation control with VKAs is unknown. In the present review article, we propose different mechanisms by which the GM could have an impact on the quality of anticoagulation control in patients taking VKA therapy.

Camelo-Castillo et al. (2021) suggested that the potential effects of gut microbiota may be mediated first, by an indirect effect of metabolites produced by gut microbiota in the availability of VKAs drugs; second, by an effect of vitamin K-producing bacteria; and, finally, by the structural modification of the molecules of VKAs. In order to implement predictive or preventive strategies before VKA therapy, there is a need for studies directly investigating the role of gut bacteria and their metabolites on this family of drugs. The use of probiotics could be proposed as an alternative given the modulation of gut microbiota compositions and their metabolic pathways. These investigators noted that most menaquinones are produced in the colon, where the bile salts are absent, suggesting a low absorption of these forms of VK. The contribution of the microbiome to vitamin K nutriture is still questionable. If any, the contribution is only accounting for an effect in the liver without any adverse effects on bleeding. The vasculature and bone do not benefit from the MKs produced by gut bacteria, as these are mainly MK-10 and up.

Ferland et al. (2019) studied whether increasing dietary VK intake by ≥150 μg/day improves anticoagulation stability of warfarin-treated patients with a history of international normalized ratio (INR) instability. In this 24-week randomized controlled trial, warfarin-treated patients were randomized to the intervention group and received dietary counsel to increase their VK intake by ≥150 μg/day through specific food choices, recipes and cooking strategies. Warfarin therapy was monitored weekly by INR. The primary clinical outcome was anticoagulation stability as defined by %TTR > 70% during weeks 4 through 24. In this trial, 49 patients (VK group 28; control 21; age 32-85 years) completed the study. Mean (±SEM) %TTR over the assessment period were 67.7±3.4 and 61.4±3.5 for the VK and control groups, respectively (ns). Increasing dietary VK intakes resulted in a greater proportion of patients with %TTR > 70% over the assessment period. Specifically, half of the patients (14 of

28) from the VK group met the criteria versus 4 of the 21 patients (19%) from the control group (P=0.026). The investigators concluded that increasing VK intake ≥150 µg/day through diet strategies improves anticoagulation stability of warfarin-treated patients with a history of anticoagulation instability. It should be noted that this study was conducted with VK that has a short half-life as compared to MK-7 or long chain menaquinones. Hence, from a safety point of view, it is likely that MK-7 may provide better anticoagulation stability given its longer half-life.

6.2.2.3.1. Role of Vitamin K in Blood Coagulation

Vitamin K is involved in the synthesis of many factors of the coagulation cascade. The role of vitamin K in blood coagulation has been extensively studied to understand the potential interference of increased dietary vitamin K in patients on anticoagulant therapy. Vitamin K-antagonists (VKA), such as warfarin, inhibit coagulation through antagonizing the action of vitamin K and can thereby interfere with the coagulation cascade. The uncarboxylated, inactive vitamin K-dependent coagulation proteins synthesized in the presence of warfarin result in reduced blood clot formation. The available information suggest that different vitamin K homologs differ in their mode or extent of action in disturbing VKA induced anticoagulation.

The biological role of vitamin K is to act as a cofactor for a specific carboxylation reaction that transforms selective glutamate (Glu) residues to gg-carboxyglutamate (Gla) residues (Figure 4). The reaction is catalyzed by a microsomal enzyme, gg-glutamyl, or vitamin K - dependent carboxylase, which in turn is linked to a cyclic salvage pathway known as the vitamin K epoxide cycle. Warfarin (VKA), 4-hydroxycoumarin, binds to the vitamin K epoxide reductase (VKOR) enzyme and inhibits recycling of vitamin K. Hence, the carboxylation of coagulation factors is inhibited. This results in species that are inactive and non-carboxylate, also known as PIVKAs (Proteins Induced by Vitamin K Antagonists).

The available information shows that in the UK, warfarin is used by over 1% of the population, while in the US over 30 million prescriptions are written annually. Over the years, the use of warfarin is declining and the recent data from 2006 to 2019 shows a steady decline in warfarin prescriptions since 2010 (when it peaked to about 35 million) to the most recent available data of 2019 (decreased to about 15 million) (available here).

Individuals with medical conditions that can make blood clot too easily and quickly require warfarin intervention. Blood clot is formed through coagulation cascade proteins that are formed in the liver and activated by vitamin K. Warfarin works by restricting the vitamin K cycle which otherwise continues to activate coagulation proteins until metabolized. Individuals at risk for developing blood clots take warfarin to prolong the usual time it takes for a clot to form, resulting in an increased INR (International Normalized Ratio)/Prothrombin Time (PT). INR and PT are laboratory test values obtained from measurements of the time it takes blood to clot. It is well known that dietary vitamin K intake counteracts the anticoagulant effect by warfarin or VKA and hence, patients on anticoagulants therapy have been advised to reduce dietary vitamin K intake to avoid changes in anticoagulation or to stabilize INR.

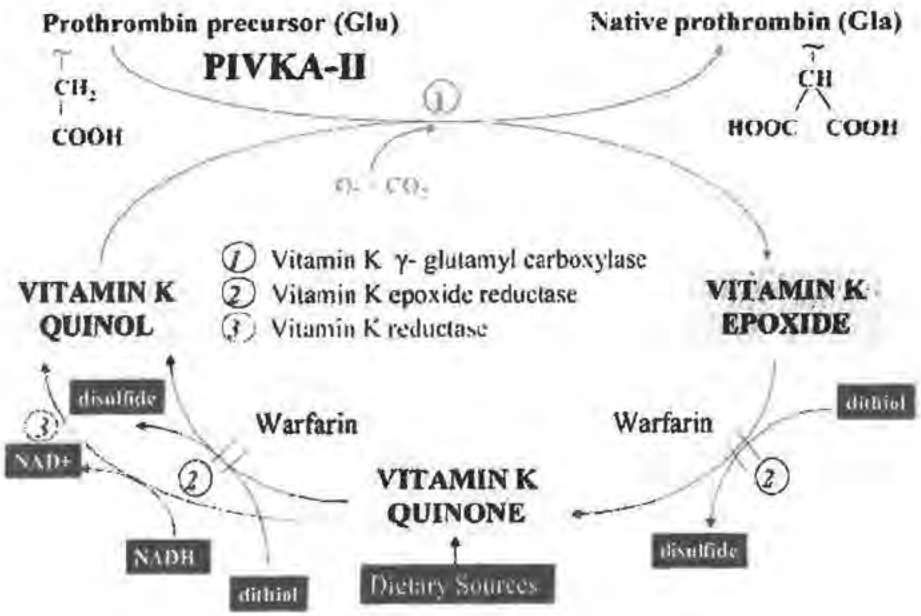

Figure 4. Vitamin K Cycle.

Scheme shows the cyclic metabolism of vitamin K in relation to the conversion of glutamate (Glu) to gg-carboxyglutamate (Gla) residues for the coagulation protein prothrombin. A general term for the glutamate precursors of vitamin K-dependent proteins is proteins induced by vitamin K absence, abbreviated PIVKA. For prothrombin (factor II) the glutamate precursor is known as PIVKA-II. The active form of vitamin K needed for carboxylation is the reduced form, vitamin K quinol. Known enzyme reactions are numbered 1, 2, and 3. The carboxylation reaction is driven by a vitamin K-dependent carboxylase activity (*reaction 1*) which simultaneously converts vitamin K quinol to vitamin K 2,3-epoxide. Vitamin K 2,3-epoxide is reduced back to the quinone and then to the quinol by vitamin K epoxide reductase (*reaction 2*). The reductase activity denoted 2 is dithiol dependent and is inhibited by coumarin anticoagulants such as warfarin. Dietary vitamin K may enter the cycle via an NAD(P)H-dependent vitamin K reductase activity (*reaction 3*), which is not inhibited by warfarin. Adapted from: http://www.fao.org/3/Y2809E/y2809e0g.htm

Given the difficulties to achieve high level of compliance to restrict vitamin K led researchers to develop and introduce non-VKA oral anticoagulants (NOACs), such as dabigatran, rivaroxaban, apixaban, endoxaban etc. for the treatment of AF and VTE. These alternatives also pose unique challenges to clinicians in the performance of invasive procedures and during acute hemorrhage. Given its low cost, VKA is still prescribed, tradition (the Dutch thrombosis service for example), and some indications such as no kidney function to clear the drugs (i.e., dialysis) (Ten Cate and Prins, 2017). Hence, VKA continues to be prescribed due to wide clinical experience. In spite of this, there is a steady decline in the number of warfarin prescriptions since 2010.

The available information suggests that patients starting treatment with VKAs are advised, with great emphasis, on nutritional information and discouraged to consume vitamin-K-rich foods, such as green leafy vegetables. It is essential to understand the putative interaction between dietary vitamin K intake and changes in INR with the VKAs. Changes in the daily dietary intake of vitamin K are inevitable. In a review article Violi et al. (2016) reported the range of daily intake of vitamin K1 variation from 76 to 217 µg. Schurgers et al.

(2004) noted that observable effects on INR were detected only at daily vitamin K intake is >150 µg.

As mentioned earlier, Schurgers et al. (2007) investigated the absorption and efficacy of pure VK1 with MK-7 during warfarin dosing. The findings from this study revealed that a dose of 315 µg/day of VK1 and 130 µg/day of MK-7 changed INR from 2.0 to 1.5. Relatively lower value of 130 µg/day for MK-7 was most likely attributed to much longer half-life and 6-fold higher cofactor activity *in vitro* (Buitenhuis et al., 1990). Further, the investigators comment that, if expressed as AUC over 24 hours (AUC24), the availability MK-7 is 2.5-fold better than that of VK1. The investigators concluded that "MK-7 supplements containing more than 50 µg/day may interfere with oral anticoagulant treatment, whereas doses of 50 µg or less are not likely to affect the INR value in a relevant way". Further the investigators stated that "MK-7 induced more complete carboxylation of osteocalcin, and hematologists should be aware that preparations supplying 50 mug/d or more of MK-7 may interfere with oral anticoagulant treatment in a clinically relevant way."

In a subsequent publication from Schurgers's group (Theuwissen et al., 2013), also described above, a more cautious advice on the use of MK-7 supplements even at a low dose of 10 µg/day for those undergoing anticoagulation treatments has been recommended. In this study, researchers chose 2.0 INR as the target and included 18 healthy volunteers. The reasoning for the selection 2.0 INR was for the safety of the healthy volunteers and for direct comparison to their previous study. Generally, INR of 2.0 to 3.0 is considered safe therapeutic range for the patients undergoing anticoagulation treatment (Baker et al., 2009). In determining a dose-response relationship, a target INR of 2.5 would have been a better choice. As described by Baker et al. (2009), the 2008 practice guidelines from the American College of Chest Physicians include a recommendation to use long-term oral anticoagulation in patients with atrial fibrillation (AF) and a recent stroke or transient ischemic attack, to a target INR of 2.5 (range 2.0 to 3.0; Grade 1A quality of evidence). At the 10 µg/day dose, variation in INR was 1.91±0.43 after one week of dosing and 1.93±0.35 after two weeks of dosing. Variation of INR of ±0.5 allows to remain within the therapeutic range with a target INR of 2.5. Two hematologists, on the study panel, had to conclude that the emerging data from the study was of clinical relevance. This can be explained by the fact that going below 2.0 is considered outside the therapeutic zone, however, if one were to shift the results to a base of 2.5 INR then the results are within the therapeutic zone. Further, in more recent review and review of vast amounts of data, Violi et al. (2016) indicated a need to carefully consider these data. Given this, it is important to critically review the available data on changes to INR during VKA therapy.

In an extensive study, van Walraven et al. (2006) evaluated 67 studies involving 50,208 patients with 57,155 patient-years of follow-up. Overall, patients taking vitamin K antagonists for a wide range of indications that included atrial fibrillation, venous thromboembolism, cardiovascular disease other than atrial fibrillation, peripheral vascular disease, valvular heart disease, and other indications were within time to therapeutic range (TTR) INR range 63.6% of the time. Patients managed in usual care (by community physicians), TTR was 12.2% lower compared with patients managed in anticoagulation clinics. In the study Baker et al. (2009), that involved meta-analysis of 22,237 warfarin-treated AF patients with 41,199 years of follow-up, the average TTR was found as 55%. Patients in anticoagulation clinics had an

average TTR of 63% whereas patients in community practice had an average TTR of 51%. These percentages reveal a gap in protection from ischemic stroke.

6.2.2.3.2. Role of Vitamin K Supplementation in INR Stability

As indicated above, it is commonly accepted that anticoagulant therapy is prescribed to have a stable target INR of 2.5 or between 2.0 to 3.0. The available evidence suggests that half of the patients receiving warfarin fail to stabilize their target range resulting in increased risk of thromboembolism and the drugs adverse effect of bleeding (Beyth et al., 2000; Heneghan et al., 20006). The factors responsible for these risk factors can be concurrent medications, comorbidity and patient compliance besides the intra-individual genetic differences in response to warfarin.

For the INR to remain in the therapeutic range, patients on warfarin are routinely monitored and advised to limit or avoid vitamin K intake from food. Avoiding vitamin K can lead to depletion of the vitamin K pool as it is utilized. A sudden increase of vitamin K intake can significantly decrease the INR with the risk of clot formation. Sconce et al. (2005) hypothesized that supplementation with oral vitamin K would improve stability in patients with previously unstable control of anticoagulation. In a double-blinded placebo-controlled parallel design study, these investigators studied increased stability of anticoagulation control through supplementation of vitamin K and reported benefits of this strategy for stable INR. Supplementation with MK-7, instead of VK1, is recommended as it is not preferentially targeted to the liver. MK-7's extrahepatic activity protects against warfarin induced calcification of arteries and osteoporosis. Stafford et al. (2007) supported this view and added that the potential benefit is greater in terms of reducing bleeding risk.

In a more recent study, Boonyawat et al. (2016) also reported that low dose oral vitamin K (LDVK) supplementation (150 µg/day) for a total of six months after a one-month run in period reduced INR excursions suggesting that LDVK did reduce extreme INR variation. In this multi-center, placebo-controlled, randomized trial, LDVK was found to be associated with a decreased number of extreme INR values (<1.5 or >4.5) without increasing risk of adverse events. In a review article, Ames (2010) noted that "A triage perspective reinforces recommendations of some experts that much of the population and warfarin/Coumadin patients may not receive sufficient vitamin K for optimal function of VKD proteins that are important to maintain long-term health."

In summary, the available information indicate that low dose vitamin K supplementation therapy favors improving the vitamin K status while simultaneously stabilizing INR. In patients on VKA therapy it is important and advisable to consider low dose vitamin K supplementation. The proposed use of MK-7, the subject of this GRAS document, at use levels of 10 µg/serving for general population, including individuals currently undergoing VKA therapy are unlikely to be negatively affected. Additionally, the available evidence from the use of warfarin over the past eight years suggest that the use of warfarin is steadily declining.

6.2.2.4. MK-7, Drug Interaction, Ligand of SXR

In addition to the above described biochemical interaction between vitamin K and VKA, metabolic interactions between these two may also have an impact on INR. Hence, it is important to consider the levels of supplementation of MK-7 in terms of any on-going therapy

and the impact of the resulting drug interaction. As discussed above, one of the important areas of concern is the VKA treatment where the anticoagulant may be interactive with the vitamin. It is well recognized that supplementation with vitamin K at high enough level is likely to affect the INR that needs to be controlled and low dose supplementation may be helpful in stabilizing INR to remain in the specific target range of INR 2.0 to 3.0. The narrow therapeutic index of warfarin poses a unique challenge to the risk of under-dosing, which can result in loss of therapeutic efficacy and potential for thrombosis, while overdosing may lead to bleeding and potentially fatal hemorrhage. While low dose MK-7 supplementation is helpful in stabilizing INR, the question remains whether it may cause any complications through the cytochrome P450 (CYP) set of genes.

The available information suggests that CYP enzymes metabolize external substances, such as medications that are ingested, and internal substances, such as toxins that are formed within cells. As these enzymes also metabolize MK-7 and warfarin, it is likely that warfarin concentration may increase if MK-7 sufficiently slows warfarin catabolism. Additionally, there is need to consider any effect of MK-7 on the transcription of the catabolizing enzymes. It is recognized that CYP enzyme polymorphism plays a role in dosage variability of warfarin and MK-7 and is generally taken into consideration by clinicians while adjusting warfarin dosage. Most of the available knowledge related to increase or decrease in metabolism is based on VK1 and MK-4 interactions with these enzymes and there is limited knowledge of MK-7 interactions. However, based on the knowledge of vitamin K1 and MK-4 catabolic pathways, the same is viewed as applicable to MK-7. Theuwissen et al. (2013) suggested that the relative ability of different vitamin K compounds to induce CYPs is an important factor if vitamin K is taken regularly with VKAs.

Among the different family of CYP enzymes, the CYP4F2 and CYP4F11 genes are part of a cluster of CYP genes on chromosome 19 and these proteins are localized to the endoplasmic reticulum. In an extensive study, Edson et al. (2013) have reported that both CYP4F2 and CYP4F11 are vitamin K1 and K2 ω-hydroxylases and that CYP4F2, at least to some extent, sequentially metabolizes vitamin K to the ω-carboxy metabolite. It is unknown whether MK-7 is a CYP4F2 and CYP4F11 substrate. In the absence of experimental proof, it is assumed that the structurally similar MK-7 will follow the same biochemistry path as with the VK1 and MK-4 and, thus, be metabolized by CYP4F2 and CYP4F11. It is recognized that warfarin is catabolized by CYP4F2, the percentage involved in this catabolism is insignificant, between 1 to 3% (Takeuchi et al., 2009; Chan et al., 2012). Hence, it is concluded that the impact of CYP4F2 in the drug interaction between MK-7 and warfarin is so small that this interaction is unlikely for any significant contribution.

The available evidence suggests that vitamin K functions as a ligand for a nuclear receptor, SXR (steroid and xenobiotic receptor), and its murine ortholog, PXR (pregnane X receptor) gene (Tabb et al., 2003). VK2 also has a transcriptional regulatory function. VK2 bound to and activated the orphan nuclear receptor SXR induces expression of the SXR target gene, CYP3A4, identifying it as a bona fide SXR ligand. MK-7, acting as a ligand for SXR, and thus, controlling transcription and translation of CYP3A4 enzyme is unlikely to change the expression of CYP3A4 significantly during low dose MK-7 supplementation. The available information suggest that warfarin is metabolized by CYP3A4 indicating that any disturbance in the concentration of CYP3A4 by MK-7 may lead to the variation in warfarin concentration resulting in the changes of INR value. However, this is very unlikely

in the light of the 1-3% catabolism by CYP4F2, indicating that the catabolizing system has great over capacitation. Furthermore, the available information indicate that the less active (R)-enantiomer of warfarin is metabolized by CYP3A4, while (S)-warfarin has a three-to-five times greater anticoagulant effect as compared to the (R)-enantiomer and accounts for 60 to 70% of warfarin's overall anticoagulant activity.

Tabb et al. (2003) reported that VK2 binds directly to SXR and activates it to express CYP3A4 in a dose-dependent manner. In this and other studies that have investigated vitamin K2 (menaquinones) as a ligand for SXR, it appears that these studies may have used MK-4 in their reported results. MK-7 has a similar structure to that of MK-4 with the only difference of having a longer side chain compared to MK-4. It is likely that MK-7 will act as a ligand to SXR in a similar way to what publications (Tabb et al., 2003; Ichikawa et al., 2006; Azuma et al., 2009) have referred to as K2. There are many confounding factors that limit the possibility to pinpoint the exact role in up-regulation of CYP3A4 by menaquinones. Vitamin D3 also contributes to the expression of CYP3A4, though not through SXR. The only available data to assess the effect of vitamin K2 (apparently MK-4) are *in vitro* results obtained by Tabb et al. (2003). These investigators reported that CYP3A4 is expressed two-fold at the VK2 concentration of 1000 nm as compared to control. Based on these observations, low level MK-7 supplementation is unlikely to affect the expression of CYP3A4. This is further supported by Schurgers et al. (2007) observation that a dose of 0.22 μm MK-7 creates highest steady-state serum concentrations of 10 nM (6 μg/L).

In summary, CYP3A4 is involved in the metabolism of approximately 30% of the prescription medications. Any concerns related to the low dose of MK-7 affecting the prescription drug metabolism in the CYP3A4 pathway would be negligible. This is based on discussion, where the effect of low dose VK2, dose of 10 μg MK-7, is unlikely to significantly affect the expression of CYP3A4.

6.2.3. Specific Toxicity Studies of MK-7

In a series of specifically designed unpublished studies such as acute, short-term and subchronic toxicity, and genotoxicity studies that included *in vitro* bacterial reverse mutation test (Ames assay) in *Salmonella typhimurium* strains and *Escherichia coli*, *in vitro* chromosomal aberration study and *in vivo* micronucleus study in rats, the effects of MK-7 were investigated. As described below, the findings from these unpublished studies did not reveal any adverse effects of MK-7.

6.2.3.1. Specific Subchronic Toxicity Study of MK-7

In a specifically designed repeat-dose 90-day toxicity study, Kang and Jeon (2021; unpublished) investigated the potential adverse effects of MK-7 preparation, the subject of this present GRAS assessment in Sprague-Dawley rats following repeated (daily) oral administration of MK-7 for 13 weeks. The study was conducted according to "OECD Principles of Good Laboratory Practice" (ENV/MC/CHEM(98)17 as revised in 1997) and following "OECD Guideline For The Testing Of Chemicals No. 408, Repeated dose 90-Day Oral Toxicity Study in Rodents: (Adopted: Sep. 21, 1998). The study was also conducted as per Korean Ministry of Food and Drug Safety, Notification No. 2018-93 (Nov. 21, 2018) following "Guideline for Toxicological Test " Ministry of Food and Drug Safety, Notification No. 2017-71(Aug. 30, 2017).

In this study, MK-7 preparation in MCT oil was administered orally (gavage) once daily at dose levels of 500, 1500 and 4500 mg/kg bw/day (low, mid, and high dose group, respectively) for at least 90 days to rats (10/sex/group). There was an excipient control group that received an excipient (vehicle control) and a negative control group that received sterile injection (water). Based on the findings from a dose range finding toxicity study, the high dose was selected as 4500 mg/kg bw/day, as no abnormal changes were noted at this dose. In order to assess the reversibility of effects (if any), three additional groups (recovery) of rats (5/sex/group) that received sterile water, excipient or high dose treatment for a period of 90 consecutive days, were observed for an additional 28-day period and served as recovery groups. During the course of the study the following observations were performed or recorded: mortality, clinical signs (twice a day), ophthalmoscopy (last week), body weights and feed consumption (once weekly). After 90 days of treatment, hematology, clinical chemistry, and urinalysis measurements were undertaken. At termination, necropsy was performed and organ weights were recorded. Over 40 tissues and organs were fixed in 10% buffered neutral formalin. Histopathological examination was carried out on the full set of tissues collected from the high dose and control groups (Kang and Jeon, 2021).

Clinical observations revealed sporadic salivation in both male and female excipient control groups and all test article administration groups. In the male excipient control group, perineal soiling and dirty nose were observed. In the male low- and mid-dose groups, soft stools, mucous stools, and diarrhea were sporadically observed. In the female excipient control group, mucous stools and perineal soiling were observed. In the female mid- and high-dose groups, food-gnawing behavior was sporadically observed. No abnormal changes were observed in the male and female negative control or recovery group. No statistically significant changes in body weight were observed in the test-article administration group compared with the negative control group. As regards feed consumption, the excipient control groups of the main group and all test- article administration groups, the feed consumption from weeks 1 to 13 was sporadically reduced compared with the negative control group. No statistically significant changes were observed in the test-article administration group of the recovery group compared with the negative control group (Kang and Jeon, 2021).

Functional observation battery revealed a statistically significant increase was observed in forelimb grip strength of the main male low-dose group as compared with the negative control group. In the main female group and test- article administration group of the recovery groups, no statistically significant change was observed compared with the negative control group. Ophthalmic examination did not reveal any abnormal changes in the main or recovery group. Urine analysis revealed ketone body, occult blood, urinary protein, urobilinogen, nitrite, leukocyte, and epithelial cells in urinary sediments were sporadically observed in some animals in the main group and male and female test- article administration groups of the recovery group (Kang and Jeon, 2021).

Hematology examination did not reveal any statistically significant changes in the test-article administration group of the main group compared with the negative control group. In the male excipient control group of the recovery group, a statistically significant reduction in the number of reticulocytes was observed compared with the negative control group. In the female high-dose group of the recovery group, a statistically significant increase in prothrombin time was observed compared with the negative control group. As regards clinical chemistry parameters, in the main male excipient control and low-dose groups, total

cholesterol level was statistically significantly reduced compared with the negative control group. In the mid-dose group, total cholesterol, sodium, and chlorine levels were statistically significantly reduced compared with the negative control group. In the high-dose group, triglyceride level was statistically significantly increased compared with the negative control group; however, sodium and chlorine levels in this group were statistically significantly reduced compared with the negative control group. In the main female low- and high-dose groups, urea level was statistically significantly reduced compared with the negative control group. In the male excipient control group of the recovery group, albumin level and albumin/globulin (A/G) ratio) were statistically significantly increased compared with the negative control group. In the female high-dose group of the recovery group, the A/G ratio was statistically significantly reduced compared with the negative control group (Kang and Jeon, 2021).

The findings from a hormone test for thyroid stimulating hormone (TSH), triiodothyronine hormone (T3) and thyroxine hormone (T4) revealed statistically significantly reduced levels of thyroxine hormone (T4) in the male mid-dose group of the main group as compared with the negative control group. In the female group of the main group and the test-article administration group of the recovery group, no statistically significant changes were observed compared with the negative control group. The sperm test in male animals in the main group and the test-article administration group of the recovery group did not reveal any statistically significant changes as compared with the negative control group. Similarly, virginal smear test in female animals did not reveal any abnormal changes in the main or recovery group (Kang and Jeon, 2021).

Absolute organ weights at the end of the study, in both the main and recovery groups showed no statistically significant changes as compared with the negative control group. As regards relative organ weights, a statistically significant increase in the relative organ weight of the lung was observed in the male high-dose group of the recovery group compared with the negative control group. No statistically significant changes were observed in the male and female test-article administration groups of the main group compared with the negative control group. Similarly, no statistically significant changes were observed in the female test-article administration group of the recovery group compared with the negative control group. The necropsy findings in the male high-dose group of the main group, yellow spots (cauda) on the left epididymides were observed in one case. The histopathological observations revealed some sporadic findings in control and treatment groups. However, findings in the high-dose treatment group were considered to be spontaneous due to incidence, significance, and severity. All findings observed were consistent with normal background lesions in clinically normal rats of the age and strain used in this study, and were considered spontaneous and/or incidental in nature and unrelated to the treatment (Kang and Jeon, 2021).

In summary, oral administration of MK-7 preparation at dose levels up to 4500 mg/kg bw/day for 90 days revealed no abnormal changes in clinical sign observation, detailed clinical sign observation, body weight measurement, feed consumption measurement, water consumption measurement, functional observation battery tests, ophthalmic tests, urinalysis test hematological tests, blood biochemical tests, hormone tests, sperm tests, vaginal smear tests, absolute organ weight measurements, relative organ weight measurements, visual observations on necropsy and histopathological examinations. The results of this subchronic

toxicity study in Sprague-Dawley rats suggest that the no observed adverse effect level (NOAEL) of MK-7 is 4500 mg/kg bw/day, the highest dose tested.

6.2.3.2. Specific 28-day Dose-Range Findings Toxicity Study of MK-7

In a short-term repeat-dose toxicity study, the effects of MK-7 were investigated in Sprague Dawley rats (Kang and Jeon, 2020). This study was designed to use its findings as a basis for setting dosages in the above mentioned 90-day oral repeated dose toxicity study. The study was conducted in accordance with the "Guideline for Toxicological Test " Ministry of Food and Drug Safety, Notification No. 2017-71(Aug. 30, 2017) and "OECD Guideline For The Testing Of Chemicals No. 408, Repeated Dose 90-day Oral Toxicity Study in Rodents" (Adopted: Sep. 21, 1998). In this study, rats (25/sex) were divided into five groups (5/sex/group). The group designation was set to the low-dose group, mid-dose group, and high-dose group administered with doses of 500, 1500, and 4500 mg/kg bw/day of MK-7, respectively, for 28 consecutive days. The control group was administered with 'sterile water for injection' and the vehicle control group was administered with vehicle. During the observation period, clinical signs were observed; body weight changes and feed consumptions were recorded. At the end of the observation period, blood and blood biochemistry tests were conducted. Organ weights were measured; gross pathology were conducted after the necropsy.

No toxicological change was observed in the clinical sign, body weight, feed consumption, hematology, blood biochemical, absolute organ weight, relative organ weight and necropsy finding. Among the significant changes, hematology revealed a statistically significant decrease of hemoglobin distribution width was observed in the male vehicle control, low and high dose group when compared to the negative control group. There was no statistically significant change observed in the female groups. Among the clinical chemistry parameters, a significant decrease of alanine aminotransferase (ALT) was observed in the male vehicle control, low, mid and high dose group when compared to the negative control group. A significant increase of albumin was observed in the male mid dose group when compared to the negative control group. There was no statistically significant change observed in the female groups. These and other changes noted were not considered as related to MK-7 treatment (Kang and Jeon, 2020).

In conclusion, the comprehensive results from the 28-day oral dose response study in Sprague Dawley rats at dose levels up to 4500 mg/kg bw/day did not reveal any toxicological (Kang and Jeon, 2020). Thus, it is judged that the maximum dose should be set at 4500 mg/kg bw (or less) for the 90 day repeated dose oral toxicity study.

6.2.3.3. Specific Acute Toxicity Study of MK-7

In an acute study, the effects of MK-7 were investigated following oral administration of a single dose to Sprague-Dawley rats (Byeoun and Jeon, 2020). In this study, the starting dose of the pre-test was set to 5000 mg/kg bw, and after confirming that the animals survived for 3 days after administration of the pre-test, the main test was conducted in which 4 animals were administered MK-7 at the same dose. For these investigations, a total of 5 animals were used: 1 pre-test and 4 main test, and mortality, general symptoms, and weight change were checked during the 14-day observation period after the administration of the test substance. At the time of necropsy after the observation period, a visual examination was performed. The results of these investigations did not reveal mortality in any animals. On the day of MK-7 administration, diarrhea was temporarily observed in the main test group, but it was not judged

as a toxic reaction caused by MK-7. Body weight measurement did not reveal any abnormal changes in the pre-test group and the main test group. Necropsy also did not show any abnormality. In summary, acute administration of MK-7 to Sprague-Dawley rats did not cause any lethality in the pre-test and main test, and there was no toxic reaction.

6.2.3.4. Specific Genotoxicity Studies of MK-7

Mutagenic potentials of MK-7 were investigated by *in vitro* bacterial reverse mutation test (Ames assay) using *Salmonella typhimurium* strains and *Escherichia coli*, by *in vitro* chromosomal aberration study and by *in vivo* micronucleus study.

6.2.3.4.1. Bacterial Reverse Mutation Test of MK-7

In this assay, conducted as per Ames test, the effects of MK-7 were investigated using histidine requiring *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and tryptophan requiring *Escherichia coli* [WP2uvrA(pKM101)] using the reverse mutation test (Kim and Jeon, 2020a). Prior to the main study, a preliminary study was conducted to determine the dose of the test substance. In this preliminary study, the highest dose of the test substance was selected as 5000 μg/plate and sequentially diluted by a geometric ratio of 4 to produce a total of 7 dose levels and growth inhibition and precipitation of test substance was studied. As a result of the preliminary study, in the presence and absence of metabolic activation, the precipitation of the test substance and growth inhibition were not observed at all dose levels of all strains.

Based on the findings from the preliminary study, the highest dose level for all strains in the presence and absence of metabolic activation of the main study was selected as 5000 μg/plate. And, sequentially diluted by a geometric ratio of 2 to produce total 5 dose levels of all strains in the presence and absence of metabolic activation. The results of main study, in the presence and absence of metabolic activation, did not reveal precipitation of the test substance or growth inhibition at all dose levels of all strains. Also, at all dose levels in the presence and absence of metabolic activation system, no dose dependent increase in the reverse mutation colonies was noted when compared to the negative control group. The mean number of revertant colonies for negative control was within the range of the historical control data and the number of revertant colonies in the positive control showed the distinct increases. Based on these findings, the test substance, MK-7 is considered as not mutagenic in the bacterial reverse mutation assay (Kim and Jeon, 2020a).

6.2.3.4.2. *In Vitro* Chromosomal Aberration Test of MK-7

This study was designed to evaluate the mutagenic potential of MK-7 in the chromosome aberration test system using Chinese hamster lung (CHL) cell line (Kim and Jeon, 2020b). A preliminary study was conducted to determine the dose of MK-7 prior to the main study. In the preliminary study, 2000 μg/mL was selected as the highest dose of the test substance and it was sequentially diluted by a geometric ratio of 2 to produce a total of 7 dose levels (31.3, 62.5, 125, 250, 500, 1,000 and 2000 μg/mL). Precipitation of the test substance and cytotoxicity were studied. In the preliminary study results, cytotoxicity was not observed at any doses of the short time treatment with and without metabolic activation system and the continuous treatment without metabolic activation system. However, the precipitation of the test substance was observed at 250 - 2000 μg/mL of the short time treatment with and without metabolic activation system, and at 125 - 2000 μg/mL of the continuous treatment without

metabolic activation system. Therefore, the dose of the main study was determined as follows: for short time exposure (6 hours; in the presence or absence of S9) dose selected was 62.5, 125, 250 μg/mL; while for 24 hours exposure in the absence of S9 the dose was 31.3, 62.5, 125 μg/mL.

The result of the main study did not reveal any statistically significant increase in chromosome aberration cells in the test substance treated groups with and without metabolic activation system compared with the negative control. In addition, the positive control group showed statistically significant increase in chromosomal abnormal cells compared with the negative control group in each condition, confirming that the test was performed properly. Based on these results, it is considered that MK-7 did not cause chromosome aberrations under the conditions of this study (Kim and Jeon, 2020b).

6.2.3.4.3. *In Vivo* Micronucleus Test of MK-7

In a dose-response study conducted according to OECD guideline (No. 474 Mammalian Erythrocyte Micronucleus Test; Adopted: Jul. 29, 2016), effects of MK-7 on induction of bone marrow micronuclei in IRC mice was investigated (Kim and Jeon, 2020c). In order to determine the highest dose of the main study, male and female mice were dosed with 500, 1,000 and 2,000 mg/kg bw of the test substance in the preliminary study. The preliminary study did not reveal any lethality or abnormal clinical signs at any of the tested doses in mice. Therefore, the highest dose for the main study was selected as 2000 mg/kg bw and, given the lack of sex differences, the main study was conducted only in male mice (5/group). The main study was conducted at dose levels of 500, 1000 and 2000 mg/kg bw. Additionally, the negative control and positive control groups were also included. Clinical signs and mortality were observed among all animals at least twice a daily during the dosing period. Clinical signs were recorded for 1 day after dosing. Individual body weights were measured before administration and prior to harvesting of bone marrow cells. The bone marrow cell was sampled at 24 hours after final administration and processed for incidence of micronucleated polychromatic erythrocytes (MNPCE) and polychromatic erythrocytes (PCE).

There were no clinical signs of toxicity and mortalities noted at any of the tested dose levels of MK-7 and no statistically significant changes were noticed in mean body weights between any of the treatment groups and control group. The average of the frequency of MNPCE in the negative control group, vehicle group, MK-7 treated groups 500, 1000 and 2000 mg/kg bw was 1.0, 0.6, 0.8, 1.4 and 0.8, respectively. The average of the frequency of MNPCE in the positive control group was 73.8, and it was significantly increased when compared with the negative control. The ratio of PCE among total erythrocyte of the negative control group, vehicle group and 500, 1000 and 2000 mg/kg bw test substance group was observed as 0.493, 0.512, 0.501, 0.540 and 0.495, respectively. The ratio of PCE among total erythrocyte of the positive control group was 0.532 (Kim and Jeon, 2020c).

In summary, the findings from the main study did not reveals any significant increases in the incidence of MNPCE within PCE in the MK-7 treated groups as compared with those of a negative control group. On the other hand, the incidence of MNPCE in PCE was significantly increased in the positive control group when compared with the negative control group. There were no statistically significant differences in the prevalence frequency ratio of PCE in all the MK-7 treated groups and positive control group when compared with the negative control

group. Based on these results, MK-7 did not induce micronuclei formation in bone marrow cells of mice under the conditions of this study (Kim and Jeon, 2020c).

6.2.4. Preclinical Toxicity Studies

6.2.4.1. Acute and Subchronic Toxicity Studies

The available published acute and subchronic toxicity studies of MK-7 are summarized in Table 10. In two separate acute toxicity studies, one in mice and other in rats, the minimal lethal dose or LD_{50} was reported to be greater than 2000 mg/kg bw (Pucaj et al., 2011; Ravishankar et al., 2015). In the first study (Pucaj et al., 2011), female NMRI mice (n=5; 8 weeks old; body weight 25-30 g) were given a single oral dose (gavage) of 2000 mg MK-7/kg bw. No adverse clinical observations as evaluated by changes in skin and fur, eyes and mucous membranes, and also respiratory, circulatory, autonomic and central nervous systems, and somatomotor activity and behavior pattern (including body weight growth) were noted during the 14-day observation period. These findings suggest that the minimum lethal dose of MK-7 is greater than 2000 mg/kg bw. In the second study, MK-7 at a dose level of 2000 mg/kg bw, was administered orally to 3 male and 3 female Wistar rats. Following treatment, the rats were observed for 14 days for signs of toxicity. None of the animals showed any adverse clinical signs during the observation period. Similar to the mice study, the results of this study suggest that LD_{50} of MK-7 is >2000 mg/kg bw.

In two separate published studies, the subchronic toxicity of MK-7 in rats has been investigated (Pucaj et al., 2011; Ravishankar et al., 2015). In the first study, Pucaj et al. (2011) investigated the effects of MK-7 in Sprague Dawley rats following oral gavage administration for 90 days. In this study, conducted as per OECD and FDA guidance, and in compliance with GLP, rats were divided into four groups (10/sex/group) and were administered MK-7 via gavage at dose levels of 0 (vehicle control, corn oil), 2.5, 5, and 10 mg/kg bw/day for 90 consecutive days. All generated data, including clinical observations, ophthalmology, clinical pathology, gross necropsy, and histopathology, revealed no compound-related toxicity in rats. Any statistically significant findings in clinical pathology parameters and/or organ weights noted were considered to be within normal biological variation. Based on the findings from this study, the investigators determined the no observed adverse effect level (NOAEL) of MK-7, following oral administration to rats for 90 days, was determined as 10 mg/kg bw/day, the highest dose tested. As compared to the 90th percentile intake of MK-7 (48 µg/person/day or 1.0 µg/kg bw/day) from the proposed uses, the rat NOAEL is over 10,000 fold higher.

In the second subchronic toxicity study, Ravishankar et al (2015) investigated the effects of MK-7 in male and female albino Wistar rats. In this study, MK-7 was administered to rats at dose levels of 0.1, 0.5 or 1 mg/kg bw/day for 90 days. The body weight and organ weight and macroscopic appearance of thymus, heart, liver, spleen, kidney, testis, prostate, seminal vesicle, and uterus were within the normal range among study groups. Female rats receiving MK-7 at doses of 0.5 and 1 mg/kg bw/day showed a significant decrease in liver weight. These changes were not considered as adverse, as no changes were noted in histopathology and in male rats. The blood and urine samples were collected on Days 0, 45, and 91. As compared to the baseline and control group, the test compound did not produce biochemical changes. The only biochemical change observed was an elevation in serum uric acid in male rats receiving MK-7 at dose levels of 0.5 and 1 mg/kg bw/day. The increase was not noted in female rats and was not considered as adverse effect. No histopathological lesions

or changes were noted in any of the organs studied, except for the following changes in reproductive organs. In ovaries of the females, an increased number and size of follicles were found, and also changes in the myometrium were found. In testicles an increased spermatogenesis was noted. These effects did not occur at the dose of 0.1 mg/kg bw/day. The histopathological changes were not considered as adverse. The results of this study suggest a NOAEL of 1 mg/kg bw/day for MK-7, the highest dose studied.

Table 10. Summary of Acute and Subchronic Toxicity Studies with MK-7

Study protocol	Observations	Findings	Reference
Acute oral toxicity test. MK-7 suspended in sunflower oil was administered to mice by single oral gavage to achieve a dose of 2000 mg/kg body weight	Mice were weighed at days 0, 7, and 14 (termination). Animals were monitored twice daily on the day of dosing and once daily thereafter. Observations included changes in skin, fur, eyes, mucous membranes, and respiratory, circulatory, autonomic, and central nervous systems. Animals were also observed for changes in motor activity and behavior pattern.	At limit dose level of 2000 mg/kg, MK-7 did not induce any signs of toxicity in any of the treated mice following dosing or during the 14-d observation period. Body weight gain of treated mice was not adversely affected. Median LD_{50} was > 2000 mg/kg body weight	Pucaj et al. (2011)
Acute oral toxicity study in rats. MK-7 administered orally by gavage at 0.5, 1.0, 10, or 20 mg/kg bw; once daily for 14 days.	Rats were monitored for general behavior, toxic signs and symptoms, or mortality during the experimental period. At end of study, mice were killed and examined for gross necropsy performed in vital organs	No effect of MK-7 on food and water consumption, no physical or behavioral changes, and no mortality observed in any group after 14 days. In the 1 mg/kg group, 2 of 8 animals had mild irritability. No statistically significant difference in body weight gain observed in any group. No adverse effects observed in either sex in any group. All rats survived, with no symptoms of distress or toxic effects. LD_{50} was > 2000 mg/kg body weight	Ravishankar et al. (2015)
Subchronic oral study. Rats were given MK-7 for 90 d at doses of 0, 2.5, 5.0, and 10 mg/kg body weight per day	Rats were observed for clinical signs and mortality twice daily throughout the study and for reaction to treatment such as changes in skin, fur, eyes and mucous membranes. Rats were also monitored for changes in respiratory, circulatory, autonomic, and central nervous systems, for changes in somato-motor activity and behavior patterns, and for any other signs of ill health. Terminal body weights were recorded on day 91-92 for main study animals. During the recovery, animal weights were determined. Hematologic and clinical chemistry data of rats were obtained and compared with	No deaths occurred, and no compound-related toxicity was indicated by clinical observations or by ophthalmology, clinical pathology, gross necropsy, or histopathology. Any statistically significant differences in clinical pathology parameters and/or organ weights noted were considered to be within normal biological variability. Median LD_{50} = 2000 mg/kg and NOAEL = 10 mg/kg body weight per day	Pucaj et al. (2011)

	baseline data.		
Subchronic oral toxicity in rats. MK-7 administered orally by gavage at 0, 0.1, 0.5, and 1.0 mg/kg bw/day for 90 days. MK-7 prepared fresh daily in propylene glycol and administered as 1 mL/100 g body weight between 8 am and 9 am	Rats were monitored for changes in behavior, mortality, body weight, and food consumption. Blood was collected on days 15, 45, and 91 (at sacrifice) to determine fasting blood sugar; levels of serum urea, creatinine, uric acid, total cholesterol, triglycerides, total protein, and serum calcium; albumin-to-globulin ratio, liver enzymes SGOT and SGPT, and alkaline phosphatase activity. Other hematologic parameters measured on those days included total WBC count, total lymphocyte count, total monocyte count, total granulocyte count, lymphocyte percentage, monocyte percentage, granulocyte percentage, RBC count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, RBC distribution width, and clotting time. Urine specific gravity and pH were measured at days 15, 45, and 91 (at sacrifice). After 90 days, rats were killed and autopsied, and histological studies of brain, pituitary, thymus, lymph node, heart, lungs, spleen, seminal vesicles, uterus, skin, trachea, liver, stomach, jejunum, kidney, testis, prostate, and ovary were performed	Normal weight gain pattern in all groups; slight increased weight gain in rats receiving MK-7 but increase was not statistically significant. Male and female rats showed significant weight increase at 90 d in all treatment groups compared with controls. Average weights of organs in male and female rats were not significantly different from those in controls (liver, thymus, kidney, spleen, testis, seminal vesicles, prostate, and uterus). However, female rats in the 0.5 mg/kg group had a statistically significant decrease in heart weight compared with controls. Liver enzymes (SGPT, SGOT and alkaline phosphatase) and, similarly, serum glucose, total protein, creatinine, and blood urea levels showed no significant changes in any group. Uric acid levels were not changed in females, but in males there was a significant decrease at day 45 in the 0.1mg/kg group. Conversely, levels in both sexes were increased significantly decreased at day 90 in both sexes; hemoglobin levels were generally the same except in males on day 45 in the 0.1 mg/kg group (increased), on day 45 in the 1.0 mg/kg group (decreased), and in control females (decreased). Mean corpuscular hemoglobin concentration, corpuscular volume, and RBC distribution width values and clotting time were not affected. Urinalysis showed no significant changes in specific gravity or pH. Histopathological study showed no remarkable changes in organs of control or treated animals except in females, in which proliferation of uterine epithelium was seen at all levels in 1-2 rats, while cytoarchitecture was normal in all other rats. Significant levels at $p<0.05$	Ravishankar et al. (2015)

*Adapted from Marles et al. (2017).
Abbreviations: LD_{50} = lethal dose 50; NOAEL = no observed adverse effect level; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvate transaminase; RBC = red blood cell; WBC = white blood cell.

6.2.4.2. Mutagenicity and Genotoxicity Studies

In two separate studies, Ravishankar et al. (2015) investigated the genotoxicity potentials of MK-7 (Ames assay and *in vivo* micronucleus assay). In the Ames assay, potential effects of MK-7 to induce reverse mutation in *Salmonella typhimurium* tester strains TA1535, TA97a, TA98, TA100, and TA102 in the presence and absence of metabolic activation system (S9) were investigated. Based upon the preliminary solubility/precipitation and cytotoxicity tests, the tester strains were exposed to MK-7 in triplicate cultures at the doses of 20, 60, 200,

600, and 2000 µg/plate, in the presence and absence of metabolic activation system (S9). Dimethyl sulfoxide was used as a vehicle. The exposed bacteria were plated onto minimal glucose agar medium supplemented with L-histidine. The plates were incubated at 37°C for 48-72 hours after which the histidine revertant colonies were counted and their frequency was compared with that in the vehicle control group. Concurrent negative control group and positive control groups were also included. Findings from this test indicated that the frequencies of histidine revertant colonies at all concentrations of MK-7 in strains TA1535, TA97a, TA98, TA100, and TA102, in the presence or absence of a metabolic activation system, were comparable to those observed in the vehicle control group. Positive controls demonstrated sensitivity of the assay with and without metabolic activation. The results of this study suggest that MK-7 is not mutagenic in *S. typhimurium* strains.

For the *in vivo* micronucleus assay by Ravishankar et al. (2015), rats were divided into six groups (10/group/sex), of which four groups received MK-7 and two control groups received the vehicle (distilled water containing Tween-20). Of the two vehicle treated control groups, one served as control for the micronucleus test (MNT) and the other was used for comet assay. In the test article treated groups, two groups received MK-7 at a dose level of 100 µg/kg bw/day, while the remaining two received MK-7 at 1000 µg/kg bw/day. All animals were treated daily for 28 consecutive days. On Day 29, all control animals received cyclophosphamide (intraperitoneal) at a dose level of 40 mg/kg bw. The control and test groups maintained for assessment in the comet assay received Colchicine at 4 mg/kg (ip.) 24 hours after cyclophosphamide administration.

In the study by Ravishankar et al. (2015), blood was collected from all groups on Day 30th for the comet assay and animals were euthanized. The parameters evaluated during the course of study and at termination included clinical observations, feed consumption (daily), body weight (weekly), chromosomal aberration, micronucleus test, and comet assay. The results of the study suggest that treatment with MK-7 at 100 and 1000 µg/kg bw/day for 28 days did not produce any clinical signs of toxicity in rats. There were no significant differences in any of the parameters in treatment groups at 100 and 1000 µg/kg bw at all intervals studied. As compared to the MK-7 treated group, the group receiving cyclophosphamide (positive control) revealed signs of clinical toxicity and genotoxicity.

6.2.5. Safety Related Studies of MK-4

In several published human clinical studies as well as animal toxicity studies, the effects of MK-4 have been investigated. Given the similar metabolic fate and structural similarity between MK-4 and MK-7, the available studies of MK-4 are applicable to the safety assessment of MK-7 with some caveat, primarily the difference in plasma half-life. These studies can provide some corroborative evidence for the safety of MK-7, the subject of present GRAS assessment.

6.2.5.1. Clinical Studies of MK-4

In the published literature, several human clinical studies investigating the effects of MK-4 have appeared. As mentioned earlier the only difference between MK-4 and MK-7 or other menaquinones is the number of side chain unsaturated isoprenyl groups at the 3-position. As MK-4 has been marketed in Japan for over 15 years as a therapeutic agent (commonly known as Menatetrenone), the effects of MK-4 have been investigated in several studies. As a therapeutic agent, the doses of MK-4 used in these studies were usually 45 mg/day and the

duration lasted from 24 weeks to 2 years. In these studies, the effect of MK-4 on various parameters related to bone metabolism were investigated. The available clinical studies of MK-4 are presented in Table 11. The dose of MK-4 used in human clinical studies is about 1000-fold higher compared to the estimated daily intake of MK-7, the subject of present GRAS assessment.

In a recent open-labelled prospective cohort study, Giri et al. (2020) investigated the effects of increasing doses of MK-4 on the improvement in osteocalcin carboxylation. In this study, healthy postmenopausal women (n=29; age 69±9 years) with osteoporotic fractures received low-dose MK-4 (0.5 mg) for 3 weeks (until the second visit), then medium-dose MK-4 (5 mg) for 3 weeks (until the third visit), then high-dose MK-4 (45 mg) for 3 weeks. Participants receiving the treatment showed that supplementation with 5 or 45 mg/day of MK-4 for 9 weeks reduced undercarboxylated osteocalcin (ucOC) to levels usually reported in young and healthy adults. MK-4 supplementation resulted in borderline increases in γ-carboxylated osteocalcin. The investigators reported that there were no major side effects of MK-4 supplementation. In postmenopausal women with osteoporotic fractures, supplementation with either 5 or 45 mg/day of MK-4 reduces ucOC to concentrations typical of healthy, pre-menopausal women.

In a comprehensive review article and meta-analysis, Su et al. (2019) evaluated the role of MK-4 in the management of osteoporosis. For this meta-analysis, the authors selected 18 randomized controlled trials with 8882 participants in the systematic review and analysis. Pooled analyses showed that MK-4 was more effective as compared to placebo in improving lumbar BMD and decreasing ucOC/OC. In this review, in addition to efficacy, the trials that reported adverse events, adverse drug reactions, gastrointestinal adverse effects, skin and subcutaneous tissue disorders, or prothrombin time were also evaluated. Compared with placebo, MK-4 significantly increased the incidence of adverse events (AEs) (two studies, N = 1949, RR = 1.47, 95% CI 1.07 to 2.02) and adverse drug reactions (four studies, N = 6102, RR = 1.29, 95% CI 1.07 to 1.56). However, no significant difference in serious adverse events, gastrointestinal adverse events or skin, and subcutaneous tissue disorders was detected between MK-4 and placebo. None of the included randomized controlled trials reported the occurrence of coagulation disorders. It should be noted that in these studies, the dose of MK-4 was quite high (45 mg/day). These investigators found that gastrointestinal disorders and skin/subcutaneous tissue disorders were the two most common adverse events that were not considered serious and could be resolved after taking action. Overall, MK-4's tolerability may be acceptable.

Table 11. Human Clinical Studies with Menaquinone-4 (MK-4)

Reference	Subject/ treatment; Doses/Duration	Observations
Takami et al., 2002	18 MDS refractory anemia patient; 0 or 45 mg/day for 16 weeks	Given the absence of toxicity associated with MK-4 administration, recommended its use for all MDS-RA patients.
Shiomi et al., 2002	25 women with liver cirrhosis, 42-72 years of age; 45 mg for 2 years	22 of 25 patients assigned to the test group completed study. No adverse effects related to treatment with vitamin K2 were noted
Sato et al., 2002	200 female patients with Alzheimer's disease, 100 healthy females as control group; Vitamin K2 (not specified) supplementation when administered concurrently with 600 mg calcium/day and 1000 IU ergocalciferol/day for 2 years	No adverse effects were reported in study participants. Combined treatment of elderly female Alzheimer's disease patients with MK-4, ergocalciferol, and calcium may represent safe and effective measure for increasing bone mass and reducing the risk of fracture.
Asakura et al., 2001	5 male, 25 female osteoporotic patients; 45 mg, 3 times/day for >3 weeks	MK4 levels increased at 4 weeks after administration and remained elevated for duration of study period. Plasma levels of phylloquinone and MK-7 unchanged. A group of vitamin K-deficient patients identified. Vitamin K2 can be administered safely without inducing hemostatic disturbances to patients not treated with anticoagulants.
Bunyaratavej et al., 2001	43 subjects in test group, 40 subjects in control group; 0 or 45 mg/day for 12 months	No adverse events were reported. At 6 months into the study period, the control group also was placed on vitamin K2 supplementation. Adverse reactions reported over the course of the study period limited to 2 incidences of mild skin rash, which subsided once treatment was discontinued.
Somekawa et al., 1999	110 Japanese females (24 to 52 years of age) diagnosed with endometriosis and/or uterine leiomyomas; All administered Leuprolide therapy for their respective estrogen dependent disease either alone (control) or in conjunction with 45 mg vitamin K2, 0.5 µg 1,25-(OH)2-D3, or 45 mg vitamin K2 and 0.5 µg 1,25-(OH)2-D3 for 6 months.	Vitamin K2 partially prevents bone loss associated with estrogen deficiency resulting from leuprolide treatment. No adverse effects were reported in study participants
Orimo et al., 1998	75 osteoporotic Patients; 90 mg or placebo for 24 weeks	Heartburn, stomach upsets, and abdominal fullness were noted. Authors noted that symptoms were unlikely to be related to treatment or could not ascertain a relationship between vitamin K2 treatment and the effects. Increases in GOT, GPT, ALP, and GGPT reportedly observed in single subject in vitamin K2 treatment group and were described as probably related to treatment. All variations were reported to return to normal levels following study completion. No significant differences were reported in prothrombin time between test subjects and the placebo control group.

Table 11. Human Clinical Studies with Menaquinone-4 (MK-4)

Reference	Subject/ treatment; Doses/Duration	Observations
Iioka et al., 1991	Pregnant mothers (number not specified); Single intravenous dose of 60 mg MK-4 or 20 mg MK-4 orally for a period of 7 days	MK-4 appears to transfer into placental tissue, where it is stored, and subsequently gradually released into fetal blood. Vitamin K2 found to be concentrated in maternal milk, where on day 4 following intravenous administration, levels 90-times greater than those identified in maternal blood for same period of time were reported. No adverse effects reported in mothers or infants.
Motohara et al., 1990	Pregnant mothers (number not specified); Oral administration of 20 mg vitamin K2/day for 7 to 10 days prior to delivery	Increased levels of vitamin K2 in mothers' plasma, cord plasma, and breast milk. Postnatally, infants observed for period of 5 days, during which no evidence of bleeding reported.
Suzuki et al., 1984	Neonates exhibiting thrombotest results below 20% 48 hours following birth (number not specified); Single oral administration of up to 6 mg of vitamin K2	Significant increase in thrombotest values without any significant changes in bleeding time or levels of plasma bilirubin and hematocrit

In summary, in multiple clinical trials conducted at high doses, MK-4 was found to be well tolerated. In one study, MK-4 at a dose level of 90 mg/day for 24 weeks did not reveal any significant treatment related adverse effects. In several other studies, conducted at dose levels of 45 mg/day, most notably for durations of six months, and for two years in one study, also did not reveal any significant treatment related adverse effects. In Japan, patients with osteoporosis are commonly prescribed MK-4 at dose levels of 45 - 90 mg/day for over 15 years without reported significant adverse effects. In a comprehensive review and meta-analysis of 18 clinical trials, the investigators reported that MK-4's tolerability as a therapeutic agent may be acceptable. The approved uses of MK-4 for therapeutic purposes are over 10,000 to 20,000 fold higher as compared to the proposed use of MK-7, as a food ingredient for the present safety assessment.

6.2.5.2. Animal Toxicity Studies of MK-4

In a study published in Japanese, Doi et al. (1995) investigated subchronic toxic effects of MK-4 in rats. No adverse effects of MK-4 were seen in a 13-week oral (gavage) toxicity study conducted in groups of Sprague-Dawley rats (10/sex/group) at 30 mg/kg bw/day. In another 13-week study in male and female beagle dogs (number per group not identified), Goldsmith et al. (1995) identified NOAEL of MK-4 as 200 mg/kg. Longer term, repeat-dose toxicity studies were also conducted in rats and dogs receiving oral MK-4 administrations for a period of 52 weeks (Hosokawa et al., 1995; Vanatta et at., 1995). In the long-term feeding study, Hosokawa et al. (1995) provided MK-4 to Fisher 344 rats (20/sex/group) at dietary levels of 0 (control and non-treated naive groups), 0.04, 0.2, or 1.0% (providing approximately 0, 20, 100, and 500 mg MK-4/kg bw/day, respectively). In this study, the LOAEL was determined to be 20 mg/kg bw/day, the lowest dose tested (NOAEL was not established). In the dog study, the l-year treatment period was followed by a 3-month recovery period (Vanatta et al., 1995). MK-4 was provided orally in capsules to groups of dogs (6/sex/group). The equivalent doses on body weight basis were determined as 0 (empty capsule), 20, 200, or 2000 mg/kg bw/day. In this study, the NOAEL was considered as 200 mg/kg bw/day.

Suzuki et al. (1971) investigated the developmental toxic effects of MK-4 in fetuses and offspring of mice and rats. The study was published in Japanese language. However, EFSA

(2008) safety assessment of VK2 described the details of the protocol and the results of these investigations. In these investigations, MK-4 was administered orally at doses of 0, 10, 500, or 1000 mg/kg bw/day or intraperitoneally at doses of 0, 5, 50, or 100 mg/kg bw/day to pregnant mice and rats for a period of 6 days from days 7 to 12 and 9 to 14 of gestation, respectively. Irrespective of the route of administration, no differences were noted in the number of total implants, percentage of resorptions, dead or live fetuses, mean body weights, and type and number of anomalies in mice or rat fetuses. Compared to the control, mouse fetuses from the group receiving oral administration of 500 and 1000 mg/kg bw/day showed an increased incidence of non-ossified forelimbs compared to fetuses of control mice. In the group receiving 500 mg/kg bw/day, skeletal anomalies were limited to an increased frequency of variations of the cervical ribs. The post-natal development observations in the test groups (results reported for only the 10 and 1000 mg/kg bw/day dose groups) revealed increased separation of ear auricular and emergence of abdominal hair in the high-dose offspring compared to controls. Compared to controls, in male fetuses from the low-dose (10 mg/kg bw/day) treated group, the descent of testes was reduced. In rat fetuses, a decrease in non-ossified forelimbs was observed in the low-dose group, while increases in undeveloped metatarsals and non-ossified hind limbs were noted in fetuses from the high-dose group. No statistically significant variations were reported in the postnatal development or weaning of rat offspring. Suzuki et al. (1971) concluded that MK-4 did not cause teratogenic effects, mortality, or inhibition of fetal growth, and it produced no effects on postnatal development or weaning of mice and rats.

In another study, published in Japanese and also reviewed by EFSA (2008), Mikami et al. (1981) studied the effects of MK-4 on fertility, and prenatal and postnatal development in rats. In this study, rats (22 to 24/sex/group) were orally administered MK-4 at dose levels of 0, 10, 100, or 1000 mg/kg bw/day for a period of 14 days. In this study, the parameters investigated included the number of corpora lutea, number of implantations, implantation ratio (total implantation/total corpora lutea) percentage of resorptions and viable fetuses, and fetal and placental weights. The findings from this study did not reveal any significant malformations in offspring or any other reproductive or developmental effects. There were no significant compound-related effects observed on the physiological, morphological, or functional development of offspring during the peri- and post-natal periods (Mikami et al., 1981).

In summary, in two long-term (52-weeks) toxicity studies of MK-4, the LOAEL in rats and NOAEL in dogs was considered as 20 mg/kg bw/day and 200 mg/kg bw/day, respectively. These levels are several orders of magnitude higher compared to the proposed uses of MK-7. For the developmental toxic effects, the EFSA Panel (2008) reviewed data from the study and stated, "... there were no compound-related effects observed on reproductive and developmental parameters measured."

6.2.6. FDA Review of MK-7 GRAS Notice

As indicated earlier, in a recent GRAS notice (GRN 887), the safety of MK-7 has been extensively summarized (Synergia, 2019). In this GRAS notice, the notifier concluded that the use of MK-7 as an ingredient and as a nutrient in nutritional beverage products for children at use level of 4 µg/serving is GRAS through scientific procedures. MK-7 was prepared by fermentation and an extraction process using *Bacillus licheniformis* DSM 24722. The subject of GRN 887, MK-7, is identical with the subject of this present GRAS assessment and hence the safety studies described in GRN 887 are applicable. In GRN 887, the notifier estimated the

intake of MK-7, VK1, VK2, and total vitamin K (VK1 and VK2) from existing dietary sources. The estimated intake of MK-7 from the intended use at the maximum use level of 4 µg/serving ranged from 20 µg/person/day for children aged 12-23 months to 44 µg/person/day for males aged 9-13 years. The cumulative eaters-only mean and 90th percentile dietary exposure for vitamin K (VK1 and VK2) ranged from 317 to 449 µg/person/day and 486 to 682 µg/person/day, respectively, for the various population groups.

In the GRAS Notice, the available data and information to support the safety of the intended use of MK-7 has been extensively summarized and discussed. The available published information shows that menaquinones are absorbed unchanged from the small intestines and distributed to the liver. As compared to the short-chain MK-4 or phylloquinone (VK1), MK-7 has higher serum bioavailability and longer half-life. In two separate published acute and subchronic (90-day) toxicity studies, oral gavage administration of MK-7 to rats did not reveal any treatment related adverse effects. In published genotoxicity studies, MK-7 did not reveal any mutagenic or genotoxic effects. In two published subchronic and chronic (1-year) toxicity studies with structurally similar MK-4, conducted in both rats and dogs, no adverse effects were observed. In 2008, an EFSA Panel reviewed the developmental toxicity studies of MK-4 and concluded that there were no significant adverse effects observed on reproductive and developmental parameters measured. These studies with MK-4 support the safety of MK-7.

In GRN 887, several published human studies with MK-7 have been discussed to support safety-in-use. These human trials also included several double-blind, placebo-controlled studies that are least likely to result in bias, will capture the adverse effects, and provide an opportunity to assess the safety and 'tolerability' of MK-7 in a diverse population. These studies did not report any significant adverse effects when consumed at levels up to 180 µg/person/day for 3 years. Additional, multiple published long-term (up to 2 years) human studies show that high doses of MK-4 (up to 90 mg/day for 24 weeks) were well tolerated and further corroborate the safety of MK-7 for the intended use.

In this GRAS notice, concerns related to MK-7 and vitamin K antagonists (anticoagulant therapy), dietary intake of vitamin K, and drug interactions has been extensively summarized and discussed. The notifier stated that the available information suggests that different vitamin K homologs differ in their mode or extent of action in disturbing vitamin K antagonist-induced anticoagulation. Synergia discussed studies and reviews indicating that MK-7 at doses ≤50 µg/day are unlikely to affect the levels of vitamin K in a clinically relevant way. Despite having higher bioavailability and longer half-life when compared to VK1 or another short-chain K2 (MK-4), the notifier concluded that regular or daily low dose supplementation of MK-7 at a dose level of 4 µg/serving and restricted use in specific nutritional beverage products for children ensures that it does not pose increased risk to children, including those undergoing anticoagulation therapy that are under the supervision of a medical professional. Additionally, the historical consumption of MK-7-containing foods like natto and different cheeses supports the safety of MK-7. Furthermore, EFSA (2008) has evaluated the safety of MK-7 and concluded that MK-7 is safe to consume in foods by the general population at use levels of 10 µg/serving.

Following its review, the FDA responded to GRN 887 that, based on the information provided in the Notification, as well as other information available to the FDA, the agency had

no questions at the time regarding Synergia's conclusion that MK-7 is GRAS under the intended conditions of use.

6.2.7. European Food Safety Authority Review

In 2008, the European Food Safety Authority (EFSA, 2008) extensively reviewed the safety of MK-7. The subject of the EFSA review, sunflower oil suspension of a MK-7-rich extract was obtained from the fermentation of soybean protein isolate and corn starch in the presence of *Bacillus subtilis natto* for use both as a food supplement and as a food ingredient. For this assessment and review, EFSA considered the data on specifications, manufacturing, anticipated intake, bioavailability, metabolism and toxicology. Following its review, the EFSA Panel concluded that the use of menaquinone-rich (primarily MK-7) edible oil in foods for the general population including food supplements and in foods for particular nutritional uses, except baby foods and infant formula, at the use levels of 10 µg/serving was not of safety concern. The overall estimated mean daily intake of MK-7 ranged from 36 µg (female adults) to 54 µg (male teenagers). High intake levels ranged from 75 µg/day (children) to 115 µg/day (male teenagers). Thus, in the European Union for over 12 years, MK-7 is permitted to be used as a source of vitamin K for nutritional purposes in foodstuffs.

6.3. GRAS Panel Review, Summary and Discussion

At the request of Amin Talati Upadhye, LLP (AminTalati), USA and its client GF Fermentech, Inc. (GF Fermentech), an independent panel of recognized experts (hereinafter referred to as the Expert Panel)[4], qualified by their scientific training and relevant national and international experience to evaluate the safety of food and food ingredients, was convened to evaluate the Generally Recognized As Safe (GRAS) status of Menaquinone-7 (MK-7), derived from *Bacillus subtilis natto*, for use as a food ingredient and as an nutrient in selected conventional foods such as Beverages and Beverage Bases, Breakfast Cereals, Cheeses, Fats and Oils, Frozen Dairy, Desserts, Grain products and pastas, Milk, Milk Products, Processed Fruits and Fruit Juices, and Processed Vegetables and Vegetables Juices at a maximum level of 10 µg MK-7 per serving of food (Reference Amounts Customarily Consumed Per Eating Occasion; 21 CFR § 101.12). A comprehensive search of the scientific literature for safety and toxicity information on MK-7 and related compounds such as VK1, VK2 was conducted through August 2021 and made available to the Expert Panel. The Expert Panel independently and critically evaluated materials submitted by AminTalati and GF Fermentech and other information deemed appropriate or necessary. Following an independent, critical evaluation, the Expert Panel conferred on August 31, 2021 and unanimously agreed to the decision described herein.

AminTalati and GF Fermentech ensured that all reasonable efforts were made to identify and select a balanced Expert Panel with expertise in food safety, toxicology, and nutrition. The Expert Panel was selected and convened in accordance with the Food and Drug Administration (FDA)'s guidance for industry on "Best Practices for Convening a GRAS Panel"[5]. Efforts were placed on identifying conflicts of interest or relevant "appearance issues" that could potentially bias the outcome of the deliberations of the Expert Panel and no such

[4]Modeled after that described in section 201(s) of the Federal Food, Drug, and Cosmetic Act, As Amended. See also attachments (curriculum vitae) documenting the expertise of the Panel members.

[5] Available at: https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm583856.htm

conflicts of interest or "appearance issues" were identified. The Expert Panel members received a reasonable honorarium as compensation for their time; the honoraria provided to the Expert Panel members were not contingent upon the outcome of their deliberations.

GF Fermentech intends to market the standardized MK-7 preparation, produced by a fermentation and extraction process, using microbial strain *Bacillus subtilis natto*. The production process and the specifications of MK-7 have been fully developed. MK-7 is produced according to the current good manufacturing practices. The extract is mixed with appropriate food grade material to a desired concentration that is intended to be marketed under the trade name MediQ7. MK-7 will be used selected food categories such as Beverages and Beverage Bases, Breakfast Cereals, Cheeses, Fats and Oils, Frozen Dairy, Desserts, Grain products and pastas, Milk, Milk Products, Processed Fruits and Fruit Juices, and Processed Vegetables and Vegetables Juices at a maximum level of 10 µg MK-7/serving. The proposed use will result in the consumer only mean and 90th percentile of intake of MK-7 is 25 µg/person/day (0.4 µg/kg-bw/day) and 48 µg/person/day (1.0 µg/kg bw/day), respectively. Among the different populations, the highest 90th percentile intake of 63 µg/person/day was noted in male adults 14-18 years. For safety assessment purposes, highest intake of 63 µg/person/day is considered.

There are two primary forms of vitamin K, commonly known as vitamin K1 (phylloquinone) and vitamin K2 (menaquinones). All K-vitamins have the same function; however, they differ in bioavailability and bioactivity. The vitamin K2 has several subtypes or homologues that differ in isoprenoid sidechain length and among these MK-7 is a prominent form. MK-7 is a form of vitamin K2 biosynthesized by bacteria. Overall MK-7 intake contributes probably less than 5 to 10% of the dietary intake of vitamin K, which is primarily as vitamin K1 in Western countries. As a member of vitamin K, MK-7 occurs naturally in fermented foods (up to 1000 µg/100g in Natto), dairy products (0.1-65 µg/100 g), and some meat (<0.5 µg/ 100 g). MK-7 is a form of vitamin K2 biosynthesized by bacteria. Japanese traditional fermented food, commonly known as Natto and has been consumed since ancient times is produced from soybeans, is one of the richest sources of MK-7. In Japan, Natto as a food has received certification under FOSHU for health claims for both bone health and gut health. In Europe, the EFSA has also recognized the use of MK-7 as a novel food for the general population. The available published literature and the historical consumption of Natto supports the safety of MK-7 at levels found in these products.

The available evidence suggests that all forms of vitamin K (VK1 and VK2) have a low order of toxicological potential, while the recommended dietary intake is several orders of magnitude lower than doses evaluated in animal and human studies. Different forms of vitamin K2 are absorbed, albeit slowly at normal dietary levels, and they contribute to maintaining function of vitamin K-reliant pathways. The available evidence, from human studies, indicate that higher and more stable plasma levels of vitamin K were reached with supplements containing VK2 (particularly long-chain) as compared to those containing VK1. VK2 appears to be absorbed unchanged from the gastrointestinal tract, released into circulation and distributed to the liver, comprising 90% (MK-6 to MK-13) of total VK. The available studies suggest that compared to MK-7 that has a half-life of 72 hours, plylloquinone (VK-1) and short-chain menaquinones (MK-4) have short-half-life just 1-2 hours. As compared to MK-4 or VK1, the bioavailability of MK-7 is 6-10 times better (serum/plasma levels) indicating that MK-7 is likely to build up more stable serum levels. This also indicate that, in patients on anti-

coagulant therapy, the stable levels of MK-7 following regular exposure from the proposed uses may provide advantage.

In multiple experimental toxicity studies, the potential adverse effects of VK2, including MK-7, have been studied. The findings from animal studies that include acute, subchronic, reproductive and developmental toxicity, genotoxicity and carcinogenicity, did not reveal any significant toxicity associated with exposure to VK2, including MK-7. Based on the findings from a subchronic toxicity study in rats, the NOAEL of MK-7 was considered as 10 mg/kg bw/day, the highest dose tested. This NOAEL is over 10,000 fold higher as compared to the 90th percentile intake of MK-7 (63 µg/day; 1 µg/kg bw/day) from the proposed uses. In long-term (1 year) toxicity studies with MK-4, the LOAEL in rats was established as 20 mg/kg bw/day, while the NOAEL in dogs was 200 mg/kg bw/day. Although these studies were conducted with MK-4, the findings indicate that MK-7 at levels of up to 10 µg/serving in the healthy population is unlikely to cause adverse effects.

In order to demonstrate the safety of exogenously administered MK-7, GF Fermentech has undertaken a series of unpublished preclinical toxicity studies. These studies included acute, short-term (28-day) and subchronic toxicity (90-day), and genotoxicity studies (Ames assay, *in vitro* chromosomal aberration study and *in vivo* micronucleus study in rats). The findings from mutagenicity studies of MK-7 as investigated by *in vitro* bacterial reverse mutation test (Ames assay), by *in vitro* chromosomal aberration study and by *in vivo* micronucleus study suggest that MK-7 is unlikely to cause any mutagenic or genotoxic effects. In the acute toxicity study, administration of MK-7 to Sprague-Dawley rats at dose levels of 5000 mg/kg bw did not cause any lethality. In the 28-day oral dose response study in Sprague Dawley rats, oral administration of MK-7 at dose levels up to 4500 mg/kg bw/day did not reveal any toxicological effects. Similarly, the findings from the subchronic toxicity study in rats, conducted as per OECD guidelines, suggest that the NOAEL of MK-7 is 4500 mg/kg bw/day, the highest dose tested. As compared to the NOAEL of 4500 mg/kg bw/day determined from the subchronic toxicity study (the highest dose tested), the maximum intake of 1 µg/kg bw/day of MK-7 from its proposed food uses is over 4,500,000-fold lower.

In addition to the above mentioned pre-clinical toxicity studies, MK-7 has been investigated in over 25 human clinical trials, in over 2500 participants, for its safety and efficacy. These clinical studies also include several double-blind, placebo-controlled trials that are least likely to result in bias, will capture the adverse effects, and provide an opportunity to assess safety and 'tolerability' of MK-7 in a diverse population. The findings from long-term high dose trials in which MK-7 administration at levels up to 180 µg/day for 3 years, or up to 360 µg/day for 12 weeks, or up to 1080 µg thrice weekly for 8 weeks did not reveal any significant adverse effects compared with placebo. Adverse effects specifically attributed to MK-7 were limited to gastrointestinal upset associated with the product's smell. Additionally, in several clinical studies, high doses of MK-4 have been well tolerated. In one trial, MK-4 at a dose level of 90 mg/day for 24 weeks did not reveal any adverse effects. These studies with MK-4 corroborate the safety of MK-7 at the proposed use levels.

The findings from multiple published human clinical studies with MK-7 did not reveal any significant adverse effects. In these studies, over 2000 individuals participated and the intake of MK-7 lasted from a few days to 3 years. Among the several clinical studies, in three long-term (two one year and one three year) clinical trials the effects of MK-7 at levels of 180 to 360 µg/day were investigated. The results of these long-term studies did not reveal any

adverse effects of MK-7. Thus, human exposure to MK-7, including from documented clinical studies, confirm that there are no reports of any significant adverse effects. Additionally, in several clinical studies, high doses of MK-4 have been well tolerated. In one of the clinical studies, MK-4 at a dose level of 90 mg/day for 24 weeks did not reveal any adverse effects. These studies with MK-4 corroborate the safety of MK-7 at the proposed use levels.

In a recent study, MK-7 supplementation at dosage of 90 µg/person/day for 30 days does not affect the hemostatic profile in healthy individuals. However, it has been well recognized that VK interferes with anticoagulation therapy and there is a risk for interaction between MK-7 and anticoagulant drugs. Patients on anticoagulation therapy receive advice from their physician, pharmacist and other health professionals who are trained to advice patients of the need to maintain a stable dietary intake of vitamin K (avoid wide fluctuations in VK intake) and the risk of an interaction with vitamin K supplements. The proposed use of MK-7 is at a very low level (10 µg/serving). As discussed earlier, as a long chain VK2, MK-7 has a longer half-life in circulation as compared to VK1 and this may account for better stability of INR values for individuals on anti-coagulant therapy. The low use levels should ensure that people currently taking Coumadin anticoagulants are not negatively affected by the proposed uses. Additionally, any concerns related to the effects of MK-7 on metabolism of prescription drug in the CYP3A4 pathway will be negligible as the low dose of MK-7 is unlikely to have any significant effect on the expression these enzymes.

Recently, FDA reviewed safety of MK-7 as part of GRN 887 and did not question the proposed uses in children at levels of 4 µg/serving. The resulting 90th percentile intake of MK-7 from the proposed uses described in this GRAS for adults on a body weight basis of 1.0 µg/kg bw/day, is similar to the cumulative maximum intake of MK-7 (0.99 µg/kg bw/day) in children described in GRN 887.

In summary, the totality of the available evidence from *in vitro,* animal and human studies, including studies for structurally-related vitamin analogues, and the historical dietary exposure to MK-7 from foods like Natto and cheese, support the safety-in-use of MK-7, at the intended use levels (10 µg/serving). On the basis of scientific procedures[6], and exposure from natural dietary sources, the consumption of MK-7 as an added food ingredient is considered to be safe at use levels up to 10 µg/serving resulting in the highest 90th percentile intake of 63 µg/person/day in male adults 14-18 years. The intended uses are compatible with current regulations, *i.e.*, MK-7 is used in selected food categories and is produced according to Korea Good Manufacturing Practices for health functional foods.

[6] 21 CFR §170.3 Definitions. (h) Scientific procedures include those human, animal, analytical, and other scientific studies, whether published or unpublished, appropriate to establish the safety of a substance.

[redacted]

Robert L. Martin., Ph.D.

August 31, 2021
Date

[redacted]

John A. Thomas, Ph.D., FATS, FACT

Date

[redacted]

Madhusudan G. Soni, Ph.D., F.A.C.N., F.A.T.S.
Advisor to Expert Panel

Sept. 3, 2021
Date

6.4. GRAS Panel Conclusion

Based on a critical evaluation of the publicly available data, summarized herein, the Expert Panel members whose signatures appear below, have individually and collectively concluded that MK-7, meeting the specifications cited herein, and when used as a nutrient [21 CFR § 170.3(o) (20)] at maximum use levels of up to 10 µg/serving (when not otherwise precluded by a Standard of Identity) in conventional foods such as Beverages and Beverage Bases, Breakfast Cereals, Cheeses, Fats and Oils, Frozen Dairy, Desserts, Grain products and pastas, Milk, Milk Products, Processed Fruits and Fruit Juices, and Processed Vegetables and Vegetables Juices, described in this assessment and resulting in the 90th percentile all-user estimated intake of 63 µg MK-7/person/day is safe.

It is also the opinion of the Expert Panelists that other qualified and competent scientists reviewing the same publicly available toxicological and safety information would reach the same conclusion. Therefore, we have also concluded that MK-7, when used as described, is GRAS based on scientific procedures.

Signatures

7. PART VII- LIST OF SUPPORTING DATA AND INFORMATION

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8. Appendix I

Certificate of Analysis from Six Nonconsecutive Lots of MK-7
Three lots for oil form and three lots powder form

(Attached separately)

CERTIFICATE OF ANALYSIS

Name of Product	**VitaminK2(MK7) 2000PD** (all-E)-2-(3,7,11,15,19,23,27-Heptamethyl-2,6,10,14,18,22,26-octacosaheptaenyl)-3-methyl-1,4-naphthalenedione
Brand Name	MediQ7 Vitamin K2 MK7
Grade	Food Grade
Mol. Formula	$C_{46}H_{64}O_2$
Mol. Weight	649.0
Lot No.	VKP200401S
Manufactured date	2020.04.10
Expiration date	2022.04.09
Certificated date	2021.03.08
Country of Origin	Made in Republic of Korea

Item	Specification	Actual Test Result	Analysis method
Appearance	Yellowish white powder	Conform	In-house method
Identification			
VitaminK2(MK7) assay (HPLC)			
Content (Menaquinone-7)	≥ 2,000 ppm	2,157 ppm	USP NF, Menaquinone-7 preparation
Isomeric Purity	≤ 1.0 %	0.00 %	
Moisture	≤ 5.0 %	2.98 %	USP <921>
Arsenic(As)	≤ 0.5 ppm	Conform	USP <233>
Cadmium(Cd)	≤ 0.5 ppm	Conform	
Lead(Pb)	≤ 0.5 ppm	Conform	
Mercury(Hg)	≤ 0.1 ppm	Conform	
Microbial limits			
Total Bacteria Count	≤ 10^3 CFU/g	Conform	USP <2021>
Total Yeast & Mold Count	≤ 10^2 CFU/g	Conform	
Salmonella	Negative	Conform	USP <2022>
E. coli	Negative	Conform	
Staphylococcus aureus	Negative	Conform	
Carrier	Maltodextrin		

Storage conditions : It is recommended that product will be stored at cool temperature in a dry and dark place, and away from high heat, humidity, and light.

Min Ju Choi
Quality Manager

CERTIFICATE OF ANALYSIS

Name of Product	**VitaminK2(MK7) 50000LM** (all-E)-2-(3,7,11,15,19,23,27-Heptamethyl-2,6,10,14,18,22,26-octacosaheptaenyl)-3-methyl-1,4-naphthalenedione
Brand Name	MediQ7 Vitamin K2 MK7
Grade	Food Grade
Mol. Formula	$C_{46}H_{64}O_2$
Mol. Weight	649.0
Lot No.	VKL200601S
Manufactured date	2020.06.04
Expiration date	2022.06.03
Certificated date	2021.03.08
Country of Origin	Made in Republic of Korea

Item	Specification	Actual Test Result	Analysis method
Appearance	Yellowish oil	Conform	In-house method
Identification			
Vitamin K2 (MK-7) assay (HPLC)			
Content (Menaquinone-7)	≥ 50,000 ppm	53,972 ppm	USP NF, Menaquinone-7 preparation
Isomeric Purity (%, cis MK-7)	≤ 1.0 %	0.01%	
Acid value	≤ 1.0 mg/g	0.01 mg/g	USP <401>
Arsenic(As)	≤ 0.5 ppm	Conform	USP <233>
Cadmium(Cd)	≤ 0.5 ppm	Conform	
Lead(Pb)	≤ 0.5 ppm	Conform	
Mercury(Hg)	≤ 0.1 ppm	Conform	
Microbial limits			
Total Bacteria Count	≤ 10^3 CFU/g	Conform	USP <2021>
Total Yeast & Mold Count	≤ 10^2 CFU/g	Conform	
Salmonella	Negative	Conform	USP <2022>
E. coli	Negative	Conform	
Staphylococcus aureus	Negative	Conform	
Carrier	MCT oil		

Storage conditions : It is recommended that product will be stored at room temperature in a dry and dark place, and away from high heat, humidity, and light. If the product is put at cool place, there can be vitamin K2 crystal due to solubility at cool temperature. Please ensure homogeneity of oil without crystal before use. In case that there are crystals in oil, please warm the bottle in closed state to get homogeneous oil.

Min Ju Choi
Quality Manager

CERTIFICATE OF ANALYSIS

Name of Product	**VitaminK2(MK7) 2000PD** (all-E)-2-(3,7,11,15,19,23,27-Heptamethyl-2,6,10,14,18,22,26-octacosaheptaenyl)-3-methyl-1,4-naphthalenedione
Brand Name	MediQ7 Vitamin K2 MK7
Grade	Food Grade
Mol. Formula	$C_{46}H_{64}O_2$
Mol. Weight	649.0
Lot No.	VKP20001
Manufactured date	2020.09.28
Expiration date	2022.09.27
Certificated date	2021.03.08
Country of Origin	Made in Republic of Korea

Item	Specification	Actual Test Result	Analysis method
Appearance	Yellowish white powder	Conform	In-house method
Identification			
VitaminK2(MK7) assay (HPLC)			
Content (Menaquinone-7)	≥ 2,000 ppm	2,046 ppm	USP NF, Menaquinone-7 preparation
Isomeric Purity	≤ 1.0 %	0.00 %	
Moisture	≤ 5.0 %	1.49 %	USP <921>
Arsenic(As)	≤ 0.5 ppm	Conform	USP <233>
Cadmium(Cd)	≤ 0.5 ppm	Conform	
Lead(Pb)	≤ 0.5 ppm	Conform	
Mercury(Hg)	≤ 0.1 ppm	Conform	
Microbial limits			
Total Bacteria Count	≤ 10^3 CFU/g	Conform	USP <2021>
Total Yeast & Mold Count	≤ 10^2 CFU/g	Conform	
Salmonella	Negative	Conform	USP <2022>
E. coli	Negative	Conform	
Staphylococcus aureus	Negative	Conform	
Carrier	Maltodextrin		

Storage conditions : It is recommended that product will be stored at cool temperature in a dry and dark place, and away from high heat, humidity, and light.

Min Ju Choi
Quality Manager

CERTIFICATE OF ANALYSIS

Name of Product	**VitaminK2(MK7) 50000LM** (all-E)-2-(3,7,11,15,19,23,27-Heptamethyl-2,6,10,14,18,22,26-octacosaheptaenyl)-3-methyl-1,4-naphthalenedione
Brand Name	MediQ7 Vitamin K2 MK7
Grade	Food Grade
Mol. Formula	$C_{46}H_{64}O_2$
Mol. Weight	649.0
Lot No.	VKL201001S
Manufactured date	2020.10.05
Expiration date	2022.10.04
Certificated date	2021.03.08
Country of Origin	Made in Republic of Korea

Item	Specification	Actual Test Result	Analysis method
Appearance	Yellowish oil	Conform	In-house method
Identification			
Vitamin K2 (MK-7) assay (HPLC)			
Content (Menaquinone-7)	≥ 50,000 ppm	53,157 ppm	USP NF, Menaquinone-7 preparation
Isomeric Purity (%, cis MK-7)	≤ 1.0 %	0.01%	
Acid value	≤ 1.0 mg/g	0.25 mg/g	USP <401>
Arsenic(As)	≤ 0.5 ppm	Conform	USP <233>
Cadmium(Cd)	≤ 0.5 ppm	Conform	
Lead(Pb)	≤ 0.5 ppm	Conform	
Mercury(Hg)	≤ 0.1 ppm	Conform	
Microbial limits			
Total Bacteria Count	≤ 10^3 CFU/g	Conform	USP <2021>
Total Yeast & Mold Count	≤ 10^2 CFU/g	Conform	
Salmonella	Negative	Conform	USP <2022>
E. coli	Negative	Conform	
Staphylococcus aureus	Negative	Conform	
Carrier	MCT oil		

Storage conditions : It is recommended that product will be stored at room temperature in a dry and dark place, and away from high heat, humidity, and light. If the product is put at cool place, there can be vitamin K2 crystal due to solubility at cool temperature. Please ensure homogeneity of oil without crystal before use. In case that there are crystals in oil, please warm the bottle in closed state to get homogeneous oil.

Min Ju Choi
Quality Manager

CERTIFICATE OF ANALYSIS

Name of Product	**VitaminK2(MK7) 2000PD** (all-E)-2-(3,7,11,15,19,23,27-Heptamethyl-2,6,10,14,18,22,26-octacosaheptaenyl)-3-methyl-1,4-naphthalenedione
Brand Name	MediQ7 Vitamin K2 MK7
Grade	Food Grade
Mol. Formula	$C_{46}H_{64}O_2$
Mol. Weight	649.0
Lot No.	VKP20003
Manufactured date	2020.12.30
Expiration date	2022.12.29
Certificated date	2021.03.08
Country of Origin	Made in Republic of Korea

Item	Specification	Actual Test Result	Analysis method
Appearance	Yellowish white powder	Conform	In-house method
Identification			
VitaminK2(MK7) assay (HPLC)			
Content (Menaquinone-7)	≥ 2,000 ppm	2,275 ppm	USP NF, Menaquinone-7 preparation
Isomeric Purity	≤ 1.0 %	0.01 %	
Moisture	≤ 5.0 %	1.22 %	USP <921>
Arsenic(As)	≤ 0.5 ppm	Conform	USP <233>
Cadmium(Cd)	≤ 0.5 ppm	Conform	
Lead(Pb)	≤ 0.5 ppm	Conform	
Mercury(Hg)	≤ 0.1 ppm	Conform	
Microbial limits			
Total Bacteria Count	≤ 10^3 CFU/g	Conform	USP <2021>
Total Yeast & Mold Count	≤ 10^2 CFU/g	Conform	
Salmonella	Negative	Conform	USP <2022>
E. coli	Negative	Conform	
Staphylococcus aureus	Negative	Conform	
Carrier	Maltodextrin		

Storage conditions : It is recommended that product will be stored at cool temperature in a dry and dark place, and away from high heat, humidity, and light.

Min Ju Choi
Quality Manager

CERTIFICATE OF ANALYSIS

Name of Product	**VitaminK2(MK7) 50000LM** (all-E)-2-(3,7,11,15,19,23,27-Heptamethyl-2,6,10,14,18,22,26-octacosaheptaenyl)-3-methyl-1,4-naphthalenedione
Brand Name	MediQ7 Vitamin K2 MK7
Grade	Food Grade
Mol. Formula	$C_{46}H_{64}O_2$
Mol. Weight	649.0
Lot No.	VKLM21002
Manufactured date	2021.02.15
Expiration date	2023.02.14
Certificated date	2021.03.08
Country of Origin	Made in Republic of Korea

Item	Specification	Actual Test Result	Analysis method
Appearance	Yellowish oil	Conform	In-house method
Identification			
VitaminK2(MK7) assay (HPLC)			
Content (Menaquinone-7)	≥ 50,000 ppm	53,788 ppm	USP NF, Menaquinone-7 preparation
Isomeric Purity (%, cis MK-7)	≤ 1.0 %	0.04 %	
Acid value	≤ 1.0 mg/g	0.13 mg/g	USP <401>
Arsenic(As)	≤ 0.5 ppm	Conform	USP <233>
Cadmium(Cd)	≤ 0.5 ppm	Conform	
Lead(Pb)	≤ 0.5 ppm	Conform	
Mercury(Hg)	≤ 0.1 ppm	Conform	
Microbial limits			
Total Bacteria Count	≤ 10^3 CFU/g	Conform	USP <2021>
Total Yeast & Mold Count	≤ 10^2 CFU/g	Conform	
Salmonella	Negative	Conform	USP <2022>
E. coli	Negative	Conform	
Staphylococcus aureus	Negative	Conform	
Carrier	MCT Oil	Conform	

Storage conditions : It is recommended that product will be stored at room temperature in a dry and dark place, and away from high heat, humidity, and light. If the product is put at cool place, there can be vitamin K2 crystal due to solubility at cool temperature. Please ensure homogeneity of oil without crystal before use. In case that there are crystals in oil, please warm the bottle in closed state to get homogeneous oil.

Min Ju Choi
Quality Manager

9. Appendix II

ESTIMATED DAILY INTAKE OF MENAQUINONE-7 (MK-7) BY THE U.S. POPULATION FROM CURRENT DIETARY SOURCES AND PROPOSED FOOD USES (2017-2018 NHANES)

Complete report from Intertek.

Attached separately

ESTIMATED DAILY INTAKE OF MENAQUINONE-7 (MK-7) BY THE U.S. POPULATION FROM CURRENT DIETARY SOURCES AND PROPOSED FOOD USES (2017-2018 NHANES)

CONFIDENTIAL

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DATE:
16 July 2021

Estimated Daily Intake of Menaquinone-7 (MK-7) by the U.S. Population from Current Dietary Sources and Proposed Food Uses (2017-2018 NHANES)

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Estimated Daily Intake of Menaquinone-7 (MK-7) by the U.S. Population from Current Dietary Sources and Proposed Food Uses (2017-2018 NHANES)

1.0 INTRODUCTION

Menaquinone-7 (MK-7) is proposed for use in the United States (U.S.) in foods such as beverages and beverage bases; cereal and cereal products; dairy products; fats and oils; and pasta, rice and other miscellaneous grains. Since vitamin K is a nutrient that is naturally present in the diet and is also added to foods and dietary supplements for fortification purposes, intakes of MK-7, as well as other vitamin K isomers, from all dietary sources were estimated to evaluate the nutritional impact of the proposed food uses of MK-7 in the diet of the U.S. population.

Overall, three intake assessments were conducted:

1. Estimated daily intake of menaquinone-4 (MK-4), MK-7, vitamin K2, vitamin K1, and total vitamin K from the background diet, *i.e.*, current sources of vitamin K, including its natural occurrence in food and current fortification uses in foods and dietary supplements;

2. Estimated daily intake of MK-7 from proposed food uses only; and

3. Cumulative estimated daily intake of MK-7, vitamin K2, and total vitamin K from proposed food uses and background diet (food and supplements)[1].

Estimates for the intake of the vitamin K isoforms (MK-4, MK-7, vitamin K1, vitamin K2, and total vitamin K) were based on the current and/or proposed levels of the nutrient in food in conjunction with food consumption data included in the U.S. National Center for Health Statistics' National Health and Nutrition Examination Surveys (NHANES) 2017-2018. Additionally, exposure estimates for vitamin K isomers from dietary supplement products were based on the supplement composition and consumption data included in the same NHANES survey (CDC, 2021a,b; USDA, 2021). Calculations for the mean and 90th percentile *per capita* and consumer-only intakes were carried out for all 3 assessments, and the percentage of consumers were determined. Similar calculations were used to estimate the intake of MK-7 resulting from each individual source (*i.e.*, current food sources, dietary supplements, proposed food uses). The impact of the proposed food uses of MK-7 in food and beverage categories was evaluated by calculating the absolute change in MK-7 intakes from the proposed uses relative to the background diet.

In all assessments, the per person and per kilogram body weight intakes were reported for the following population groups, the age groups for which were based on the recommended intakes (IOM, 2001) established for vitamin K:

- Infants, 0 to 6 months (both gender groups combined);
- Infants, 7 to 11 months (both gender groups combined);
- Young children, ages 1 to 3 years (both gender groups combined);
- Children, ages 4 to 8 years (both gender groups combined);

[1] Intakes of MK-4 and vitamin K1 were not included in the cumulative intakes assessment, as they are not part of the proposed uses.

- Female teenagers, ages 9 to 13 years;
- Male teenagers, ages 9 to 13 years;
- Female adolescents, ages 14 to 18 years;
- Male adolescents, ages 14 to 18 years;
- Female adults, ages 19 years and older;
- Male adults, ages 19 years and older; and
- Total population, ages 1 and older.

2.0 FOOD CONSUMPTION SURVEY DATA

2.1 Survey Description

NHANES for the years 2017-2018 are available for public use (CDC, 2021a,b; USDA, 2021). NHANES are conducted as continuous, annual surveys, and they are released in 2-year cycles. During each year of the ongoing NHANES program, individuals from the U.S. are sampled from up to 30 different study locations in a complex multi-stage probability design intended to ensure the data are a nationally representative sample of the U.S. population.

NHANES 2017-2018 dietary survey data were collected from individuals and households *via* 24-hour dietary recalls administered on 2 non-consecutive days (Day 1 and Day 2) throughout all 4 seasons of the year. Day 1 data were collected in-person, and Day 2 data were collected by telephone in the following 3 to 10 days, on different days of the week, to achieve the desired degree of statistical independence. The data were collected by first selecting primary sampling units (PSUs), which were counties throughout the U.S., of which 30 PSUs are visited per year. Smaller contiguous counties were combined to attain a minimum population size. These PSUs were segmented, and households were chosen within each segment. One or more participants within a household were interviewed. For NHANES 2017-2018, 16,211 individuals were selected for the sample, 9,254 were interviewed (51.9%), and 8,704 were examined (48.8%).

Participants who completed the dietary intake data collection were also asked to complete a similar recall in which they documented the supplement products consumed within the previous 24 hours on 2 non-consecutive days. The participants were asked to record the name and manufacturer of the supplement, which is visually confirmed by the interviewer if possible. The amounts of individual ingredients present in the supplement are then itemized and entered into the NHANES database, which allows the data to be incorporated into the dietary intake estimates.

In addition to collecting information on the types and quantities of foods being consumed, NHANES 2017-2018 collected socio-economic, physiological, and demographic information from individual participants in the survey, such as sex, age, body weight, and other variables (such as height and race-ethnicity) that may be useful in characterizing consumption. The inclusion of this information allows for further assessment of food intake based on consumption by specific population groups of interest within the total population. The primary sample design for NHANES 2017-2018 includes an oversample of non-Hispanic Asian persons, Hispanic persons, non-Hispanic black persons, non-Hispanic white and "other" older persons (≥80 years), and non-Hispanic low income white and "others" persons (≤185% of the Department of Health and Human Services poverty guidelines); however, sample weights were incorporated to allow estimates from these subgroups to be combined to obtain national estimates that reflect the relative proportions of these groups in the population as a whole (CDC, 2021a,b; USDA, 2021).

2.2 Nutrient Values (Foods and Supplements)

2.2.1 Foods

Nutrient values for vitamin K isomers associated with food codes, and ultimately food consumption data, for the 2017-2018 NHANES dataset were obtained from 3 sources:

1. United States Department of Agriculture's Food and Nutrient Database for Dietary Studies (FNDDS) 2017-2018 (USDA ARS, 2021)

    a. For each food represented in the NHANES, the FNDDS provides information on the concentration values for 64 nutrients/food components per 100 g food (USDA ARS, 2021), including vitamin K1 as phylloquinone only. Data was not available for vitamin K2.

2. USDA National Nutrient Database for Standard Reference 28 (SR 28) (USDA, 2020)

    a. This database provides the foundation for most food composition database in the FNDDS. The SR 28 database contains data on the level of vitamin K2 as MK-4. The available values from this dataset were reviewed and, where applicable, applied to similar codes.

3. Published literature

    a. The above-mentioned sources were supplemented with information from the published literature with respect to the levels of MK-4, MK-7 and vitamin K2. A literature review was conducted in April 2021 to identify studies reporting levels of these isomers (Schurgers and Sakamoto *et al.*, 1999; Vermeer, 2000; Elder *et al.*, 2006; Fu *et al.*, 2016; Fu *et al.*, 2017; Vermeer *et al.*, 2018).

For reference, Table 2.2-1 provides details on the source for each of the isomers. MK-4 was obtained from SR28 or for the published literature, while MK-7 was only available from the published literature. Values for overall vitamin K2 utilised MK-4 as a surrogate or was based on data directly from the literature. All values for vitamin K1 were obtained rom the FNDDS. Finally, total vitamin K was calculated as the sum of vitamin K2 and vitamin K1.

Table 2.2-1 Source of Vitamin K Isomer Data for Foods

Vitamin K isomer	Source
MK-4	SR28
	Published literature
MK-7	Published literature
Vitamin K2	MK-4 value from SR28 as a surrogate
	Published literature (reported directly)
Vitamin K1	FNDDS 2017-2018
Total Vitamin K	Sum of vitamin K2 and vitamin K1

SR28 = USDA National Nutrient Database for Standard Reference 28; FNDDS 2017-2018 = United States Department of Agriculture's Food and Nutrient Database for Dietary Studies (FNDDS) 2017-2018

For the assessment of the vitamin K isomers from the background diet, food codes representative of food and beverages products identified to contain vitamin K were chosen from NHANES 2017-2018

(CDC, 2021a,b; USDA, 2021). The average levels for the respective vitamin K isomers were applied. The full list of food codes and associated vitamin K levels are provided in Appendix C.

2.2.2 Dietary Supplements

The amounts of vitamin K associated with food supplement codes, and ultimately supplement consumption data, from the 2017-2018 NHANES dataset were obtained from 3 sources:

1. Dietary Supplement Ingredient Information (DSII) dataset
    a. This is one component of the NHANES Dietary Supplement Database (NHANES-DSD) (CDC, 2021b). The NHANES-DSD contains product label information for all dietary supplements reported to be consumed by NHANES survey participants since 1999; ingredient information is taken directly form the supplement facts box on the label or carton (CDC, 2020). The DSII identified values for vitamin K/menadione: phytonadione.
2. National Institutes of Health (NIH) Dietary Supplement Label Database (DSLD) (NIH, 2020)
    a. Dietary supplements were identified as containing vitamin K, vitamin K1 (phylloquinone) and vitamin K2 (menaquinone).
3. NHANES supplement code list
    a. The list was searched to identify any products contain the following terms in the product name: "K2", "MK-4" "MK-7", "menaquinone", "menatetrenone", "natto".

The reported levels of vitamin K were applied to the associated food supplement codes. As the ingredient amount is expressed on a serving basis, a serving was assumed to be equivalent to 1 g in food equivalents. The full list of food supplement codes and associated vitamin K levels are provided in Appendix C.

2.3 Statistical Methods

For the 3 intake assessments (background; proposed; background + proposed), consumption data from individual dietary records, detailing food and supplement items ingested by each survey participant, were collated by computer and used to generate estimates for the intake of vitamin K isomers by the U.S. population[2]. Estimates for the daily intake of vitamin K isomers represent projected 2-day averages for each individual from Day 1 and Day 2 of NHANES 2017-2018 (*i.e.*, a value was established for each person). From these average amounts, a distribution was established from which the mean and percentile intake estimates for the cohort of interest were determined, which incorporated survey weights in order to provide representative intakes for the entire U.S. population. *"Per capita"* intake refers to the estimated intake of the vitamin K value averaged over all individuals surveyed, regardless of whether they consumed food products in which vitamin K is proposed for use and/or is present naturally or by fortification, and therefore includes individuals with "zero" intakes (*i.e.*, including individuals who reported no intake of food products containing the selected vitamin K isomer during the 2 survey days). "Consumer-only" intake refers to the estimated intake of vitamin K by only those individuals who reported consuming food products of interest on either Day 1 or Day 2 of the survey. The definition of a consumer differs according to the assessment.

Mean and 90th percentile intake estimates based on sample sizes of less than 30 and 80, respectively, may not be considered statistically reliable due to the limited sampling size (CDC, 2013). As such, the reliability of estimates for the intake based on consumption estimates derived from individual population groups of a limited sample size should be interpreted with caution. These values are marked with an asterisk in the relevant data tables.

3.0 FOOD USAGE DATA

3.1 Background Diet

All food codes and supplement codes identified as containing vitamin K based on the above-mentioned sources (FNDDS, SR 28, or published literature for foods; DSII, DSLD, and NHANES for dietary supplements) were selected from the NHANES 2017-2018 dataset (USDA, 2020; USDA ARS, 2021). Values for the following parameters were applied to food codes and supplements codes:

- MK-4;
- MK-7;
- Vitamin K2;
- Vitamin K1; and
- Total vitamin K.

The full list of food codes and supplement codes identified as containing MK-7, along with their associated MK-7 content (µg/100 g or mL), is provided in Appendix C. Results for this assessment are presented in Section 4.1.

[2] Statistical analysis and data management were conducted in DaDiet Software (Dazult Ltd., 2018). DaDiet Software is a web-based software tool that allows accurate estimate of exposure to nutrients and to substances added to foods, including contaminants, food additives and novel ingredients. The main input components are concentration (use level) data and food consumption data. Data sets are combined in the software to provide accurate and efficient exposure assessments.

3.2 Proposed Food Uses

The proposed food uses and use levels for MK-7 are summarized in Table 3.2-1. Food codes representative of each proposed food use were chosen from the NHANES 2017-2018 (CDC, 2021b). Food codes were grouped in food use categories according to Title 21, Section §170.3 of the *Code of Federal Regulations* (U.S. FDA, 2019a). If necessary, product-specific adjustment factors were developed for composite foods/mixtures based on data provided in the FNDDS (USDA ARS, 2020) or the Food Commodity Intake Database (U.S. EPA & USDA, 2021). All food codes included in the current intake assessment are listed in Appendix B. Results for this assessment are presented in Section 4.2.

Table 3.2-1 Summary of the Individual Proposed Food Uses and Use Levels for MK-7 in the U.S.

Food Category (21 CFR §170.3) (U.S. FDA, 2020a)	Food Uses	Proposed MK-7 Use Level (mcg/serving)	RACC[a] (g or mL)	Proposed MK-7 Use Levels (mcg/100 mL or 100 g)
Beverages and Beverage Bases	Soft drinks	10	360 mL	2.8
Breakfast Cereals	Breakfast cereals			
	Puffed cereals	10	15 g	66.7
	High-fiber cereals	10	40 g	25.0
	Biscuit-type cereals	10	60 g	16.7
Cheeses	Cottage cheese	10	110 g	9.1
	Low-fat cheese	10	30 g	33.3
Fats and Oils	Low fat margarine	10	15 mL	66.7
	Low fat mayonnaise	10	15 g	66.7
	Olive oil	10	15 mL	66.7
Frozen Dairy Desserts	Frozen yogurt	10	90 g	11.1
	Ice cream	10	130 g	7.7
Grain Products and Pastas	Cereal bars	10	40 g	25.0
	Pasta	10	140 g	7.1
	Pizza crust	10	55 g	18.2
Milk	Milk	10	240 mL	4.2
Milk Products	Other milks	10	240 mL	4.2
	Creams	10	15 mL	66.7
	Yogurt	10	170 g	5.9
	Yogurt drinks	10	90 to 207 g	11.1
	Fromage frais[b]	10	110 g	9.1
Processed Fruits and Fruit Juices	Fruit juices	10	240 mL	4.2
Processed Vegetables and Vegetables Juices	Vegetable juices	10	240 mL	4.2

CFR = *Code of Federal Regulations*; MK-7 = menaquinone-7; RACC = Reference Amounts Customarily Consumed per Eating Occasion; U.S. = United States.

[a] RACC based on values established in 21 CFR §101.12 (U.S. FDA, 2020b).

[b] No food codes were identified; however, consumption is expected to be similar to yogurts, therefore no change is expected versus the intakes calculated amongst consumers.

[c] Lowest RACC value was used to determine the use level per 100 mL or 100 g.

Values are rounded as relevant.

3.3 Cumulative Intake

The cumulative intake assessments of MK-7, vitamin K2, and total vitamin K considered current dietary sources from the background diet (see Section 4.1) and the proposed food uses of MK-7 in food and beverage categories (see Section 4.2), combined. Values were summed when there was overlap from background (which was typically naturally present) and proposed levels. Results for this assessment are presented in Section 4.3. Intakes of MK-4 and vitamin K1 were not included in the cumulative intakes assessment as they are not part of the proposed uses.

4.0 FOOD SURVEY RESULTS

Estimates for the intakes of all vitamin K isomers (MK-4, MK-7, vitamin K1, vitamin K2, and total vitamin K) from the background diet are provided in Section 4.1. The estimated daily intakes for MK-7 alone under the proposed conditions of use are provided in Section 4.2. The cumulative intakes of MK-7 vitamin K2 and total vitamin K considering the background and proposed uses of MK-7 are provided in Section 4.3. Finally, the impact of the proposed conditions of use on estimated intakes of MK-7, vitamin K2 and total vitamin K associated with the proposed conditions of use is examined in Section 4.4. In all cases, dietary intake estimates are presented on an absolute basis (µg/person/day) and on a body weight basis (µg/kg body weight/day).

4.1 Estimated Daily Intake from the Background Diet in the U.S.

4.1.1 MK-4

Table 4.1.1-1 summarizes estimated daily intakes of MK-4 (µg/person/day) from the background diet (foods and dietary supplements) in the U.S. population group. Nearly all individuals surveyed in the NHANES over 1 year of age were consumers of MK-4 (99.4 to 100% consumers); thus, the resulting *per capita* and the consumer-only intakes are very similar. The consumer-only intakes are discussed below.

Among the total population (ages 1 and older), mean and 90th percentile intakes of MK-4 from the background diet were determined to be 19 and 33 µg/person/day, respectively. Of the individual population groups, males ages 19 years and older were determined to have the greatest mean and 90th percentile intakes of MK-4 from the background diet, at 22 and 40 µg/person/day, respectively. Infants (7 to 11 months) had the lowest statistically reliable mean and 90th percentile intake of MK-4, at 6 and 13 µg/person/day (see Table 4.1.1-1).

Table 4.1.1-1 Summary of the Estimated Daily Intakes of MK-4 from the Background Diet (Food and Dietary Supplements) in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/day)		Consumer-Only Intake (µg/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
Infants						
0 to 6 months	<1*	<1*	11.5	18	1*	2*
7 to 11 months	5	13	87.0	106	6	13
Children						
1 to 3 years	12	21	99.9	414	12	21
4 to 8 years	15	26	100	530	15	26
Females						
9 to 13 years	15	26	100	307	15	26
14 to 18 years	14	26	99.4	281	14	26
19 years and older	19	27	99.8	2,212	19	28
Males						
9 to 13 years	17	32	100	282	17	32
14 to 18 years	19	32	99.7	280	19	32
19 years and older	22	40	99.7	2,019	22	40
Total Population						
All ages (≥1 year)	19	33	99.8	6,325	19	33

MK-4 = menaquinone-4; n = sample size; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.

On a body weight basis, the total population (ages 1 and older) mean and 90th percentile consumer-only intakes of MK-4 were determined to be 0.3 and 0.6 µg/kg body weight/day, respectively. Among the individual population groups, children (ages 1 to 3 years old) were identified as having the highest mean and 90th percentile consumer-only intakes of any population group, of 0.9 and 1.5 µg/kg body weight/day, respectively. Females ages 14 to 18 years had the lowest statistically reliable mean and 90th percentile of 0.2 and 0.4 µg/kg body weight/day (see Table 4.1.1-2).

Table 4.1.1-2 Summary of the Estimated Daily Per Kilogram Body Weight Intake of MK-4 from the Background Diet in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/kg bw/day)		Consumer-Only Intake (µg/kg bw/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
Infants						
0 to 6 months	<0.1*	<0.1*	11.5	18	0.2*	0.2*
7 to 11 months	0.5	1.4	87.0	106	0.6	1.5
Children						
1 to 3 years	0.9	1.5	99.9	404	0.9	1.5
4 to 8 years	0.6	1.2	100	529	0.6	1.2
Females						
9 to 13 years	0.3	0.7	100	306	0.3	0.7
14 to 18 years	0.2	0.4	99.4	279	0.2	0.4
19 years and older	0.3	0.4	99.8	2,189	0.3	0.4
Males						
9 to 13 years	0.4	0.8	100	280	0.4	0.8
14 to 18 years	0.3	0.5	99.7	279	0.3	0.5

Table 4.1.1-2 Summary of the Estimated Daily Per Kilogram Body Weight Intake of MK-4 from the Background Diet in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/kg bw/day)		Consumer-Only Intake (µg/kg bw/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
19 years and older	0.3	0.5	99.7	2,003	0.3	0.5
Total Population						
All ages (≥1 year)	0.3	0.6	99.8	6,269	0.3	0.6

bw = body weight; MK-4 = menaquinone-4; n = sample size; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.

4.1.2 MK-7

Table 4.1.2-1 summarizes estimated daily intakes of MK-7 (µg/person/day) from the background diet (foods and dietary supplements) in the U.S. population group. It is noted that among adults (males and females) ages 19 years and older, and also amongst the total population ages 1 year and over, the mean value is higher than the 90th percentile estimate. This pattern of intake is related to the consumption of dietary supplements with extremely high values of MK-7 (see Appendix C for the full list of dietary supplements and related concentration values). The consumption of these supplement products has skewed the mean values, resulting in an artificially high estimates. These values should be interpreted with caution.

The mean and 90th percentile consumer only intakes of MK-7 among the total population (ages 1 and older), and the individual age groups, were 1.1 and 0.4 µg/person/day (see Table 4.1.2-1). Mean values range from 0.1 to 0.2 µg/person/day amongst most groups, with the exception of female and male adults, at up to 1.9 and 0.7 µg/person/day. Estimated 90th percentile values ranged from 0.2 to 0.5 µg/person/day amongst the individual age groups.

Table 4.1.2-1 Summary of the Estimated Daily Intakes of MK-7 from the Background Diet (Food and Dietary Supplements) in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/day)		Consumer-Only Intake (µg/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
Infants						
0 to 6 months	0	0	0.0	0	0	0
7 to 11 months	<0.1	0.1*	33.2	36	0.1	0.1*
Children						
1 to 3 years	0.1	0.2	65.4	252	0.1	0.2
4 to 8 years	0.1	0.3	64.9	332	0.1	0.4
Females						
9 to 13 years	0.1	0.2	71.1	192	0.1	0.3
14 to 18 years	0.1	0.2	63.3	168	0.1	0.3
19 years and older	1.3¥	0.3	69.8	1,399	1.9¥	0.4
Males						
9 to 13 years	0.1	0.2	60.9	165	0.1	0.3
14 to 18 years	0.1	0.2	66.7	182	0.2	0.4
19 years and older	0.5¥	0.4	68.9	1,212	0.7¥	0.5
Total Population						
All ages (≥1 year)	0.7¥	0.3	68.4	3,902	1.1¥	0.4

Table 4.1.2-1 Summary of the Estimated Daily Intakes of MK-7 from the Background Diet (Food and Dietary Supplements) in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/day)		Consumer-Only Intake (µg/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile

MK-7 = menaquinone-7; n = sample size; na = not available; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.

* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements (mean n<30; 90th percentile n<80).

[¥] Results skewed by consumption of high MK-7-containing dietary supplements by mean consumers.

When the intakes of MK-7 were expressed on a body weight basis, the estimated values by all age groups were less than <0.1 µg/kg body weight/day (see Table 4.1.2-2).

Table 4.1.2-2 Summary of the Estimated Daily Per Kilogram Body Weight Intake of MK-7 from the Background Diet in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/kg bw/day)		Consumer-Only Intake (µg/kg bw/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
Infants						
0 to 6 months	na	na	0.0	0	na	na
7 to 11 months	<0.1	<0.1*	33.2	36	<0.1	<0.1*
Children						
1 to 3 years	<0.1	<0.1	66.1	249	<0.1	<0.1
4 to 8 years	<0.1	<0.1	64.9	331	<0.1	<0.1
Females						
9 to 13 years	<0.1	<0.1	71.2	192	<0.1	<0.1
14 to 18 years	<0.1	<0.1	62.9	166	<0.1	<0.1
19 years and older	<0.1	<0.1	69.8	1,384	<0.1	<0.1
Males						
9 to 13 years	<0.1	<0.1	60.9	164	<0.1	<0.1
14 to 18 years	<0.1	<0.1	67.0	182	<0.1	<0.1
19 years and older	<0.1	<0.1	68.8	1,200	<0.1	<0.1
Total Population						
All ages (≥1 year)	<0.1	<0.1	68.4	3,868	<0.1	<0.1

bw = body weight; MK-7 = menaquinone-7; n = sample size; na = not available; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.

* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements (mean n<30; 90th percentile n<80).

4.1.3 Vitamin K2

Table 4.1.3-1 summarizes estimated daily intakes of vitamin K2 (µg/person/day) from the background diet (foods and dietary supplements) in the U.S. population group. The percent consumers of vitamin K2 was high amongst all age groups over 1 year of age (99.4 to 100% consumers). The consumer-only intakes are discussed below.

Among the total population (ages 1 and older), mean and 90th percentile intakes of vitamin K2 from the background diet were determined to be 114 and 229 µg/person/day, respectively. Of the individual

population groups, children (ages 1 to 3 years old) were determined to have the greatest mean and 90th percentile intakes of vitamin K2 from the background diet, at 131 and 260 µg/person/day, respectively.

Table 4.1.3-1 Summary of the Estimated Daily Intakes of Vitamin K2 from the Background Diet (Food and Dietary Supplements) in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/day)		Consumer-Only Intake (µg/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
Infants						
0 to 6 months	<1*	<1*	11.0	18	3*	9*
7 to 11 months	50	184	87.0	106	58	188
Children						
1 to 3 years	131	260	99.9	414	131	260
4 to 8 years	113	217	100	530	113	217
Females						
9 to 13 years	107	213	100	307	107	213
14 to 18 years	86	177	99.4	281	86	177
19 years and older	105	205	99.8	2,212	105	205
Males						
9 to 13 years	108	206	100	282	108	206
14 to 18 years	120	240	99.7	280	121	240
19 years and older	125	255	99.7	2,019	125	255
Total Population						
All ages (≥1 year)	114	229	99.8	6,325	114	229

n = sample size; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.
* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements (mean n<30; 90th percentile n<80).

On a body weight basis, the total population (ages 1 and older) mean and 90th percentile consumer-only intakes of vitamin K2 were determined to be 2.0 and 4.2 µg/kg body weight/day, respectively. Among the individual population groups, children (ages 1 to 3 years old) were identified as having the highest mean and 90th percentile consumer-only intakes of any population group, of 9.8 and 19.9 µg/kg body weight/day, respectively. Females ages 19 years and older had the lowest statistically reliable intakes of vitamin K2 of 1.4 and 2.8 µg/kg body weight/day, respectively (see Table 4.1.3-2).

Table 4.1.3-2 Summary of the Estimated Daily Per Kilogram Body Weight Intake of Vitamin K2 from the Background Diet in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/kg bw/day)		Consumers -Only Intake (µg/kg bw/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
Infants						
0 to 6 months	<0.1*	<0.1*	11.0	18	0.4*	1.1*
7 to 11 months	5.6	20.5	87.0	106	6.5	23.0
Children						
1 to 3 years	9.8	19.9	99.9	404	9.8	19.9
4 to 8 years	4.8	9.6	100	529	4.8	9.6
Females						
9 to 13 years	2.5	5.5	100	306	2.5	5.5

Table 4.1.3-2 Summary of the Estimated Daily Per Kilogram Body Weight Intake of Vitamin K2 from the Background Diet in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/kg bw/day)		Consumers -Only Intake (µg/kg bw/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
14 to 18 years	1.4	3.0	99.4	279	1.4	3.0
19 years and older	1.4	2.8	99.8	2,189	1.4	2.8
Males						
9 to 13 years	2.5	5.6	100	280	2.5	5.6
14 to 18 years	1.8	3.2	99.7	279	1.8	3.2
19 years and older	1.4	3.1	99.7	2,003	1.4	3.1
Total Population						
All ages (≥1 year)	2.0	4.2	99.8	6,269	2.0	4.2

bw = body weight; n = sample size; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.
* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements (mean n<30; 90th percentile n<80).

4.1.4 Vitamin K1

Table 4.1.4-1 summarizes estimated daily intakes of vitamin K1 (µg/person/day) from the background diet (foods and dietary supplements) in the U.S. population group. All NHANES participants were identified as consumers of vitamin K1. As such, the *per capita* and consumer only intakes are identical.

Among the total population (ages 1 and older), mean and 90th percentile intakes of vitamin K1 from the background diet were determined to be 115 and 229 µg/person/day, respectively. Of the individual population groups, males (ages 19 years and older) were determined to have the greatest mean and 90th percentile intakes of vitamin K1 from the background diet, at 130 and 237 µg/person/day, respectively. Infants (<6 months old) had the lowest mean and 90th percentile intake of vitamin K1, at 34 and 72 µg/person/day (see Table 4.1.4-1).

Table 4.1.4-1 Summary of the Estimated Daily Intakes of Vitamin K1 from the Background Diet (Food and Dietary Supplements) in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/day)		Consumer-Only Intake (µg/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
Infants						
0 to 6 months	34	72	100	177	34	72
7 to 11 months	50	85	100	124	50	85
Children						
1 to 3 years	51	87	100	415	51	87
4 to 8 years	59	107	100	530	59	107
Females						
9 to 13 years	81	155	100	307	81	155
14 to 18 years	82	135	100	283	82	135
19 years and older	129	263	100	2,215	129	263
Males						
9 to 13 years	71	118	100	282	71	118
14 to 18 years	81	140	100	281	81	140
19 years and older	130	237	100	2,025	130	237

Table 4.1.4-1 Summary of the Estimated Daily Intakes of Vitamin K1 from the Background Diet (Food and Dietary Supplements) in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/day)		Consumer-Only Intake (µg/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
Total Population						
All ages (≥1 year)	115	229	100	6,338	115	229

n = sample size; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.

On a body weight basis, the total population (ages 1 and older) mean and 90th percentile intakes of vitamin K1 were determined to be 1.8 and 3.5 µg/kg body weight/day, respectively. Among the individual population groups, infants (<6 months old) were identified as having the highest mean and 90th percentile consumer-only intakes of any population group, of 5.4 and 11.2 µg/kg body weight/day, respectively. Males (ages 14 to 18 old) had the lowest mean and 90th percentile consumer-only intakes of 1.2 and 2.2 µg/kg body weight/day, respectively (see Table 4.1.4-2).

Table 4.1.4-2 Summary of the Estimated Daily Per Kilogram Body Weight Intake of Vitamin K1 from the Background Diet in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/kg bw/day)		Consumer-Only Intake (µg/kg bw/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
Infants						
0 to 6 months	5.4	11.2	100	177	5.4	11.2
7 to 11 months	5.4	9.4	100	124	5.4	9.4
Children						
1 to 3 years	3.7	7.0	100	405	3.7	7.0
4 to 8 years	2.5	4.8	100	529	2.5	4.8
Females						
9 to 13 years	1.8	3.3	100	306	1.8	3.3
14 to 18 years	1.4	2.4	100	281	1.4	2.4
19 years and older	1.8	3.7	100	2,192	1.8	3.7
Males						
9 to 13 years	1.6	3.1	100	280	1.6	3.1
14 to 18 years	1.2	2.2	100	280	1.2	2.2
19 years and older	1.5	3.1	100	2,009	1.5	3.1
Total Population						
All ages (≥1 year)	1.8	3.5	100	6,282	1.8	3.5

bw = body weight; n = sample size; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.

4.1.5 Total Vitamin K

Table 4.1.5-1 summarizes estimated daily intakes of total vitamin K (µg/person/day) from the background diet (foods and dietary supplements) in the U.S. population group. All NHANES participants were identified as consumers of vitamin K.

Among the total population (ages 1 and older), mean and 90th percentile intakes of total vitamin K from the background diet were determined to be 229 and 404 µg/person/day, respectively. Of the individual population groups, males (ages 19 years and older) were determined to have the greatest mean and

90th percentile intakes of total vitamin K from the background diet, at 254 and 469 µg/person/day, respectively. Infants (<6 months old) had the lowest mean and 90th percentile intake of total vitamin K, at 34 and 72 µg/person/day (see Table 4.1.5-1).

Table 4.1.5-1 Summary of the Estimated Daily Intakes of Total Vitamin K from the Background Diet (Food and Dietary Supplements) in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/day)		Consumer-Only Intake (µg/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
Infants						
0 to 6 months	34	72	100	177	34	72
7 to 11 months	100	223	100	124	100	223
Children						
1 to 3 years	182	312	100	415	182	312
4 to 8 years	172	289	100	530	172	289
Females						
9 to 13 years	188	322	100	307	188	322
14 to 18 years	168	281	100	283	168	281
19 years and older	235	401	100	2,215	235	401
Males						
9 to 13 years	179	303	100	282	179	303
14 to 18 years	201	350	100	281	201	350
19 years and older	254	469	100	2,025	254	469
Total Population						
All ages (≥1 year)	229	404	100	6,338	229	404

n = sample size; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.

On a body weight basis, the total population (ages 1 and older) mean and 90th percentile intakes of vitamin K were determined to be 3.8 and 7.3 µg/kg body weight/day, respectively. Among the individual population groups, children (ages 1 to 3 years old) were identified as having the highest mean intakes of any population group, of 13.5 µg/kg body weight/day, while infants ages 7 to 11 months had the highest 90th percentile intakes of 24.7 µg/kg body weight/day. Females (14 to 18 years old) had the lowest mean and 90th percentile consumer-only intakes of 2.7 and 4.7 µg/kg body weight/day, respectively (see Table 4.1.5-2).

Table 4.1.5-2 Summary of the Estimated Daily Per Kilogram Body Weight Intake of Total Vitamin K from the Background Diet in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/kg bw/day)		Consumer-Only Intake (µg/kg bw/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
Infants						
0 to 6 months	5.5	11.2	100	177	5.5	11.2
7 to 11 months	11.1	24.7	100	124	11.1	24.7
Children						
1 to 3 years	13.5	24.0	100	405	13.5	24.0
4 to 8 years	7.2	12.3	100	529	7.2	12.3
Females						
9 to 13 years	4.3	7.7	100	306	4.3	7.7
14 to 18 years	2.7	4.7	100	281	2.7	4.7
19 years and older	3.2	5.7	100	2,192	3.2	5.7
Males						
9 to 13 years	4.1	8.4	100	280	4.1	8.4
14 to 18 years	2.9	5.0	100	280	2.9	5.0
19 years and older	2.9	5.1	100	2,009	2.9	5.1
Total Population						
All ages (≥1 year)	3.8	7.3	100	6,282	3.8	7.3

bw = body weight; n = sample size; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.

4.2 Estimated Daily Intake of MK-7 from All Proposed Food Uses in the U.S.

Table 4.2-1 summarizes the estimated total intake of MK-7 (µg/person/day) from all proposed food uses in the U.S. population. Table 4.2-2 presents this data on a per kilogram body weight basis (µg/kg body weight/day). The percentage of consumers was high among all age groups evaluated in the current intake assessment [with the exception of infants ages 0 to 6 months (3.1% consumers)], whereby more than 65.9% of the population groups consisted of consumers of food products in which MK-7 is currently proposed for use (see Table 4.2-1). Children (ages 1 to 3 years old) and females (ages 9 to 13 years old) had the greatest proportion of consumers at 98.8%.

Among the total population (ages 1 and older), the mean and 90th percentile consumer-only intakes of MK-7 were determined to be 24.7 and 47.8 µg/person/day, respectively (see Table 4.2-1). Of the individual population groups, males (ages 14 to 18 years old) were determined to have the greatest mean and 90th percentile consumer-only intakes of MK-7 on an absolute basis, at 32.6 and 63.2 µg/person/day, respectively, while infants (ages 7 to 11 months) had the lowest statistically reliable estimates of 11.1 and 34.9 µg/person/day (intakes by infants were not statistically reliable due to the low number of consumers).

Table 4.2-1 Summary of the Estimated Daily Intake of MK-7 from Proposed Food Uses in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/day)		Consumer-Only Intake (µg/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
Infants						
0 to 6 months	<0.1*	na	3.1	9	1.2*	2.7*
7 to 11 months	7.3	27.5	65.	81	11.1	34.9

Table 4.2-1 Summary of the Estimated Daily Intake of MK-7 from Proposed Food Uses in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/day)		Consumer-Only Intake (µg/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
Children						
1 to 3 years	25.9	42.4	98.8	408	26.2	42.6
4 to 8 years	25.9	46.8	97.9	522	26.5	46.8
Females						
9 to 13 years	26.9	52.6	98.8	301	27.2	52.6
14 to 18 years	19.5	45.3	94.9	265	20.6	45.3
19 years and older	19.8	42.4	92.6	2,026	21.4	43.4
Males						
9 to 13 years	27.7	48.2	97.7	274	28.4	48.2
14 to 18 years	30.8	58.2	94.5	264	32.6	63.2
19 years and older	24.7	51.7	92.2	1,831	26.8	53.3
Total Population						
All ages (≥1 year)	23.1	46.8	93.5	5,891	24.7	47.8

MK-7 = menaquinone-7; n = sample size; na = not available; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.
* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements (mean n<30; 90th percentile n<80).

On a body weight basis, the total population (ages 1 and older) mean and 90th percentile consumer-only intakes of MK-7 were determined to be 0.4 and 1.0 µg/kg body weight/day, respectively. Among the individual population groups, children (ages 1 to 3 years old) were identified as having the highest mean and 90th percentile consumer-only intakes of any population group, of 1.9 and 3.3 µg/kg body weight/day, respectively. Females and males (ages 19 years and older) had the lowest mean and 90th percentile consumer-only intakes of 0.3 and 0.6 µg/kg body weight/day, respectively (see Table 4.2-2).

Table 4.2-2 Summary of the Estimated Daily Per Kilogram Body Weight Intake of MK-7 from Proposed Food Uses in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/kg bw/day)		Consumer-Only Intake (µg/kg bw/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
Infants						
0 to 6 months	<0.1*	na	3.1	9	0.2*	0.4*
7 to 11 months	0.8	3.0	65.9	81	1.2	4.4
Children						
1 to 3 years	1.9	3.3	98.8	398	1.9	3.3
4 to 8 years	1.1	1.9	97.9	521	1.1	1.9
Females						
9 to 13 years	0.6	1.2	98.8	300	0.6	1.2
14 to 18 years	0.3	0.6	94.8	263	0.3	0.6
19 years and older	0.3	0.6	92.7	2,006	0.3	0.6
Males						
9 to 13 years	0.7	1.4	97.7	272	0.7	1.4
14 to 18 years	0.5	1.0	94.5	263	0.5	1.0

Table 4.2-2 Summary of the Estimated Daily Per Kilogram Body Weight Intake of MK-7 from Proposed Food Uses in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/kg bw/day)		Consumer-Only Intake (µg/kg bw/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
19 years and older	0.3	0.6	92.3	1,819	0.3	0.6
Total Population						
All ages (≥1 year)	0.4	0.9	93.6	5,842	0.4	1.0

bw = body weight; MK-7 = menaquinone-7; n = sample size; na = not available; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.

* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements (mean n<30; 90th percentile n<80).

The total U.S. population (ages 1 year and older) was identified as being significant consumers of milk (39 to 79% consumers), breakfast cereals (26 to 59% consumers), soft drinks (21 to 57% consumers), fruit juices (19 to 56% consumers), and pizza crusts (17 to 47% consumers).

In terms of contribution to total mean intake of MK-7, milk (which contributed up to 43% to total mean intakes) and soft drinks (which contributed up to 28% to total mean intakes) were the 2 main sources of intake across all population groups. Fruit juices, breakfast cereals, cottage cheese, low fat cheese, low fat margarine, low fat mayonnaise, olive oil, frozen yogurt, ice cream, cereal bars, pasta, pizza crust, other milks, creams, yogurt, yogurt drinks, and vegetable juices all individually contributed ≤18% to total mean MK-7 intakes across all population groups.

4.3 Cumulative Estimated Daily Intake from the Background Diet and Proposed Uses in the U.S.

4.3.1 MK-7

Cumulative estimated daily intakes of MK-7 from the background diet (per Section 4.1.2) and proposed food uses (per Section 4.2) combined, are summarized in this section. Table 4.3.1-1 presents this information on an absolute basis (µg/person/day), while Table 4.3.1-2 presents this information on a body weight basis (µg/kg body weight/day).

In the total population (ages 1 and older), the cumulative mean and 90th percentile consumer-only estimated daily intakes of MK-7 from the background diet and proposed food uses were determined to be 24.3 and 47.6 µg/person/day. Among individual population groups, males (ages 14 to 18 years) were identified as having the highest mean and 90th percentile consumer-only intake of MK-7, at 31.6 and 60.6 µg/person/day. Infants (7 to 11 months old) had the lowest statistically reliable mean and 90th percentile consumer-only intakes of 10.8 and 34.9 µg/person/day, respectively (see Table 4.3.1-1).

Table 4.3.1-1 Cumulative Estimated Daily Intake of MK-7 from the Background Diet and Proposed Use in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/day)		Consumer-Only Intake (µg/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
Infants						
0 to 6 months	<0.1*	na	3.1	9	1.2*	2.7*
7 to 11 months	7.3	27.5	68.2	83	10.8	34.9
Children						
1 to 3 years	25.9	42.4	99.0	410	26.2	42.6
4 to 8 years	26.0	46.9	99.1	526	26.2	46.9
Females						
9 to 13 years	27.0	52.7	99.6	306	27.1	52.7
14 to 18 years	19.6	45.5	97.9	275	20.0	45.5
19 years and older	21.2	43.3	97.5	2,127	21.7	43.3
Males						
9 to 13 years	27.8	48.3	99.3	279	28.0	48.3
14 to 18 years	30.9	58.3	97.8	273	31.6	60.6
19 years and older	25.2	52.5	97.7	1,932	25.7	53.3
Total Population						
All ages (≥1 year)	23.8	47.2	97.9	6,128	24.3	47.6

MK-7 = menaquinone-7; n = sample size; na = not available; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.
* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements (mean n<30; 90th percentile n<80).

On a body weight basis, the total population (ages 1 and older) mean and 90th percentile consumer-only intakes of MK-7 were determined to be 0.4 and 1.0 µg/kg body weight/day, respectively. Among the individual population groups, children (ages 1 to 3 years old) were identified as having the highest mean and 90th percentile consumer-only intakes of any population group, of 1.9 and 4.4 µg/kg body weight/day, respectively. Females ages 14 years and over and adults (females and males) ages 19 years and over had the lowest mean and 90th percentile consumer-only intakes of 0.3 and 0.6 µg/kg body weight/day, respectively (see Table 4.3.1-2).

Table 4.3.1-2 Cumulative Estimated Daily Per Kilogram Body Weight Intake of MK-7 from the Background Diet and Proposed Use in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/kg bw/day)		Consumer-Only Intake (µg/kg bw/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
Infants						
0 to 6 months	<0.1*	na	3.1	9	0.2*	0.4*
7 to 11 months	0.8	3.0	68.2	83	1.2	4.4
Children						
1 to 3 years	1.9	3.3	98.9	400	1.9	3.3
4 to 8 years	1.1	1.9	99.1	525	1.1	1.9
Females						
9 to 13 years	0.6	1.2	99.6	305	0.6	1.2
14 to 18 years	0.3	0.6	97.9	273	0.3	0.6

Table 4.3.1-2 Cumulative Estimated Daily Per Kilogram Body Weight Intake of MK-7 from the Background Diet and Proposed Use in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/kg bw/day)		Consumer-Only Intake (µg/kg bw/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
19 years and older	0.3	0.6	97.5	2,105	0.3	0.6
Males						
9 to 13 years	0.7	1.4	99.3	277	0.7	1.4
14 to 18 years	0.5	1.0	97.8	272	0.5	1.0
19 years and older	0.3	0.6	97.7	1,916	0.3	0.6
Total Population						
All ages (≥1 year)	0.4	0.9	97.9	6,073	0.4	1.0

bw = body weight; MK-7 = menaquinone-7; n = sample size; na = not available; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.
* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements (mean n<30; 90th percentile n<80).

4.3.2 Vitamin K2

Cumulative estimated daily intakes of vitamin K2 from the background diet (per Section 4.1.3) and the proposed food uses of MK-7 (as vitamin K2) combined, are summarized in Table 4.3.2-1.

In the total population (ages 1 and older), the cumulative mean and 90th percentile consumer-only estimated daily intakes of vitamin K2 from the background diet and proposed food uses were determined to be 137 and 262 µg/person/day. Among individual population groups, children (ages 1 to 3 years) were identified as having the highest mean and 90th percentile consumer-only intake of vitamin K2, at 157 and 302 µg/person/day. Infants (7 to 11 months) had the lowest statistically reliable mean intakes of 66 µg/person/day, while males ages 9 to 13 years had the lowest statistically reliable 90th percentile intakes of 235 µg/person/day.

Table 4.3.2-1 Cumulative Estimated Daily Intake of Vitamin K2 from the Background Diet and Proposed Use in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/day)		Consumer-Only Intake (µg/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
Infants						
0 to 6 months	<1*	<1*	12.1	21	3*	9*
7 to 11 months	58	203	88.1	108	66	241
Children						
1 to 3 years	157	302	99.9	414	157	302
4 to 8 years	139	252	100	530	139	252
Females						
9 to 13 years	134	242	100	307	134	242
14 to 18 years	105	187	100	283	105	187
19 years and older	125	230	99.8	2,213	125	230
Males						
9 to 13 years	136	235	100	282	136	235
14 to 18 years	151	275	100	281	151	275

Table 4.3.2-1 Cumulative Estimated Daily Intake of Vitamin K2 from the Background Diet and Proposed Use in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/day)		Consumer-Only Intake (µg/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
19 years and older	149	295	99.9	2,022	149	295
Total Population						
All ages (≥1 year)	137	261	99.9	6,332	137	262

n = sample size; na = not available; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.
* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements (mean n<30; 90th percentile n<80).

On a body weight basis, the total population (ages 1 and older) mean and 90th percentile consumer-only intakes of vitamin K2 were determined to be 2.5 and 4.9 µg/kg body weight/day, respectively. Among the individual population groups, children (ages 1 to 3 years old) were identified as having the highest mean intakes of any population group, of 11.7, while infants ages 7 to 11 months had the highest 90th percentile values of 24.9 µg/kg body weight/day. Female adults ages 19 years and older had the lowest statistically reliable results of 1.7 and 3.2 µg/kg body weight/day (see Table 4.3.2-2).

Table 4.3.2-2 Cumulative Estimated Daily Per Kilogram Body Weight Intake of Vitamin K2 from the Background Diet and Proposed Use in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/kg bw/day)		Consumer-Only Intake (µg/kg bw/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
Infants						
0 to 6 months	0.1*	na	12.1	21	0.4*	1.1*
7 to 11 months	6.5	24.3	88.1	108	7.3	24.9
Children						
1 to 3 years	11.7	22.9	99.9	404	11.7	22.9
4 to 8 years	5.9	11.0	100	529	5.9	11.0
Females						
9 to 13 years	3.1	6.5	100	306	3.1	6.5
14 to 18 years	1.7	3.3	100	281	1.7	3.3
19 years and older	1.7	3.2	99.8	2,190	1.7	3.2
Males						
9 to 13 years	3.2	6.5	100	280	3.2	6.5
14 to 18 years	2.2	4.4	100	280	2.2	4.4
19 years and older	1.7	3.5	99.9	2,006	1.7	3.5
Total Population						
All ages (≥1 year)	2.4	4.9	99.9	6,276	2.5	4.9

bw = body weight; n = sample size; na = not available; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.
* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements (mean n<30; 90th percentile n<80).

4.3.3 Total Vitamin K

Cumulative estimated daily intakes of total vitamin K from the background diet and proposed food uses, combined, are summarized in Table 4.3.3-1.

In the total population (ages 1 and older), the cumulative mean and 90th percentile estimated daily intakes of total vitamin K from the background diet and proposed food uses were determined to be 252 and 436 µg/person/day. Among individual population groups, males ages 19 years and older were identified as having the highest mean and 90th percentile consumer-only intake of total vitamin K, at 278 and 505 µg/person/day. Infants (0 to 6 months) had the lowest estimated intakes at 34 and 72 µg/person/day at the mean and 90th percentile (see Table 4.3.3-1).

Table 4.3.3-1 Cumulative Estimated Daily Intake of Total Vitamin K from the Background Diet and Proposed Use in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/day)		Consumer-Only Intake (µg/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
Infants						
0 to 6 months	34	72	100	177	34	72
7 to 11 months	107	250	100	124	107	250
Children						
1 to 3 years	208	338	100	415	208	338
4 to 8 years	198	326	100	530	198	326
Females						
9 to 13 years	214	345	100	307	214	345
14 to 18 years	188	300	100	283	188	300
19 years and older	254	427	100	2,215	254	427
Males						
9 to 13 years	207	334	100	282	207	334
14 to 18 years	232	396	100	281	232	396
19 years and older	279	505	100	2,025	278	505
Total Population						
All ages (≥1 year)	252	436	100	6,338	252	436

n = sample size; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.

On a body weight basis, the total population (ages 1 and older) mean and 90th percentile consumer-only intakes of vitamin K were determined to be 4.2 and 8.0 µg/kg body weight/day, respectively. Among the individual population groups, children (ages 1 to 3 years old) were identified as having the highest mean and 90th percentile consumer-only intakes of any population group, of 15.4 and 27.5 µg/kg body weight/day, respectively. Females (ages 14 to 18 years) had the lowest mean and 90th percentile consumer-only intakes of 3.1 and 5.0 µg/kg body weight/day, respectively (see Table 4.3.3-2).

Table 4.3.3-2 Cumulative Estimated Daily Per Kilogram Body Weight Intake of Vitamin K from the Background Diet and Proposed Use in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (µg/kg bw/day)		Consumer-Only Intake (µg/kg bw/day)			
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile
Infants						
0 to 6 months	5.5	11.2	100	177	5.5	11.2
7 to 11 months	11.9	29.1	100	124	11.9	29.1
Children						
1 to 3 years	15.4	27.5	100	405	15.4	27.5
4 to 8 years	8.3	14.2	100	529	8.3	14.2
Females						
9 to 13 years	4.9	8.5	100	306	4.9	8.5
14 to 18 years	3.1	5.0	100	281	3.1	5.0
19 years and older	3.5	6.0	100	2,192	3.5	6.0
Males						
9 to 13 years	4.8	9.0	100	280	4.8	9.0
14 to 18 years	3.4	6.1	100	280	3.4	6.1
19 years and older	3.2	5.5	100	2,009	3.2	5.5
Total Population						
All ages (≥1 year)	4.2	8.0	100	6,282	4.2	8.0

bw = body weight; n = sample size; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.

4.4 Impact of the Proposed Use of MK-7 on Absolute Intakes of Vitamin K in the U.S. Population

This section examines the impact of the proposed uses of MK-7 on the background intakes of this vitamin K isomer. As MK-7 is a form of vitamin K2, the increase in total dietary intakes is also examined for vitamin K2 and total vitamin K (see Section 4.4.2 and 4.4.3).

4.4.1 MK-7

The absolute change in the consumer only mean and 90th percentile estimated daily intakes of MK-7 in the U.S. population from the introduction of the proposed uses of MK-7 in foods and beverages is presented in Table 4.4.1-1. The absolute difference was calculated by subtracting intake estimates calculated in Section 4.1.2 (background diet only) from intake estimates calculated in Section 4.3.1 (background diet and proposed uses combined).

The proposed food uses for the MK-7 resulted in a notable increase by all age groups; the mean and 90th percentile intakes by the total cohort (1 year and over) increased by +23.2 and +47.2 µg/person/day, with a range of +19.8 to +31.4 µg/person/day at the mean and +42.4 to +60.2 µg/person/day at the 90th percentile amongst the individual population groups. The largest increase in MK-7 intakes (+60.2 µg/person/day at the 90th percentile) was observed in males (ages 14 to 18 years old). The increases in the estimated daily intakes by infants ages 7 to 11 months were lower, increasing by +10.7 and +34.8 µg/person/day at the mean and 90th percentile; intakes by infants up to 6 months were not statistically reliable. There was no clear pattern in the estimated changes according to gender.

These large increases in the absolutely estimated intakes were associated with the very low levels of this nutrient in the background diet, considering both foods and dietary supplements, as described in Section 4.1.2.

Table 4.4.1-1 Absolute Difference in Consumer-Only Estimated Daily Intakes of MK-7 from the Proposed Uses in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group/ Age Group (Years)	Background Diet (µg/day)[a]		Background Diet + Proposed (µg/day)[b]		Absolute Difference (µg/day)[c]	
	Mean	90th Percentile	Mean	90th Percentile	Mean	90th Percentile
Infants						
0 to 6 months	0	0	1.2*	2.7*	*+1.2**	*+2.7**
7 to 11 months	0.1*	0.1*	10.8	34.9	*+10.7*	*+34.8*
Children						
1 to 3 years	0.1	0.2	26.2	42.6	*+26.1*	*+42.4*
4 to 8 years	0.1	0.4	26.2	46.9	*+26.1*	*+46.5*
Females						
9 to 13 years	0.1	0.3	27.1	52.7	*+27.0*	*+52.4*
14 to 18 years	0.1	0.3	20.0	45.5	*+19.9*	*+45.1*
19 years and older	1.9[¥]	0.4	21.7	43.3	*+19.8*	*+42.9*
Males						
9 to 13 years	0.1	0.3	28.0	48.3	*+27.9*	*+48.0*
14 to 18 years	0.2	0.4	31.6	60.6	*+31.4*	*+60.2*
19 years and older	0.7[¥]	0.5	25.7	53.3	*+25.0*	*+52.8*
Total Population						
All ages (≥1 year)	1.1[¥]	0.4	24.3	47.6	*+23.2*	*+47.2*

EDI = estimated daily intake; MK-7 = menaquinone-7; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.

[a] Results from Section 4.1.2 (background diet only).

[b] Results from Section 4.3.1 (background diet and proposed food uses combined).

[c] Calculation: absolute different = (EDI background diet + proposed extension of use) - (EDI from background diet only).

* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements (mean n<30; 90th percentile n<80).

[¥] Results skewed by consumption of high MK-7-containing dietary supplements by mean consumers.

4.4.2 Vitamin K2

The absolute change in mean and 90th percentile estimated daily intakes of vitamin K2 in the U.S. population from the introduction of the proposed extensions of use of MK-7, as a surrogate for vitamin K2, is presented in Table 4.4.2-1. As above, the absolute difference was calculated by subtracting intake estimates calculated in the background diet only (see Section 4.1.3) from intake estimates calculated from the background diet and proposed uses combined (see Section 4.3.2).

The proposed food and beverage uses of MK-7 resulted in moderate increased estimated daily intakes of vitamin K2 by the total cohort over 1 year of age by +23 and +33 µg/person/day at the mean and 90th percentile, respectively. Amongst the individual population groups, the range of increases was +19 to +30 µg/person/day at the mean, and +10 to +42 µg/person/day at the 90th percentile. The intakes were lower at the mean amongst infants (no change to +8 µg/person/day) but were higher at the 90th percentile (up to +53 µg/person/day) when compared with the rest of the population. Overall, increases in vitamin K2 intakes were generally higher in males than females (see Table 4.4.2-1).

The overall impact of the proposed uses of MK-7 was not as notable when compared to the background intakes of this form of vitamin K (versus the increases noted for MK-7 as presented in Section 4.4.1 above) due to higher background intakes of vitamin K2.

Table 4.4.2-1 Absolute Difference in Consumer-Only Estimated Daily Intakes of Vitamin K2 from the Proposed Uses in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group/ Age Group (Years)	Background Diet (µg/day)[a]		Background Diet + Proposed (µg/day)[b]		Absolute Difference (µg/day)[c]	
	Mean	90th Percentile	Mean	90th Percentile	Mean	90th Percentile
Infants						
0 to 6 months	3*	9*	3*	9*	*NC*	*NC*
7 to 11 months	58	188	66	241	*+8*	*+53*
Children						
1 to 3 years	131	260	157	302	*+26*	*+42*
4 to 8 years	113	217	139	252	*+26*	*+35*
Females						
9 to 13 years	107	213	134	242	*+27*	*+29*
14 to 18 years	86	177	105	187	*+19*	*+10*
19 years and older	105	205	125	230	*+20*	*+25*
Males						
9 to 13 years	108	206	136	235	*+28*	*+29*
14 to 18 years	121	240	151	275	*+30*	*+35*
19 years and older	125	255	149	295	*+24*	*+40*
Total Population						
All ages (≥1 year)	114	229	137	262	*+23*	*+33*

EDI = estimated daily intake; NC = no change; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.
[a] Results from Section 4.1.3 (background diet only).
[b] Results from Section 4.3.2 (background diet and proposed food uses combined).
[c] Calculation: absolute different = (EDI background diet + proposed extension of use) - (EDI from background diet only).

4.4.3 Total Vitamin K

The absolute change in mean and 90th percentile estimated daily intakes of total vitamin K in the U.S. population from the introduction of the proposed use of MK-7 is presented in Table 4.4.3-1. The approach for calculating the difference was as per the sections above, whereby the background diet only estimates were taken from Section 4.1.5 above, and the cumulative intakes were taken from Section 4.3.3 above.

The proposed uses of MK-7 resulted in overall mean and 90th percentile increases in the intakes of total vitamin K of +23 and +32 µg/person/day, respectively, among the total cohort over 1 year of age. Considering the individual population groups, the absolute difference ranged from +19 to +31 µg/person/day at the mean, and +19 to +46 µg/person/day at the 90th percentile. The largest increase in total vitamin K intakes (+46 µg/person/day) was observed in males (ages 14 to 18 years old). There was no change in dietary intakes of MK-7 in infants (<6 months old); while the infants ages 7 to 11 months increased by +7 and +27 µg/person/day at the mean and 90th percentile, respectively. In population groups evaluated according to gender, increases in total vitamin K intakes were generally higher in males than females (see Table 4.4.3-1).

As per the results presented for vitamin K2 above (see Section 4.4.2), the overall impact of the proposed uses of MK-7 on the total vitamin K intakes was not as significant as those seen in Section 4.4.1 (for MK-7 alone) due to the higher background intakes of total vitamin K.

Table 4.4.3-1 Absolute Difference in Consumer-Only Estimated Daily Intakes of Vitamin K from the Proposed Uses in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group/ Age Group (Years)	Background Diet (µg/day)[a]		Background Diet + Proposed (µg/day)[b]		Absolute Difference (µg/day)[c]	
	Mean	90th Percentile	Mean	90th Percentile	Mean	90th Percentile
Infants						
0 to 6 months	34	72	34	72	*NC*	*NC*
7 to 11 months	100	223	107	250	*+7*	*+27*
Children						
1 to 3 years	182	312	208	338	*+26*	*+26*
4 to 8 years	172	289	198	326	*+26*	*+37*
Females						
9 to 13 years	188	322	214	345	*+26*	*+23*
14 to 18 years	168	281	188	300	*+20*	*+19*
19 years and older	235	401	254	427	*+19*	*+26*
Males						
9 to 13 years	179	303	207	334	*+28*	*+31*
14 to 18 years	201	350	232	396	*+31*	*+46*
19 years and older	254	469	278	505	*+24*	*+36*
Total Population						
All ages (≥1 year)	229	404	252	436	*+23*	*+32*

EDI = estimated daily intake; NC = no change; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.
[a] Results from Section 4.1.5 (background diet only).
[b] Results from Section 4.3.3 (background diet and proposed food uses combined).
[c] Calculation: absolute different = (EDI background diet + proposed extension of use) - (EDI from background diet only).

5.0 SUMMARY AND CONCLUSIONS

Consumption data and information pertaining to the occurrence and levels of vitamin K isomers from current sources in the background diet and from the proposed food uses of MK-7 were used to estimate the *per capita* and consumer-only intakes of MK-7 and related vitamin K isomers for the U.S. population. Dietary intakes were evaluated for (i) the background diet, considering naturally occurring sources and fortification uses in food and dietary supplements of MK-4, MK-7, vitamin K1, vitamin K2, and total vitamin K; (ii) the proposed food uses of MK-7 in specific food and beverage categories; and (iii) the cumulative intake from current sources of MK-7, vitamin K2, and total vitamin K from the background diet and the proposed food uses.

There were a number of assumptions included in the assessment which render exposure estimates that may be considered conservative. For example, it has been assumed in the simulations for proposed MK-7 uses that all food products within a food category contain MK-7 at the maximum proposed level of use. In reality, levels added to specific beverages will vary depending on the nature of the food product and it is unlikely that MK-7 will have 100% market penetration in all identified food categories. Furthermore, the cumulative exposure assessment assumed that MK-7 was present *in addition to* current background sources of this nutrient (as MK-7 directly, or as vitamin K2 or total vitamin K), and did not replace the levels present

in these foods. With respect to the background levels of the vitamin K isomers, as described in Section 2.2, there were large gaps in the available information – particularly for vitamin K2. In order to develop a comprehensive dataset for this isomer – multiple sources were used, including data from the published literature. As such, there are limitations associated with the levels of these isomers applied to the foods and dietary supplements, whereby the available data may not reflect all vitamin K2 that could potentially be present in foods or supplement products.

The intakes of MK-4 and vitamin K1 were assessed only from background diet, as the estimated daily intakes of these vitamin K isomers would not change with proposed uses of MK-7. The mean and 90th percentile estimates of MK-4 among the total population (ages 1 year and older) were 17 and 33 µg/person/day, respectively. The highest mean and 90th percentile consumer-only intakes of MK-4 from current sources were determined to be 22 and 40 µg/person/day, respectively, as identified in males (ages 19 years and older). For vitamin K1, the mean and 90th percentile estimates among the total population (ages 1 year and older) of 115 and 229 µg/person/day, respectively. The highest mean and 90th percentile consumer-only intakes of vitamin K1 from current sources were determined to be 130 and 237 µg/person/day, respectively, as identified in males (ages 19 years and older).

For MK-7, the proposed uses were estimated to result in consumer only intakes of 24.7 µg/person/day (0.4 µg/kg body weight/day) and 47.8 µg/person/day (1.0 µg/kg body weight/day) and the mean and 90th percentile respectively, among the total U.S. population over 1 year of age. Among the individual population groups, the highest mean and 90th percentile consumer-only intakes of MK-7 were determined to be 32.6 µg/person/day (0.5 µg/kg body weight/day) and 63.2 µg/person/day (1.0 µg/kg body weight/day), respectively, as identified among males (ages 14 to 18 years old). Infants ages 7 to 11 months had the lowest statistically reliable estimates of 11.1 and 34.9 µg/person/day.

These estimated daily intakes from the proposed conditions of use of MK-7 resulted in a notable increase when compared with the background values for this vitamin K isomer, whereby the mean and 90th percentile intakes by the total cohort (1 year and over) increased by +23.2 and +47.2 µg/person/day, from 1.1 and 0.4 µg/person/day to 24.3 and 47.6 µg/person/day at the mean and 90th percentile, respectively. This increase in intakes was also seen amongst each of the individual age groups (over 1 year of age), with a range of +19.8 to +31.4 µg/person/day at the mean and +42.4 to +60.2 µg/person/day at the 90th percentile, whereby the highest mean and 90th percentile cumulative consumer-only intakes of MK-7 were determined to be 31.6 and 60.6 µg/person/day, respectively. The increases in the estimated daily intakes by infants ages 7 to 11 months were lower, increasing by +10.7 and +34.8 µg/person/day at the mean and 90th percentile, resulting in cumulative intakes of 10.8 and 34.9 µg/person/day; intakes by infants up to 6 months were not statistically reliable. There was no clear pattern in the estimated changes according to gender.

For vitamin K2, the proposed uses of MK-7 resulted in a moderate increase in the total estimated daily intakes of this nutrient from the background diet. Considering the total population 1 year and over, the increase was estimated at +23 and +33 µg/person/day at the mean and 90th percentile, respectively, resulting in total cumulative intakes of 137 and 262 µg/person/day (from 114 and 229 µg/person/day from the background diet only). Amongst the individual age groups over 1 year of age, the increase ranged from +19 to +30 µg/person/day at the mean and +10 to +42 µg/person/day at the 95th percentile. Among individual population groups, children (ages 1 to 3 years) were identified as having the highest cumulative mean and 90th percentile consumer-only intake of vitamin K2, at 157 and 302 µg/person/day. The overall impact of the proposed uses of MK-7 on the background intakes of vitamin K2 was not as notable when compared with those for MK-7 above, due to the higher background intakes of vitamin K2.

Lastly, there was a similarly moderate increase in estimated daily intakes of total vitamin K when the proposed food uses of MK-7 were considered in combination with current sources of total vitamin K from the background diet. The proposed extensions of use increased estimated daily intakes of total vitamin K by up to +23 and +32 µg/person/day at the mean and 90th percentile for the total cohort over 1 year of age; with the highest increases seen in males (ages 14 to 18 years old) at +31 µg/person/day at the mean and +46 µg/person/day at the 90th percentile. The total cumulative intakes were estimated at 252 and 436 µg/person/day by all ages over 1 year. Among individual population groups, males ages 19 years and older were identified as having the highest mean and 90th percentile cumulative intakes of total vitamin K, at 278 and 505 µg/person/day. Infants (0 to 6 months) had the lowest estimated cumulative intakes at 34 and 72 µg/person/day at the mean and 90th percentile, respectively.

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APPENDIX A

Estimated Daily Intake of Vitamin K Isomers from Background Diet and Proposed Food Uses by Individual Population Group within the U.S. (2017-2018 NHANES Data)

Table A-1 **Estimated Daily Intake of MK-7 from the Background Diet (Current Food Sources and Dietary Supplements) and Proposed Food Uses by Individual Population Group within the U.S. (2017-2018 NHANES Data)**

Population Groups	Current or Proposed Uses	% Contribution to Total Mean Intake[a]	*Per Capita* Intake (µg/day)		Consumer-Only Intake (µg/day)			
			Mean	90th Percentile	%	n	Mean	90th Percentile
Infants								
0 to 6 m	***All***	***100***	***<0.1****	***na***	***3.1***	***9***	***1.2****	***2.7****
	Current Food Sources	0.0	0	0	0	0	0	0
	Dietary Supplements	0.0	0	0	0	0	0	0
	Proposed Food Uses	100	<0.1*	na	3.1	9	1.2*	2.7*
7 to 11 m	***All***	***100***	***7.3***	***27.5***	***68.2***	***83***	***10.8***	***34.9***
	Current Food Sources	0.2	<0.1*	0.1	27.8	29	0.1*	0.1*
	Dietary Supplements	0.0	0	0	0	0	0	0
	Proposed Food Uses	99.8	7.3	27.5	65.9	81	11.1	34.9
Children								
1 to 3 y	***All***	***100***	***25.9***	***42.4***	***99.0***	***410***	***26.2***	***42.6***
	Current Food Sources	0.2	0.1	0.1	57.4	220	0.1	0.2
	Dietary Supplements	0.0	0	0	0.0	0	0	0
	Proposed Food Uses	99.8	25.9	42.4	98.8	408	26.2	42.6
4 to 8 y	***All***	***100***	***26.0***	***46.9***	***99.1***	***526***	***26.2***	***46.9***
	Current Food Sources	0.3	0.1	0.2	59.0	294	0.1	0.3
	Dietary Supplements	0	0	0	0	0	0	0
	Proposed Food Uses	99.7	25.9	46.8	97.9	522	26.5	46.8
Females								
9 to 13 y	***All***	***100***	***27.0***	***52.7***	***99.6***	***306***	***27.1***	***52.7***
	Current Food Sources	0.3	0.1	0.2	64.1	175	0.1	0.3
	Dietary Supplements	0.0	0	0	0	0	0	0
	Proposed Food Uses	99.7	26.9	52.6	98.8	301	27.2	52.6
14 to 18 y	***All***	***100***	***19.6***	***45.5***	***97.9***	***275***	***20.0***	***45.5***
	Current Food Sources	0.4	0.1	0.2	57.6	158	0.1	0.3
	Dietary Supplements	0.0	0	0	0	0	0	0
	Proposed Food Uses	99.6	19.5	45.3	94.9	265	20.6	45.3
19 y and older	***All***	***100***	***21.2***	***43.3***	***97.5***	***2,127***	***21.7***	***43.3***
	Current Food Sources	0.5	0.1	0.3	65.9	1,303	0.2	0.3
	Dietary Supplements	5.7	1.2*	na	0.6	5	216.0*	525.3
	Proposed Food Uses	93.8	19.8	42.5	92.6	2,026	21.4	43.4
Males								
9 to 13 y	***All***	***100***	***27.8***	***48.3***	***99.3***	***279***	***28.0***	***48.3***
	Current Food Sources	0.2	0.1	0.2	56.7	154	0.1	0.3
	Dietary Supplements	0.0	0	0	0	0	0	0
	Proposed Food Uses	99.8	27.7	48.2	97.7	274	28.4	48.2
14 to 18 y	***All***	***100***	***30.9***	***58.3***	***97.8***	***273***	***31.6***	***60.6***
	Current Food Sources	0.3	0.1	0.2	61.8	172	0.1	0.4
	Dietary Supplements	0.0	0	0	0	0	0	0
	Proposed Food Uses	99.7	30.8	58.2	94.5	264	32.6	63.4

Table A-1 Estimated Daily Intake of MK-7 from the Background Diet (Current Food Sources and Dietary Supplements) and Proposed Food Uses by Individual Population Group within the U.S. (2017-2018 NHANES Data)

Population Groups	Current or Proposed Uses	% Contribution to Total Mean Intake[a]	*Per Capita* Intake (µg/day)		Consumer-Only Intake (µg/day)			
			Mean	90th Percentile	%	n	Mean	90th Percentile
19 y and older	***All***	***100***	***25.2***	***52.5***	***97.7***	***1,932***	***25.7***	***53.3***
	Current Food Sources	0.5	0.1	0.4	66.7	1,166	0.2	0.4
	Dietary Supplements	1.4	0.3*	na	0.4	3	97.6*	96.2*
	Proposed Food Uses	98.1	24.7	51.7	92.2	1,831	26.8	53.3
Total Population								
All ages (≥1 y)	***All***	***100***	***23.8***	***47.2***	***97.9***	***6,128***	***24.3***	***47.6***
	Current Food Sources	0.5	0.1	0.3	64.7	3,642	0.2	0.4
	Dietary Supplements	2.6	0.6*	na	0.4	8	172.3*	482.2*
	Proposed Food Uses	97.0	23.1	46.8	93.5	5,891	24.7	47.8

m = months; MK-7 = menaquinone-7; n = sample size; na = not available; NHANES = National Health and Nutrition Examination Survey; U.S. = United States; y = years.

[a] Mean MK-7 intakes from current food sources, dietary supplements, or proposed food uses as proportion of total mean dietary intake.

* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements (mean n<30; 90th percentile n<80).

Table A-2 Estimated Daily Intake of Vitamin K2 from the Background Diet (Current Food Sources and Dietary Supplements) and Proposed Food Uses by Individual Population Group within the U.S. (2017-2018 NHANES Data)

Population Groups	Current or Proposed Uses[a]	% Contribution to Total Mean Intake[b]	*Per Capita* Intake (µg/day)		Consumer-Only Intake (µg/day)			
			Mean	90th Percentile	%	n	Mean	90th Percentile
Infants								
0 to 6 m	***All***	***100***	***<1****	***<1****	***12.1***	***21***	***3****	***9****
	Current Food Sources	89.5	<1*	<1*	10.7	17	3*	9*
	Dietary Supplements	0.0	0	0	0	0	0	0
	Proposed Food Uses	10.6	<1*	<1*	3.1	9	1*	3*
7 to 11 m	***All***	***100***	***58***	***203***	***88.1***	***108***	***66***	***241***
	Current Food Sources	18.8	11	32	84.0	102	13	35
	Dietary Supplements	0.0	0	0	0	0	0	0
	Proposed Food Uses	81.2	47	175	65.9	81	71	248
Children								
1 to 3 y	***All***	***100***	***157***	***302***	***99.9***	***414***	***157***	***302***
	Current Food Sources	29.1	46	108	99.8	413	46	108
	Dietary Supplements	0.0	0	0	0	0	0	0
	Proposed Food Uses	70.9	111	251	98.8	408	113	251
4 to 8 y	***All***	***100***	***139***	***252***	***100***	***530***	***139***	***252***
	Current Food Sources	44.5	62	132	99.4	527	62	132
	Dietary Supplements	0.0	0	0	0	0	0	0
	Proposed Food Uses	55.5	77	154	97.9	522	79	154
Females								
9 to 13 y	***All***	***100***	***134***	***242***	***100***	***307***	***134***	***242***
	Current Food Sources	46.6	62	135	98.9	304	63	135
	Dietary Supplements	0.0	0	0	0	0	0	0
	Proposed Food Uses	53.4	72	147	98.8	301	72	147
14 to 18 y	***All***	***100***	***105***	***187***	***100***	***283***	***105***	***187***
	Current Food Sources	59.2	62	130	97.5	275	64	130
	Dietary Supplements	0.0	0	0	0	0	0	0
	Proposed Food Uses	40.8	43	96	94.8	265	45	96
19 years and older	***All***	***100***	***125***	***230***	***99.8***	***2,213***	***125***	***230***
	Current Food Sources	56.3	70	158	99.6	2,205	71	158
	Dietary Supplements	4.4	6*	na	0.7	7	823*	1,875*
	Proposed Food Uses	39.3	49	114	92.6	2,026	53	117
Males								
9 to 13 y	***All***	***100***	***136***	***235***	***100***	***282***	***136***	***235***
	Current Food Sources	46.2	63	163	99.5	279	63	163
	Dietary Supplements	0.0	0	0	0	0	0	0
	Proposed Food Uses	53.8	73	162	97.7	274	75	163
14 to 18 y	***All***	***100***	***151***	***275***	***100***	***281***	***151***	***275***
	Current Food Sources	48.9	74	153	98.5	275	75	154
	Dietary Supplements	0.0	0	0	0	0	0	0
	Proposed Food Uses	51.1	77	156	94.5	264	82	160

Table A-2 Estimated Daily Intake of Vitamin K2 from the Background Diet (Current Food Sources and Dietary Supplements) and Proposed Food Uses by Individual Population Group within the U.S. (2017-2018 NHANES Data)

Population Groups	Current or Proposed Uses[a]	% Contribution to Total Mean Intake[b]	*Per Capita* Intake (µg/day)		Consumer-Only Intake (µg/day)			
			Mean	90th Percentile	%	n	Mean	90th Percentile
19 y and older	***All***	***100***	***149***	***295***	***99.9***	***2,022***	***149***	***295***
	Current Food Sources	60.7	91	200	99.5	2,009	91	200
	Dietary Supplements	0.3	1*	na	0.4	3	146*	96*
	Proposed Food Uses	38.9	58	139	92.2	1,831	63	148
Total Population								
All ages (≥1 y)	***All***	***100***	***137***	***261***	***99.9***	***6,332***	***137***	***262***
	Current Food Sources	55.2	76	168	99.4	6,287	76	169
	Dietary Supplements	1.8	2*	na	0.4	10	602*	3,045*
	Proposed Food Uses	43.0	59	135	93.5	5,891	63	141

m = months; n = sample size; na = not available; NHANES = National Health and Nutrition Examination Survey; U.S. = United States; y = years.

[a] Proposed food uses reflect the use of MK-7, as vitamin K2.

[b] Mean MK-7 intakes from current food sources, dietary supplements, or proposed food uses as proportion of total mean dietary intake.

* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements (mean n<30; 90th percentile n<80).

Table A-3 Estimated Daily Intake of Total Vitamin K from the Background Diet (Current Food Sources and Dietary Supplements), and Proposed Food Uses by Individual Population Group within the U.S. (2017-2018 NHANES Data)

Population Groups	Current or Proposed Uses[a]	% Contribution to Total Mean Intake[b]	*Per Capita* Intake (µg/day)		Consumer-Only Intake (µg/day)			
			Mean	90th Percentile	%	n	Mean	90th Percentile
Infants								
0 to 6 m	***All***	***100***	***34***	***72***	***100***	***177***	***34***	***72***
	Current Food Sources	99.9	34	72	100	177	34	72
	Dietary Supplements	0.0	0	0	0	0	0	0
	Proposed Food Uses	0.1	<1*	na	3.1	9	1*	3*
7 to 11 m	***All***	***100***	***107***	***250***	***100***	***124***	***107***	***250***
	Current Food Sources	55.8	60	99	100	124	60	99
	Dietary Supplements	0.1	<1*	na	1.1	1	5*	5*
	Proposed Food Uses	44.1	47	177	65.9	81	72	250
Children								
1 to 3 y	***All***	***100***	***208***	***338***	***100***	***415***	***208***	***338***
	Current Food Sources	44.1	92	168	100	415	92	168
	Dietary Supplements	0.5	1*	na	3.0	18	33*	55*
	Proposed Food Uses	55.4	115	256	98.8	408	116	259
4 to 8 y	***All***	***100***	***198***	***326***	***100***	***530***	***198***	***326***
	Current Food Sources	57.5	114	203	100	530	114	203
	Dietary Supplements	1.0	2*	na	5.8	27	35*	55*
	Proposed Food Uses	41.5	82	158	97.9	522	84	161
Females								
9 to 13 y	***All***	***100***	***214***	***345***	***100***	***307***	***214***	***345***
	Current Food Sources	62.8	135	260	100	307	135	260
	Dietary Supplements	1.4	3*	na	8.3	15	35*	57*
	Proposed Food Uses	35.9	77	156	98.8	301	78	156
14 to 18 y	***All***	***100***	***188***	***300***	***100***	***283***	***188***	***300***
	Current Food Sources	73.2	137	264	100	283	137	264
	Dietary Supplements	0.9	2*	na	6.4	11	27*	42*
	Proposed Food Uses	25.9	48	106	94.9	265	51	107
19 y and older	***All***	***100***	***254***	***427***	***100***	***2,215***	***254***	***427***
	Current Food Sources	73.7	188	349	100	2,215	188	349
	Dietary Supplements	5.2	13	25	21.1	408	63	80
	Proposed Food Uses	21.0	54	120	92.6	2,026	58	125
Males								
9 to 13 y	***All***	***100***	***207***	***334***	***100***	***282***	***207***	***334***
	Current Food Sources	60.3	125	256	100	282	125	256
	Dietary Supplements	1.6	3*	na	7.5	12	44*	55*
	Proposed Food Uses	38.1	79	171	97.7	274	81	171
14 to 18 y	***All***	***100***	***232***	***396***	***100***	***281***	***232***	***396***
	Current Food Sources	62.2	144	256	100	281	144	256
	Dietary Supplements	1.4	3*	na	6.6	12	50*	56*
	Proposed Food Uses	36.4	84	176	94.5	264	89	183

Table A-3 Estimated Daily Intake of Total Vitamin K from the Background Diet (Current Food Sources and Dietary Supplements), and Proposed Food Uses by Individual Population Group within the U.S. (2017-2018 NHANES Data)

Population Groups	Current or Proposed Uses[a]	% Contribution to Total Mean Intake[b]	*Per Capita* Intake (µg/day)		Consumer-Only Intake (µg/day)			
			Mean	90th Percentile	%	n	Mean	90th Percentile
19 y and older	***All***	***100***	***279***	***505***	***100***	***2,025***	***279***	***505***
	Current Food Sources	74.8	209	390	100	2,024	209	390
	Dietary Supplements	2.5	7	25	19.7	362	35	60
	Proposed Food Uses	22.7	63	150	92.2	1,831	69	156
Total Population								
All ages (≥1 y)	***All***	***100***	***252***	***436***	***100***	***6,338***	***252***	***436***
	Current Food Sources	71.4	180	343	100	6,337	180	343
	Dietary Supplements	3.3	8	25	17.1	865	49	75
	Proposed Food Uses	25.3	64	146	93.5	5,891	68	148

m = months; n = sample size; na = not available; NHANES = National Health and Nutrition Examination Survey; U.S. = United States; y = years.

[a] Proposed food uses reflect the use of MK-7, as vitamin K.

[b] Mean MK-7 intakes from current food sources, dietary supplements, or proposed food uses as proportion of total mean dietary intake.

* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements (mean n<30; 90th percentile n<80).

APPENDIX B
Representative Food Codes for the Proposed Food Uses of MK-7 (2017-2018 NHANES Data)

Representative Food Codes for Proposed Food Uses of MK-7 in the U.S. (2017-2018 NHANES Data)

Beverages and Beverage Bases

Soft Drinks
[MK-7] = 2.8 µg/100 g

92400000	Soft drink, NFS
92400100	Soft drink, NFS, diet
92410310	Soft drink, cola
92410315	Soft drink, cola, reduced sugar
92410320	Soft drink, cola, diet
92410340	Soft drink, cola, decaffeinated
92410350	Soft drink, cola, decaffeinated, diet
92410360	Soft drink, pepper type
92410370	Soft drink, pepper type, diet
92410390	Soft drink, pepper type, decaffeinated
92410400	Soft drink, pepper type, decaffeinated, diet
92410410	Soft drink, cream soda
92410420	Soft drink, cream soda, diet
92410510	Soft drink, fruit flavored, caffeine free
92410520	Soft drink, fruit flavored, diet, caffeine free
92410550	Soft drink, fruit flavored, caffeine containing
92410560	Soft drink, fruit flavored, caffeine containing, diet
92410610	Soft drink, ginger ale
92410620	Soft drink, ginger ale, diet
92410710	Soft drink, root beer
92410720	Soft drink, root beer, diet
92410810	Soft drink, chocolate flavored
92410820	Soft drink, chocolate flavored, diet
92411510	Soft drink, cola, fruit or vanilla flavored
92411520	Soft drink, cola, chocolate flavored
92411610	Soft drink, cola, fruit or vanilla flavored, diet
92411620	Soft drink, cola, chocolate flavored, diet
92432000	Fruit juice drink, citrus, carbonated
92433000	Fruit juice drink, noncitrus, carbonated

Breakfast Cereals

[MK-7] = 16.7 to 66.7 µg/100 g

57000100	Cereal, oat, NFS
57100100	Cereal, ready-to-eat, NFS
57101000	Cereal (Kellogg's All-Bran)
57103000	Cereal (Post Alpha-Bits)
57103100	Cereal (General Mills Cheerios Apple Cinnamon)
57104000	Cereal (Kellogg's Apple Jacks)
57106050	Cereal (Post Great Grains Banana Nut Crunch)
57106060	Cereal (General Mills Cheerios Banana Nut)
57106260	Cereal (General Mills Cheerios Berry Burst)
57117000	Cereal (Quaker Cap'n Crunch)
57117500	Cereal (Quaker Christmas Crunch)
57119000	Cereal (Quaker Cap'n Crunch's Crunchberries)
57120000	Cereal (Quaker Cap'n Crunch's Peanut Butter Crunch)
57123000	Cereal (General Mills Cheerios)
57124030	Cereal (General Mills Chex Chocolate)
57124050	Cereal (General Mills Chex Cinnamon)
57124100	Cereal (General Mills Cheerios Chocolate)
57124200	Cereal, chocolate flavored, frosted, puffed corn
57124300	Cereal (General Mills Lucky Charms Chocolate)
57125000	Cereal (General Mills Cinnamon Toast Crunch)
57125010	Cereal (General Mills 25% Less Sugar Cinnamon Toast Crunch)
57125900	Cereal (General Mills Honey Nut Clusters)
57126000	Cereal (Kellogg's Cocoa Krispies)
57127000	Cereal (Post Cocoa Pebbles)
57128000	Cereal (General Mills Cocoa Puffs)
57130000	Cereal (General Mills Cookie Crisp)
57132000	Cereal (General Mills Chex Corn)
57134000	Cereal, corn flakes
57135000	Cereal (Kellogg's Corn Flakes)
57137000	Cereal, corn puffs
57139000	Cereal (General Mills Count Chocula)
57143000	Cereal (Kellogg's Cracklin' Oat Bran)
57143500	Cereal (Post Great Grains, Cranberry Almond Crunch)
57148000	Cereal (Kellogg's Crispix)
57151000	Cereal, crispy rice
57206700	Cereal (General Mills Fiber One)
57206710	Cereal (General Mills Fiber One Honey Clusters)
57206715	Cereal (General Mills Fiber One Raisin Bran Clusters)
57207000	Cereal, bran flakes
57208000	Cereal (Kellogg's All-Bran Complete Wheat Flakes)

57209000	Cereal (Post Bran Flakes)
57211000	Cereal (General Mills Frankenberry)
57213000	Cereal (Kellogg's Froot Loops)
57213010	Cereal (Kellogg's Froot Loops Marshmallow)
57213850	Cereal (General Mills Cheerios Frosted)
57214000	Cereal (Kellogg's Frosted Mini-Wheats)
57216000	Cereal, frosted rice
57221700	Cereal, fruit rings
57221810	Cereal (General Mills Cheerios Fruity)
57223000	Cereal (Post Fruity Pebbles)
57224000	Cereal (General Mills Golden Grahams)
57227000	Cereal, granola
57229000	Cereal (Kellogg's Low Fat Granola)
57230000	Cereal (Post Grape-Nuts)
57231200	Cereal (Post Great Grains Raisins, Dates, and Pecans)
57237100	Cereal (Post Honey Bunches of Oats Honey Roasted)
57237200	Cereal (Post Honey Bunches of Oats with Vanilla Bunches)
57237300	Cereal (Post Honey Bunches of Oats with Almonds)
57238000	Cereal (Post Honeycomb)
57240100	Cereal (General Mills Chex Honey Nut)
57241000	Cereal (General Mills Cheerios Honey Nut)
57241200	Cereal (Post Shredded Wheat Honey Nut)
57243000	Cereal (Kellogg's Honey Smacks)
57301500	Cereal (Kashi 7 Whole Grain Puffs)
57301505	Cereal (Kashi Autumn Wheat)
57301510	Cereal (Kashi GOLEAN)
57301511	Cereal (Kashi GOLEAN Crunch)
57301512	Cereal (Kashi GOLEAN Crunch Honey Almond Flax)
57301530	Cereal (Kashi Heart to Heart Honey Toasted Oat)
57303100	Cereal (General Mills Kix)
57303105	Cereal (General Mills Honey Kix)
57303200	Cereal (Kellogg's Krave)
57304100	Cereal (Quaker Life)
57305100	Cereal (General Mills Lucky Charms)
57305150	Cereal, frosted oat cereal with marshmallows
57305160	Cereal (Malt-O-Meal Blueberry Muffin Tops)
57305165	Cereal (Malt-O-Meal Cinnamon Toasters)
57305170	Cereal (Malt-O-Meal Coco-Roos)
57305174	Cereal (Malt-O-Meal Colossal Crunch)
57305175	Cereal (Malt-O-Meal Cocoa Dyno-Bites)
57305180	Cereal (Malt-O-Meal Corn Bursts)
57305210	Cereal (Malt-O-Meal Frosted Flakes)
57305300	Cereal (Malt-O-Meal Fruity Dyno-Bites)

57305400	Cereal (Malt-O-Meal Honey Graham Squares)
57305500	Cereal (Malt-O-Meal Honey Nut Toasty O's)
57305600	Cereal (Malt-O-Meal Marshmallow Mateys)
57306500	Cereal (Malt-O-Meal Golden Puffs)
57306700	Cereal (Malt-O-Meal Toasted Oat Cereal)
57306800	Cereal (Malt-O-Meal Tootie Fruities)
57308190	Cereal, muesli
57308400	Cereal (General Mills Cheerios Multigrain)
57309100	Cereal (Nature Valley Granola)
57316380	Cereal (General Mills Cheerios Oat Cluster Crunch)
57316385	Cereal (General Mills Cheerios Protein)
57316450	Cereal (General Mills Oatmeal Crisp with Almonds)
57316710	Cereal (Quaker Honey Graham Oh's)
57320500	Cereal (Quaker Granola with Oats, Honey, and Raisins)
57321900	Cereal (Nature's Path Organic Flax Plus)
57326000	Cereal (Barbara's Puffins)
57327450	Cereal (Quaker Toasted Oat Bran)
57327500	Cereal (Quaker Oatmeal Squares)
57329000	Cereal, raisin bran
57330000	Cereal (Kellogg's Raisin Bran)
57330010	Cereal (Kellogg's Raisin Bran Crunch)
57331000	Cereal (Post Raisin Bran)
57332100	Cereal (General Mills Raisin Nut Bran)
57335550	Cereal (General Mills Reese's Puffs)
57336000	Cereal (General Mills Chex Rice)
57337000	Cereal, rice flakes
57339000	Cereal (Kellogg's Rice Krispies)
57339500	Cereal (Kellogg's Rice Krispies Treats Cereal)
57340000	Cereal, puffed rice
57341200	Cereal (Kellogg's Smart Start Strong)
57341300	Cereal (Kellogg's Smorz)
57344000	Cereal (Kellogg's Special K)
57344001	Cereal (Kellogg's Special K Blueberry)
57344005	Cereal (Kellogg's Special K Chocolatey Delight)
57344010	Cereal (Kellogg's Special K Red Berries)
57344015	Cereal (Kellogg's Special K Fruit & Yogurt)
57344020	Cereal (Kellogg's Special K Vanilla Almond)
57344025	Cereal (Kellogg's Special K Cinnamon Pecan)
57347000	Cereal (Kellogg's Corn Pops)
57348000	Cereal, frosted corn flakes
57349000	Cereal (Kellogg's Frosted Flakes)
57355000	Cereal (Post Golden Crisp)
57401100	Cereal, toasted oat

57407100 Cereal (General Mills Trix)
57408100 Cereal (Uncle Sam)
57411000 Cereal (General Mills Chex Wheat)
57416000 Cereal, puffed wheat, plain
57416010 Cereal, puffed wheat, sweetened
57417000 Cereal (Post Shredded Wheat)
57418000 Cereal (General Mills Wheaties)

Cheeses

Cottage Cheese
[MK-7] = 9.1 µg/100 g

14200100 Cheese, cottage, NFS
14201010 Cheese, cottage, creamed, large or small curd
14201200 Cottage cheese, farmer's
14202010 Cheese, cottage, with fruit
14202020 Cheese, cottage, with vegetables
14203010 Cheese, cottage, dry curd
14203020 Cheese, cottage, salted, dry curd
14204010 Cheese, cottage, low fat
14204020 Cheese, cottage, lowfat, with fruit
14206010 Cheese, cottage, lowfat, low sodium
14207010 Cheese, cottage, lowfat, lactose reduced

Mixed foods containing cottage cheese - Adjusted for cottage cheese content of 36 to 66%
[MK-7] = 3.3 to 6.0

14610200 Cheese, cottage cheese, with gelatin dessert
14610210 Cheese, cottage cheese, with gelatin dessert and fruit
14610250 Cheese, cottage cheese, with gelatin dessert and vegetables

Low Fat Cheese
[MK-7] = 33.3 µg/100 g

14104110 Cheese, Cheddar, reduced fat
14104115 Cheese, Cheddar, nonfat or fat free
14106500 Cheese, Monterey, reduced fat
14107030 Cheese, Mozzarella, part skim
14107040 Cheese, Mozzarella, reduced sodium
14107060 Cheese, Mozzarella, nonfat or fat free
14107250 Cheese, Muenster, reduced fat
14108015 Cheese, Parmesan, dry grated, reduced fat
14108060 Cheese, Parmesan, dry grated, fat free
14108420 Cheese, provolone, reduced fat

14109030 Cheese, Swiss, reduced fat
14109040 Cheese, Swiss, nonfat or fat free
14120020 Cheese, Mexican blend, reduced fat
14201500 Cheese, Ricotta
14303010 Cream cheese, light
14410120 Cheese, American, reduced fat
14410130 Cheese, American, nonfat or fat free
14410330 Cheese spread, American or Cheddar cheese base, reduced fat
14410380 Cream cheese spread, fat free
14420210 Cheese spread, cream cheese, light

Mixed foods containing cheddar cheese - Adjusted for cottage cheese content of 36 to 41%
[MK-7] = 12.1 to 13.7

14640014 Cheese sandwich, reduced fat American cheese, on white bread, no spread
14640016 Cheese sandwich, reduced fat American cheese, on wheat bread, no spread
14640018 Cheese sandwich, reduced fat American cheese, on whole wheat bread, no spread
14640020 Cheese sandwich, reduced fat Cheddar cheese, on white bread, no spread
14640022 Cheese sandwich, reduced fat Cheddar cheese, on wheat bread, no spread
14640024 Cheese sandwich, reduced fat Cheddar cheese, on whole wheat bread, no spread
14640038 Cheese sandwich, reduced fat American cheese, on white bread, with mayonnaise
14640040 Cheese sandwich, reduced fat American cheese,, on wheat bread, with mayonnaise
14640042 Cheese sandwich, reduced fat American cheese, on whole wheat bread, with mayonnaise
14640044 Cheese sandwich, reduced fat Cheddar cheese, on white bread, with mayonnaise
14640046 Cheese sandwich, reduced fat Cheddar cheese, on wheat bread, with mayonnaise
14640048 Cheese sandwich, reduced fat Cheddar cheese, on whole wheat bread, with mayonnaise
14640062 Cheese sandwich, reduced fat American cheese, on white bread, with butter
14640064 Cheese sandwich, reduced fat American cheese, on wheat bread, with butter
14640066 Cheese sandwich, reduced fat American cheese, on whole wheat bread, with butter
14640068 Cheese sandwich, reduced fat Cheddar cheese, on white bread, with butter
14640070 Cheese sandwich, reduced fat Cheddar cheese, on wheat bread, with butter
14640072 Cheese sandwich, reduced fat Cheddar cheese, on whole wheat bread, with butter
14640155 Grilled cheese sandwich, reduced fat American cheese, on white bread
14640160 Grilled cheese sandwich, reduced fat American cheese, on wheat bread
14640165 Grilled cheese sandwich, reduced fat American cheese, on whole wheat bread
14640185 Grilled cheese sandwich, reduced fat Cheddar cheese, on white bread
14640190 Grilled cheese sandwich, reduced fat Cheddar cheese, on wheat bread
14640195 Grilled cheese sandwich, reduced fat Cheddar cheese, on whole wheat bread

Fats and Oils

Low Fat Margarine
[MK-7] = 66.7 µg/100 g

81104010 Margarine-oil blend, tub, light
81104020 Margarine-oil blend, stick, light

Low Fat Mayonnaise
[MK-7] = 66.7 µg/100 g

83204000 Mayonnaise, light
83204030 Mayonnaise, reduced fat, with olive oil
83300700 Mayonnaise, fat free

Mixed foods containing mayonnaise - Adjusted for mayonnaise content of 14 to 22%
[MK-7] = 9.3 to 14.8 µg/100 g

27446225 Chicken or turkey salad, made with light mayonnaise
27450061 Tuna salad, made with light mayonnaise
32103015 Egg salad, made with light mayonnaise
58148111 Macaroni or pasta salad, made with light mayonnaise
71601015 Potato salad with egg, made with light mayonnaise
71603015 Potato salad, made with light mayonnaise

Olive Oil
[MK-7] = 66.7 µg/100 g

82104000 Olive oil

Frozen Dairy Desserts

Frozen Yogurt
[MK-7] = 11.1 µg/100 g

11459990 Frozen yogurt, NFS
11460000 Frozen yogurt, vanilla
11460100 Frozen yogurt, chocolate
11460500 Frozen yogurt, soft serve, vanilla
11460510 Frozen yogurt, soft serve, chocolate
11461200 Frozen yogurt sandwich
11461210 Frozen yogurt bar, vanilla
11461220 Frozen yogurt bar, chocolate
11461250 Frozen yogurt cone, chocolate
11461260 Frozen yogurt cone, vanilla
11461300 Frozen yogurt cone, vanilla, waffle cone

11461320	Frozen yogurt cone, chocolate, waffle cone

Ice Cream
[MK-7] = 7.7 µg/100 g

13110000	Ice cream, NFS
13110100	Ice cream, vanilla
13110102	Ice cream, vanilla, with additional ingredients
13110110	Ice cream, chocolate
13110112	Ice cream, chocolate, with additional ingredients
13110200	Ice cream, soft serve, vanilla
13110210	Ice cream, soft serve, chocolate
13110460	Gelato, vanilla
13110470	Gelato, chocolate
13120050	Ice cream bar, vanilla
13120100	Ice cream bar, vanilla, chocolate coated
13120110	Ice cream candy bar
13120140	Ice cream bar, chocolate
13120500	Ice cream sandwich, vanilla
13120510	Ice cream sandwich, chocolate
13120550	Ice cream cookie sandwich
13120730	Ice cream cone, scooped, vanilla
13120735	Ice cream cone, scooped, vanilla, waffle cone
13120740	Ice cream cone, NFS
13120770	Ice cream cone, scooped, chocolate
13120775	Ice cream cone, scooped, chocolate, waffle cone
13120782	Ice cream cone, soft serve, vanilla
13120784	Ice cream cone, soft serve, chocolate
13120786	Ice cream cone, soft serve, vanilla, waffle cone
13120788	Ice cream cone, soft serve, chocolate, waffle cone
13120790	Ice cream cone, vanilla, prepackaged
13120792	Ice cream cone, chocolate, prepackaged
13120800	Ice cream soda, flavors other than chocolate
13120810	Ice cream soda, chocolate
13121000	Ice cream sundae, NFS
13121100	Ice cream sundae, fruit topping
13121300	Ice cream sundae, hot fudge topping
13121400	Ice cream sundae, caramel topping
13126000	Ice cream, fried
13130100	Light ice cream, NFS
13130300	Light ice cream, vanilla
13130310	Light ice cream, chocolate
13130700	Soft serve, blended with candy or cookies, from fast food
13135000	Light ice cream sandwich, vanilla

13135010 Light ice cream sandwich, chocolate
13140000 Light ice cream bar, vanilla
13140100 Light ice cream bar, vanilla, chocolate coated
13140115 Light ice cream bar, chocolate
13142100 Light ice cream cone, vanilla, prepackaged
13142110 Light ice cream cone, chocolate, prepackaged

Mixed foods containing ice cream - Adjusted for mayonnaise content of 49%
[MK-7] = 3.8 µg/100 g

13121120 Banana split

Grain Products and Pastas

Cereal Bars
[MK-7] = 25.0 µg/100 g

53710400 Cereal or granola bar (General Mills Fiber One Chewy Bar)
53710500 Cereal or granola bar (Kellogg's Nutri-Grain Cereal Bar)
53710502 Cereal or granola bar (Kellogg's Nutri-Grain Yogurt Bar)
53710504 Cereal or granola bar (Kellogg's Nutri-Grain Fruit and Nut Bar)
53710600 Milk 'n Cereal bar
53710700 Cereal or granola bar (Kellogg's Special K bar)
53710800 Cereal or granola bar (Kashi Chewy)
53710802 Cereal or granola bar (Kashi Crunchy)
53710810 Cereal or granola bar (KIND Fruit and Nut Bar)
53710900 Cereal or granola bar (General Mills Nature Valley Chewy Trail Mix)
53710902 Cereal or granola bar, with yogurt coating (General Mills Nature Valley Chewy Granola Bar)
53710904 Cereal or granola bar (General Mills Nature Valley Sweet and Salty Granola Bar)
53710906 Cereal or granola bar (General Mills Nature Valley Crunchy Granola Bar)
53711000 Cereal or granola bar (Quaker Chewy Granola Bar)
53711002 Cereal or granola bar (Quaker Chewy 90 Calorie Granola Bar)
53711004 Cereal or granola bar (Quaker Chewy 25% Less Sugar Granola Bar)
53711006 Cereal or granola bar (Quaker Chewy Dipps Granola Bar)
53711100 Cereal or granola bar (Quaker Granola Bites)
53712000 Snack bar, oatmeal
53712100 Cereal or Granola bar, NFS
53712200 Cereal or granola bar, lowfat, NFS
53712210 Cereal or granola bar, nonfat
53713000 Cereal or granola bar, reduced sugar, NFS
53713010 Cereal or granola bar, fruit and nut
53713100 Cereal or granola bar, peanuts , oats, sugar, wheat germ
53714200 Cereal or granola bar, chocolate coated, NFS
53714210 Cereal or granola bar, with coconut, chocolate coated

53714220	Cereal or granola bar with nuts, chocolate coated
53714230	Cereal or granola bar, oats, nuts, coated with non-chocolate coating
53714250	Cereal or granola bar, coated with non-chocolate coating
53714300	Cereal or granola bar, high fiber, coated with non-chocolate yogurt coating
53714400	Cereal or granola bar, with rice cereal
53714500	Breakfast bar, NFS
53714510	Breakfast bar, date, with yogurt coating
53714520	Breakfast bar, cereal crust with fruit filling, lowfat

Pasta
[MK-7] = 7.1 µg/100 g

56104000	Pasta, vegetable, cooked
56112000	Noodles, cooked
56113000	Noodles, whole grain, cooked
56113990	Noodles, vegetable, cooked
56116990	Long rice noodles, made from mung beans, cooked
56117090	Rice noodles, cooked
56130000	Pasta, cooked
56132990	Pasta, whole grain, cooked
56140100	Pasta, gluten free
58122210	Gnocchi, cheese
58122220	Gnocchi, potato

Mixed foods containing pasta - Adjusted for pasta content of 24 to 68%
[MK-7] = 1.7 to 4.8 µg/100 g

58304200	Ravioli, cheese-filled, with tomato sauce, diet frozen meal
58301050	Lasagna with cheese and meat sauce, diet frozen meal
58133130	Manicotti, cheese-filled, with meat sauce
58130020	Lasagna with meat and spinach
58130150	Lasagna, with chicken or turkey, and spinach
58301110	Vegetable lasagna, frozen meal
58130011	Lasagna with meat
58130013	Lasagna with meat, canned
58130014	Lasagna with meat, from restaurant
58130016	Lasagna with meat, frozen
58130140	Lasagna with chicken or turkey
58130310	Lasagna, meatless
58130320	Lasagna, meatless, with vegetables
58133120	Manicotti, cheese-filled, with tomato sauce, meatless
58133140	Manicotti, vegetable- and cheese-filled, with tomato sauce, meatless
58134130	Stuffed shells, cheese-filled, with meat sauce
58145117	Macaroni or noodles with cheese, Easy Mac type
58134120	Stuffed shells, cheese-filled, with tomato sauce, meatless

58131600	Ravioli, cheese and spinach-filled, with cream sauce
58131535	Ravioli, cheese-filled, with cream sauce
58134310	Stuffed shells, with fish and/or shellfish, with tomato sauce
58134210	Stuffed shells, with chicken, with tomato sauce
58146120	Pasta with tomato-based sauce, cheese and meat
58145112	Macaroni or noodles with cheese, made from packaged mix
58131520	Ravioli, cheese-filled, with tomato sauce
58131523	Ravioli, cheese-filled, with tomato sauce, canned
58131610	Ravioli, cheese and spinach filled, with tomato sauce
58145119	Macaroni or noodles with cheese, made from reduced fat packaged mix
58131120	Ravioli, NS as to filling, with cream sauce
58131530	Ravioli, cheese-filled, with meat sauce
58146150	Pasta with tomato-based sauce and cheese
58145136	Macaroni or noodles with cheese and meat, prepared from Hamburger Helper mix
58131330	Ravioli, meat-filled, with cream sauce
58134660	Tortellini, cheese-filled, with cream sauce
58304010	Spaghetti and meatballs dinner, NFS, frozen meal
58134810	Cannelloni, cheese- and spinach-filled, no sauce
58131110	Ravioli, NS as to filling, with tomato sauce
58304050	Spaghetti with meat and mushroom sauce, diet frozen meal
58304060	Spaghetti with meat sauce, diet frozen meal
58131320	Ravioli, meat-filled, with tomato sauce or meat sauce
58131323	Ravioli, meat-filled, with tomato sauce or meat sauce, canned
58302000	Macaroni and cheese, diet frozen meal
58133110	Manicotti, cheese-filled, no sauce
58140310	Macaroni with tuna, Puerto Rican style
58145110	Macaroni or noodles with cheese
58145111	Macaroni or noodles with cheese, from restaurant
58145113	Macaroni or noodles with cheese, canned
58145120	Macaroni or noodles with cheese and tuna
58145135	Macaroni or noodles with cheese and meat
58145140	Macaroni or noodles with cheese and tomato
58145160	Macaroni or noodles with cheese and frankfurters or hot dogs
58145170	Macaroni or noodles with cheese and egg
58145190	Macaroni or noodles with cheese and chicken or turkey
58145300	Macaroni or noodles with cheese, whole grain
58140110	Spaghetti with corned beef, Puerto Rican style
58134110	Stuffed shells, cheese-filled, no sauce
58134613	Tortellini, meat-filled, with tomato sauce, canned
58146315	Pasta with sauce and meat, from school lunch
58134640	Tortellini, cheese-filled, meatless, with vinaigrette dressing
58146381	Pasta with cream sauce, restaurant
58146391	Pasta with cream sauce and added vegetables, restaurant

58146401	Pasta with cream sauce and meat, restaurant
58146411	Pasta with cream sauce, meat, and added vegetables, restaurant
58146421	Pasta with cream sauce and poultry, restaurant
58146431	Pasta with cream sauce, poultry, and added vegetables, restaurant
58146441	Pasta with cream sauce and seafood, restaurant
58146451	Pasta with cream sauce, seafood, and added vegetables, restaurant
58146681	Pasta, whole grain, with cream sauce, restaurant
58146691	Pasta, whole grain, with cream sauce, and added vegetables, restaurant
58146701	Pasta, whole grain, with cream sauce and meat, restaurant
58146711	Pasta, whole grain, with cream sauce, meat, and added vegetables, restaurant
58146721	Pasta, whole grain, with cream sauce and poultry, restaurant
58146731	Pasta, whole grain, with cream sauce, poultry, and added vegetables, restaurant
58146741	Pasta, whole grain, with cream sauce and seafood, restaurant
58146751	Pasta, whole grain, with cream sauce, seafood, and added vegetables, restaurant
58146221	Pasta with tomato-based sauce, restaurant
58146301	Pasta with tomato-based sauce, and added vegetables, restaurant
58146321	Pasta with tomato-based sauce and meat, restaurant
58146331	Pasta with tomato-based sauce, meat, and added vegetables, restaurant
58146341	Pasta with tomato-based sauce and poultry, restaurant
58146351	Pasta with tomato-based sauce, poultry, and added vegetables, restaurant
58146361	Pasta with tomato-based sauce and seafood, restaurant
58146371	Pasta with tomato-based sauce, seafood, and added vegetables, restaurant
58146601	Pasta, whole grain, with tomato-based sauce, restaurant
58146611	Pasta, whole grain, with tomato-based sauce and added vegetables, restaurant
58146621	Pasta, whole grain, with tomato-based sauce and meat, restaurant
58146631	Pasta, whole grain, with tomato-based sauce, meat, and added vegetables, restaurant
58146641	Pasta, whole grain, with tomato-based sauce and poultry, restaurant
58146651	Pasta, whole grain, with tomato-based sauce, poultry, and added vegetables, restaurant
58146661	Pasta, whole grain, with tomato-based sauce and seafood, restaurant
58146671	Pasta, whole grain, with tomato-based sauce, seafood, and added vegetables, restaurant
58131590	Ravioli, cheese and spinach-filled, no sauce
58134160	Stuffed shells, cheese- and spinach- filled, no sauce
58131510	Ravioli, cheese-filled, no sauce
58146210	Pasta with sauce, NFS
58147110	Pasta with tomato-based sauce and beans or lentils
58147510	Flavored pasta
58146223	Pasta with tomato-based sauce, ready-to-heat
58146303	Pasta with tomato-based sauce, and added vegetables, ready-to-heat
58146323	Pasta with tomato-based sauce and meat, ready-to-heat
58146333	Pasta with tomato-based sauce, meat, and added vegetables, ready-to-heat
58146343	Pasta with tomato-based sauce and poultry, ready-to-heat
58146353	Pasta with tomato-based sauce, poultry, and added vegetables, ready-to-heat
58146363	Pasta with tomato-based sauce and seafood, ready-to-heat

58146373	Pasta with tomato-based sauce, seafood, and added vegetables, ready-to-heat
58146383	Pasta with cream sauce, ready-to-heat
58146393	Pasta with cream sauce and added vegetables, ready-to-heat
58146403	Pasta with cream sauce and meat, ready-to-heat
58146413	Pasta with cream sauce, meat, and added vegetables, ready-to-heat
58146423	Pasta with cream sauce and poultry, ready-to-heat
58146433	Pasta with cream sauce, poultry, and added vegetables, ready-to-heat
58146443	Pasta with cream sauce and seafood, ready-to-heat
58146453	Pasta with cream sauce, seafood, and added vegetables, ready-to-heat
58146603	Pasta, whole grain, with tomato-based sauce, ready-to-heat
58146613	Pasta, whole grain, with tomato-based sauce and added vegetables, ready-to-heat
58146623	Pasta, whole grain, with tomato-based sauce and meat, ready-to-heat
58146633	Pasta, whole grain, with tomato-based sauce, meat, and added vegetables, ready-to-heat
58146643	Pasta, whole grain, with tomato-based sauce and poultry, ready-to-heat
58146653	Pasta, whole grain, with tomato-based sauce, poultry, and added vegetables, ready-to-heat
58146663	Pasta, whole grain, with tomato-based sauce and seafood, ready-to-heat
58146673	Pasta, whole grain, with tomato-based sauce, seafood, and added vegetables, ready-to-heat
58146683	Pasta, whole grain, with cream sauce, ready-to-heat
58146693	Pasta, whole grain, with cream sauce, and added vegetables, ready-to-heat
58146703	Pasta, whole grain, with cream sauce and meat, ready-to-heat
58146713	Pasta, whole grain, with cream sauce, meat, and added vegetables, ready-to-heat
58146723	Pasta, whole grain, with cream sauce and poultry, ready-to-heat
58146733	Pasta, whole grain, with cream sauce, poultry, and added vegetables, ready-to-heat
58146743	Pasta, whole grain, with cream sauce and seafood, ready-to-heat
58146753	Pasta, whole grain, with cream sauce, seafood, and added vegetables, ready-to-heat
58146215	Pasta with sauce, meatless, school lunch
58305250	Pasta with vegetable and cheese sauce, diet frozen meal
58131100	Ravioli, NS as to filling, no sauce
58134620	Tortellini, cheese-filled, meatless, with tomato sauce
58134623	Tortellini, cheese-filled, meatless, with tomato sauce, canned
58147340	Macaroni or noodles, creamed, with cheese and tuna
58131310	Ravioli, meat-filled, no sauce
58134650	Tortellini, meat-filled, no sauce
58134680	Tortellini, cheese-filled, no sauce
58134710	Tortellini, spinach-filled, with tomato sauce
58134610	Tortellini, meat-filled, with tomato sauce
58134720	Tortellini, spinach-filled, no sauce
58146160	Pasta with vegetables, no sauce or dressing
58147330	Macaroni or noodles, creamed, with cheese

Pizza Crust

Mixed foods containing pasta - Adjusted for pasta content of 24 to 68%
[MK-7] = 6.8 to 11.3 µg/100 g

58107232	White pizza, cheese, with meat and vegetables, thin crust
58107212	White pizza, cheese, with vegetables, thin crust
58109050	Pizza, cheese and vegetables, whole wheat thin crust
58109140	Pizza, cheese and vegetables, gluten-free thin crust
58107222	White pizza, cheese, with meat, thin crust
58109120	Pizza, with meat, gluten-free thin crust
58109030	Pizza, with meat, whole wheat thin crust
58108000	Calzone, with cheese, meatless
58106220	Pizza, cheese, from restaurant or fast food, thin crust
58106235	Pizza, cheese, from school lunch, thin crust
58106250	Pizza, extra cheese, thin crust
58106300	Pizza, cheese, with vegetables, from frozen, thin crust
58106320	Pizza, cheese, with vegetables, from restaurant or fast food, thin crust
58106345	Pizza with cheese and extra vegetables, thin crust
58106358	Pizza, cheese, with fruit, thin crust
58106512	Pizza with pepperoni, from frozen, thin crust
58106550	Pizza with pepperoni, from restaurant or fast food, thin crust
58106570	Pizza with pepperoni, from school lunch, thin crust
58106602	Pizza with meat other than pepperoni, from frozen, thin crust
58106620	Pizza with meat other than pepperoni, from restaurant or fast food, thin crust
58106635	Pizza, with meat other than pepperoni, from school lunch, thin crust
58106650	Pizza with extra meat, thin crust
58106700	Pizza with meat and vegetables, from frozen, thin crust
58106720	Pizza with meat and vegetables, from restaurant or fast food, thin crust
58106736	Pizza with extra meat and extra vegetables, thin crust
58106750	Pizza with meat and fruit, thin crust
58106820	Pizza with beans and vegetables, thin crust
58107050	Pizza, no cheese, thin crust
58107234	White pizza, cheese, with meat and vegetables, thick crust
58108050	Pizza rolls
58106205	Pizza, cheese, from frozen, thick crust
58106210	Pizza, cheese, from restaurant or fast food, NS as to type of crust
58108010	Calzone, with meat and cheese
58106225	Pizza, cheese, from restaurant or fast food, medium crust
58106234	Pizza, cheese, from school lunch, medium crust
58106325	Pizza, cheese, with vegetables, from restaurant or fast food, medium crust
58106347	Pizza with cheese and extra vegetables, medium crust
58106359	Pizza, cheese, with fruit, medium crust
58106514	Pizza with pepperoni, from frozen, medium crust

58106540	Pizza with pepperoni, from restaurant or fast food, NS as to type of crust
58106555	Pizza with pepperoni, from restaurant or fast food, medium crust
58106578	Pizza, with pepperoni, from school lunch, medium crust
58106604	Pizza with meat other than pepperoni, from frozen, medium crust
58106610	Pizza with meat other than pepperoni, from restaurant or fast food, NS as to type of crust
58106625	Pizza with meat other than pepperoni, from restaurant or fast food, medium crust
58106634	Pizza, with meat other than pepperoni, from school lunch, medium crust
58106655	Pizza with extra meat, medium crust
58106702	Pizza with meat and vegetables, from frozen, medium crust
58106725	Pizza with meat and vegetables, from restaurant or fast food, medium crust
58106738	Pizza with extra meat and extra vegetables, medium crust
58106755	Pizza with meat and fruit, medium crust
58106200	Pizza, cheese, from frozen, thin crust
58107214	White pizza, cheese, with vegetables, thick crust
58107205	White pizza, cheese, thin crust
58109060	Pizza, cheese and vegetables, whole wheat thick crust
58109150	Pizza, cheese and vegetables, gluten-free thick crust
58107224	White pizza, cheese, with meat, thick crust
58109015	Pizza, cheese, whole wheat thin crust
58109100	Pizza, cheese, gluten-free thin crust
58109040	Pizza, with meat, whole wheat thick crust
58109130	Pizza, with meat, gluten-free thick crust
58106230	Pizza, cheese, from restaurant or fast food, thick crust
58106233	Pizza, cheese, stuffed crust
58106236	Pizza, cheese, from school lunch, thick crust
58106260	Pizza, extra cheese, thick crust
58106305	Pizza, cheese with vegetables, from frozen, thick crust
58106330	Pizza, cheese, with vegetables, from restaurant or fast food, thick crust
58106350	Pizza with cheese and extra vegetables, thick crust
58106360	Pizza, cheese, with fruit, thick crust
58106516	Pizza with pepperoni, from frozen, thick crust
58106560	Pizza with pepperoni, from restaurant or fast food, thick crust
58106565	Pizza with pepperoni, stuffed crust
58106580	Pizza with pepperoni, from school lunch, thick crust
58106606	Pizza with meat other than pepperoni, from frozen, thick crust
58106630	Pizza with meat other than pepperoni, from restaurant or fast food, thick crust
58106633	Pizza, with meat other than pepperoni, stuffed crust
58106636	Pizza, with meat other than pepperoni, from school lunch, thick crust
58106660	Pizza with extra meat, thick crust
58106705	Pizza with meat and vegetables, from frozen, thick crust
58106730	Pizza with meat and vegetables, from restaurant or fast food, thick crust
58106737	Pizza with extra meat and extra vegetables, thick crust
58106760	Pizza with meat and fruit, thick crust

58106830	Pizza with beans and vegetables, thick crust
58107100	Pizza, no cheese, thick crust
58107207	White pizza, cheese, thick crust
58109020	Pizza, cheese, whole wheat thick crust
58109110	Pizza, cheese, gluten-free thick crust

Milk

[MK-7] = 4.2 µg/100 g

11100000	Milk, NFS
11111000	Milk, whole
11111100	Milk, low sodium, whole
11111150	Milk, calcium fortified, whole
11111160	Milk, calcium fortified, low fat (1%)
11111170	Milk, calcium fortified, fat free (skim)
11112110	Milk, reduced fat (2%)
11112120	Milk, acidophilus, low fat (1%)
11112130	Milk, acidophilus, reduced fat (2%)
11112210	Milk, low fat (1%)
11113000	Milk, fat free (skim)
11114300	Milk, lactose free, low fat (1%)
11114320	Milk, lactose free, fat free (skim)
11114330	Milk, lactose free, reduced fat (2%)
11114350	Milk, lactose free, whole

Milk Products

Other Milks
[MK-7] = 4.2 µg/100 g

11115000	Buttermilk, fat free (skim)
11115100	Buttermilk, low fat (1%)
11115200	Buttermilk, reduced fat (2%)
11115300	Buttermilk, whole
11115400	Kefir, NS as to fat content
11116000	Goat's milk, whole
11210050	Milk, evaporated, NS as to fat content
11211050	Milk, evaporated, whole
11211400	Milk, evaporated, reduced fat (2%)
11212050	Milk, evaporated, fat free (skim)
11220000	Milk, condensed, sweetened

Creams
[MK-7] = 66.7 µg/100 g

12100100	Cream, NS as to light, heavy, or half and half
12110100	Cream, light
12120100	Cream, half and half
12120106	Cream, half and half, flavored
12120110	Cream, half and half, fat free
12130100	Cream, heavy

Yogurt
[MK-7] = 5.9 µg/100 g

11400000	Yogurt, NFS
11400010	Yogurt, Greek, NS as to type of milk or flavor
11410000	Yogurt, NS as to type of milk or flavor
11411010	Yogurt, NS as to type of milk, plain
11411100	Yogurt, whole milk, plain
11411200	Yogurt, low fat milk, plain
11411300	Yogurt, nonfat milk, plain
11411390	Yogurt, Greek, NS as to type of milk, plain
11411400	Yogurt, Greek, whole milk, plain
11411410	Yogurt, Greek, low fat milk, plain
11411420	Yogurt, Greek, nonfat milk, plain
11430000	Yogurt, NS as to type of milk, fruit
11431000	Yogurt, whole milk, fruit
11432000	Yogurt, low fat milk, fruit
11433000	Yogurt, nonfat milk, fruit
11433990	Yogurt, Greek, NS as to type of milk, fruit
11434000	Yogurt, Greek, whole milk, fruit
11434010	Yogurt, Greek, low fat milk, fruit
11434020	Yogurt, Greek, nonfat milk, fruit
11434090	Yogurt, NS as to type of milk, flavors other than fruit
11434100	Yogurt, whole milk, flavors other than fruit
11434200	Yogurt, low fat milk, flavors other than fruit
11434300	Yogurt, nonfat milk, flavors other than fruit
11435000	Yogurt, Greek, NS as to type of milk, flavors other than fruit
11435010	Yogurt, Greek, whole milk, flavors other than fruit
11435020	Yogurt, Greek, low fat milk, flavors other than fruit
11435030	Yogurt, Greek, nonfat milk, flavors other than fruit
11435100	Yogurt, Greek, with oats
11446000	Yogurt parfait, low fat, with fruit

Yogurt Drinks
[MK-7] = 11.1 µg/100 g

11436000 Yogurt, liquid

Processed Fruits and Fruit Juices

Fruit Juices
[MK-7] = 4.2 µg/100 g

61201020 Grapefruit juice, 100%, NS as to form
61201220 Grapefruit juice, 100%, canned, bottled or in a carton
61201225 Grapefruit juice, 100%, with calcium added
61201620 Grapefruit juice,100%, frozen, reconstituted
61210000 Orange juice, 100%, NFS
61210220 Orange juice, 100%, canned, bottled or in a carton
61210250 Orange juice, 100%, with calcium added, canned, bottled or in a carton
61210620 Orange juice, 100%, frozen, reconstituted
61210720 Orange juice, 100%, frozen, not reconstituted
61210820 Orange juice, 100%, with calcium added, frozen, reconstituted
61213220 Tangerine juice, 100%
61213800 Fruit juice blend, citrus, 100% juice
61213900 Fruit juice blend, citrus, 100% juice, with calcium added
64100100 Fruit juice, NFS
64100110 Fruit juice blend, 100% juice
64100200 Cranberry juice blend, 100% juice
64100220 Cranberry juice blend, 100% juice, with calcium added
64101010 Apple cider
64104010 Apple juice, 100%
64104030 Apple juice, 100%, with calcium added
64104600 Blackberry juice, 100%
64104610 Blueberry juice
64105400 Cranberry juice, 100%, not a blend
64116020 Grape juice, 100%
64116060 Grape juice, 100%, with calcium added
64120010 Papaya juice, 100%
64121000 Passion fruit juice, 100%
64124020 Pineapple juice, 100%
64126000 Pomegranate juice, 100%
64132010 Prune juice, 100%
64132500 Strawberry juice, 100%
64133100 Watermelon juice, 100%
92510720 Fruit punch, made with fruit juice and soda
92510730 Fruit punch, made with soda, fruit juice, and sherbet or ice cream

95342000 Fruit juice, acai blend

Processed Vegetables and Vegetable Juices

Vegetable Juices
[MK-7] = 4.2 µg/100 g

73105000 Beet juice
73105010 Carrot juice, 100%
74301100 Tomato juice, 100%
74301150 Tomato juice, 100%, low sodium
74302000 Tomato juice cocktail
74303000 Tomato and vegetable juice, 100%
74303100 Tomato and vegetable juice, 100%, low sodium
75132000 Mixed vegetable juice
75132100 Celery juice
75200700 Aloe vera juice drink
78101000 Vegetable and fruit juice, 100% juice, with high vitamin C

Proposed Food Uses

Food Code	Main Food Description	MK-7 Content (µg/100 g)
92400000	Soft drink, NFS	2.8
92400100	Soft drink, NFS, diet	2.8
92410310	Soft drink, cola	2.8
92410315	Soft drink, cola, reduced sugar	2.8
92410320	Soft drink, cola, diet	2.8
92410340	Soft drink, cola, decaffeinated	2.8
92410350	Soft drink, cola, decaffeinated, diet	2.8
92410360	Soft drink, pepper type	2.8
92410370	Soft drink, pepper type, diet	2.8
92410390	Soft drink, pepper type, decaffeinated	2.8
92410400	Soft drink, pepper type, decaffeinated, diet	2.8
92410410	Soft drink, cream soda	2.8
92410420	Soft drink, cream soda, diet	2.8
92410510	Soft drink, fruit flavored, caffeine free	2.8
92410520	Soft drink, fruit flavored, diet, caffeine free	2.8
92410550	Soft drink, fruit flavored, caffeine containing	2.8
92410560	Soft drink, fruit flavored, caffeine containing, diet	2.8
92410610	Soft drink, ginger ale	2.8
92410620	Soft drink, ginger ale, diet	2.8
92410710	Soft drink, root beer	2.8
92410720	Soft drink, root beer, diet	2.8
92410810	Soft drink, chocolate flavored	2.8
92410820	Soft drink, chocolate flavored, diet	2.8
92411510	Soft drink, cola, fruit or vanilla flavored	2.8
92411520	Soft drink, cola, chocolate flavored	2.8
92411610	Soft drink, cola, fruit or vanilla flavored, diet	2.8
92411620	Soft drink, cola, chocolate flavored, diet	2.8
92432000	Fruit juice drink, citrus, carbonated	2.8
92433000	Fruit juice drink, noncitrus, carbonated	2.8
57000100	Cereal, oat, NFS	66.7
57100100	Cereal, ready-to-eat, NFS	66.7
57101000	Cereal (Kellogg's All-Bran)	66.7
57103000	Cereal (Post Alpha-Bits)	66.7
57103100	Cereal (General Mills Cheerios Apple Cinnamon)	66.7
57104000	Cereal (Kellogg's Apple Jacks)	66.7
57106050	Cereal (Post Great Grains Banana Nut Crunch)	66.7
57106060	Cereal (General Mills Cheerios Banana Nut)	66.7
57106260	Cereal (General Mills Cheerios Berry Burst)	66.7
57117000	Cereal (Quaker Cap'n Crunch)	66.7
57117500	Cereal (Quaker Christmas Crunch)	66.7
57119000	Cereal (Quaker Cap'n Crunch's Crunchberries)	66.7

Food Code	Main Food Description	MK-7 Content (µg/100 g)
57120000	Cereal (Quaker Cap'n Crunch's Peanut Butter Crunch)	66.7
57123000	Cereal (General Mills Cheerios)	66.7
57124030	Cereal (General Mills Chex Chocolate)	66.7
57124050	Cereal (General Mills Chex Cinnamon)	66.7
57124100	Cereal (General Mills Cheerios Chocolate)	66.7
57124200	Cereal, chocolate flavored, frosted, puffed corn	66.7
57124300	Cereal (General Mills Lucky Charms Chocolate)	66.7
57125000	Cereal (General Mills Cinnamon Toast Crunch)	66.7
57125010	Cereal (General Mills 25% Less Sugar Cinnamon Toast Crunch)	66.7
57125900	Cereal (General Mills Honey Nut Clusters)	66.7
57126000	Cereal (Kellogg's Cocoa Krispies)	66.7
57127000	Cereal (Post Cocoa Pebbles)	66.7
57128000	Cereal (General Mills Cocoa Puffs)	66.7
57130000	Cereal (General Mills Cookie Crisp)	66.7
57132000	Cereal (General Mills Chex Corn)	66.7
57134000	Cereal, corn flakes	66.7
57135000	Cereal (Kellogg's Corn Flakes)	66.7
57137000	Cereal, corn puffs	66.7
57139000	Cereal (General Mills Count Chocula)	66.7
57143000	Cereal (Kellogg's Cracklin' Oat Bran)	66.7
57143500	Cereal (Post Great Grains, Cranberry Almond Crunch)	66.7
57148000	Cereal (Kellogg's Crispix)	66.7
57151000	Cereal, crispy rice	66.7
57206700	Cereal (General Mills Fiber One)	66.7
57206710	Cereal (General Mills Fiber One Honey Clusters)	66.7
57206715	Cereal (General Mills Fiber One Raisin Bran Clusters)	66.7
57207000	Cereal, bran flakes	66.7
57208000	Cereal (Kellogg's All-Bran Complete Wheat Flakes)	66.7
57209000	Cereal (Post Bran Flakes)	66.7
57211000	Cereal (General Mills Frankenberry)	66.7
57213000	Cereal (Kellogg's Froot Loops)	66.7
57213010	Cereal (Kellogg's Froot Loops Marshmallow)	66.7
57213850	Cereal (General Mills Cheerios Frosted)	66.7
57214000	Cereal (Kellogg's Frosted Mini-Wheats)	66.7
57216000	Cereal, frosted rice	66.7
57221700	Cereal, fruit rings	66.7
57221810	Cereal (General Mills Cheerios Fruity)	66.7
57223000	Cereal (Post Fruity Pebbles)	66.7
57224000	Cereal (General Mills Golden Grahams)	66.7
57227000	Cereal, granola	66.7
57229000	Cereal (Kellogg's Low Fat Granola)	66.7
57230000	Cereal (Post Grape-Nuts)	66.7
57231200	Cereal (Post Great Grains Raisins, Dates, and Pecans)	66.7
57237100	Cereal (Post Honey Bunches of Oats Honey Roasted)	66.7

Food Code	Main Food Description	MK-7 Content (µg/100 g)
57237200	Cereal (Post Honey Bunches of Oats with Vanilla Bunches)	66.7
57237300	Cereal (Post Honey Bunches of Oats with Almonds)	66.7
57238000	Cereal (Post Honeycomb)	66.7
57240100	Cereal (General Mills Chex Honey Nut)	66.7
57241000	Cereal (General Mills Cheerios Honey Nut)	66.7
57241200	Cereal (Post Shredded Wheat Honey Nut)	66.7
57243000	Cereal (Kellogg's Honey Smacks)	66.7
57301500	Cereal (Kashi 7 Whole Grain Puffs)	66.7
57301505	Cereal (Kashi Autumn Wheat)	66.7
57301510	Cereal (Kashi GOLEAN)	66.7
57301511	Cereal (Kashi GOLEAN Crunch)	66.7
57301512	Cereal (Kashi GOLEAN Crunch Honey Almond Flax)	66.7
57301530	Cereal (Kashi Heart to Heart Honey Toasted Oat)	66.7
57303100	Cereal (General Mills Kix)	66.7
57303105	Cereal (General Mills Honey Kix)	66.7
57303200	Cereal (Kellogg's Krave)	66.7
57304100	Cereal (Quaker Life)	66.7
57305100	Cereal (General Mills Lucky Charms)	66.7
57305150	Cereal, frosted oat cereal with marshmallows	66.7
57305160	Cereal (Malt-O-Meal Blueberry Muffin Tops)	66.7
57305165	Cereal (Malt-O-Meal Cinnamon Toasters)	66.7
57305170	Cereal (Malt-O-Meal Coco-Roos)	66.7
57305174	Cereal (Malt-O-Meal Colossal Crunch)	66.7
57305175	Cereal (Malt-O-Meal Cocoa Dyno-Bites)	66.7
57305180	Cereal (Malt-O-Meal Corn Bursts)	66.7
57305210	Cereal (Malt-O-Meal Frosted Flakes)	66.7
57305300	Cereal (Malt-O-Meal Fruity Dyno-Bites)	66.7
57305400	Cereal (Malt-O-Meal Honey Graham Squares)	66.7
57305500	Cereal (Malt-O-Meal Honey Nut Toasty O's)	66.7
57305600	Cereal (Malt-O-Meal Marshmallow Mateys)	66.7
57306500	Cereal (Malt-O-Meal Golden Puffs)	66.7
57306700	Cereal (Malt-O-Meal Toasted Oat Cereal)	66.7
57306800	Cereal (Malt-O-Meal Tootie Fruities)	66.7
57308190	Cereal, muesli	66.7
57308400	Cereal (General Mills Cheerios Multigrain)	66.7
57309100	Cereal (Nature Valley Granola)	66.7
57316380	Cereal (General Mills Cheerios Oat Cluster Crunch)	66.7
57316385	Cereal (General Mills Cheerios Protein)	66.7
57316450	Cereal (General Mills Oatmeal Crisp with Almonds)	66.7
57316710	Cereal (Quaker Honey Graham Oh's)	66.7
57320500	Cereal (Quaker Granola with Oats, Honey, and Raisins)	66.7
57321900	Cereal (Nature's Path Organic Flax Plus)	66.7
57326000	Cereal (Barbara's Puffins)	66.7
57327450	Cereal (Quaker Toasted Oat Bran)	66.7

Food Code	Main Food Description	MK-7 Content (µg/100 g)
57327500	Cereal (Quaker Oatmeal Squares)	66.7
57329000	Cereal, raisin bran	66.7
57330000	Cereal (Kellogg's Raisin Bran)	66.7
57330010	Cereal (Kellogg's Raisin Bran Crunch)	66.7
57331000	Cereal (Post Raisin Bran)	66.7
57332100	Cereal (General Mills Raisin Nut Bran)	66.7
57335550	Cereal (General Mills Reese's Puffs)	66.7
57336000	Cereal (General Mills Chex Rice)	66.7
57337000	Cereal, rice flakes	66.7
57339000	Cereal (Kellogg's Rice Krispies)	66.7
57339500	Cereal (Kellogg's Rice Krispies Treats Cereal)	66.7
57340000	Cereal, puffed rice	66.7
57341200	Cereal (Kellogg's Smart Start Strong)	66.7
57341300	Cereal (Kellogg's Smorz)	66.7
57344000	Cereal (Kellogg's Special K)	66.7
57344001	Cereal (Kellogg's Special K Blueberry)	66.7
57344005	Cereal (Kellogg's Special K Chocolatey Delight)	66.7
57344010	Cereal (Kellogg's Special K Red Berries)	66.7
57344015	Cereal (Kellogg's Special K Fruit & Yogurt)	66.7
57344020	Cereal (Kellogg's Special K Vanilla Almond)	66.7
57344025	Cereal (Kellogg's Special K Cinnamon Pecan)	66.7
57347000	Cereal (Kellogg's Corn Pops)	66.7
57348000	Cereal, frosted corn flakes	66.7
57349000	Cereal (Kellogg's Frosted Flakes)	66.7
57355000	Cereal (Post Golden Crisp)	66.7
57401100	Cereal, toasted oat	66.7
57407100	Cereal (General Mills Trix)	66.7
57408100	Cereal (Uncle Sam)	66.7
57411000	Cereal (General Mills Chex Wheat)	66.7
57416000	Cereal, puffed wheat, plain	66.7
57416010	Cereal, puffed wheat, sweetened	66.7
57417000	Cereal (Post Shredded Wheat)	66.7
57418000	Cereal (General Mills Wheaties)	66.7
14610200	Cheese, cottage cheese, with gelatin dessert	9.1
14610210	Cheese, cottage cheese, with gelatin dessert and fruit	9.1
14610250	Cheese, cottage cheese, with gelatin dessert and vegetables	9.1
14200100	Cheese, cottage, NFS	9.1
14201010	Cheese, cottage, creamed, large or small curd	9.1
14201200	Cottage cheese, farmer's	9.1
14202010	Cheese, cottage, with fruit	9.1
14202020	Cheese, cottage, with vegetables	9.1
14203010	Cheese, cottage, dry curd	9.1
14203020	Cheese, cottage, salted, dry curd	9.1
14204010	Cheese, cottage, low fat	9.1

Food Code	Main Food Description	MK-7 Content (µg/100 g)
14204020	Cheese, cottage, lowfat, with fruit	9.1
14206010	Cheese, cottage, lowfat, low sodium	9.1
14207010	Cheese, cottage, lowfat, lactose reduced	9.1
14104110	Cheese, Cheddar, reduced fat	33.3
14104115	Cheese, Cheddar, nonfat or fat free	33.3
14106500	Cheese, Monterey, reduced fat	33.3
14107030	Cheese, Mozzarella, part skim	33.3
14107040	Cheese, Mozzarella, reduced sodium	33.3
14107060	Cheese, Mozzarella, nonfat or fat free	33.3
14107250	Cheese, Muenster, reduced fat	33.3
14108015	Cheese, Parmesan, dry grated, reduced fat	33.3
14108060	Cheese, Parmesan, dry grated, fat free	33.3
14108420	Cheese, provolone, reduced fat	33.3
14109030	Cheese, Swiss, reduced fat	33.3
14109040	Cheese, Swiss, nonfat or fat free	33.3
14120020	Cheese, Mexican blend, reduced fat	33.3
14201500	Cheese, Ricotta	33.3
14303010	Cream cheese, light	33.3
14410120	Cheese, American, reduced fat	33.3
14410130	Cheese, American, nonfat or fat free	33.3
14410330	Cheese spread, American or Cheddar cheese base, reduced fat	33.3
14410380	Cream cheese spread, fat free	33.3
14420210	Cheese spread, cream cheese, light	33.3
14640014	Cheese sandwich, reduced fat American cheese, on white bread, no spread	33.3
14640016	Cheese sandwich, reduced fat American cheese, on wheat bread, no spread	33.3
14640018	Cheese sandwich, reduced fat American cheese, on whole wheat bread, no spread	33.3
14640020	Cheese sandwich, reduced fat Cheddar cheese, on white bread, no spread	33.3
14640022	Cheese sandwich, reduced fat Cheddar cheese, on wheat bread, no spread	33.3
14640024	Cheese sandwich, reduced fat Cheddar cheese, on whole wheat bread, no spread	33.3
14640038	Cheese sandwich, reduced fat American cheese, on white bread, with mayonnaise	33.3
14640040	Cheese sandwich, reduced fat American cheese,, on wheat bread, with mayonnaise	33.3
14640042	Cheese sandwich, reduced fat American cheese, on whole wheat bread, with mayonnaise	33.3
14640044	Cheese sandwich, reduced fat Cheddar cheese, on white bread, with mayonnaise	33.3
14640046	Cheese sandwich, reduced fat Cheddar cheese, on wheat bread, with mayonnaise	33.3
14640048	Cheese sandwich, reduced fat Cheddar cheese, on whole wheat bread, with mayonnaise	33.3
14640062	Cheese sandwich, reduced fat American cheese, on white bread, with butter	33.3
14640064	Cheese sandwich, reduced fat American cheese, on wheat bread, with butter	33.3
14640066	Cheese sandwich, reduced fat American cheese, on whole wheat bread, with butter	33.3
14640068	Cheese sandwich, reduced fat Cheddar cheese, on white bread, with butter	33.3
14640070	Cheese sandwich, reduced fat Cheddar cheese, on wheat bread, with butter	33.3
14640072	Cheese sandwich, reduced fat Cheddar cheese, on whole wheat bread, with butter	33.3
14640155	Grilled cheese sandwich, reduced fat American cheese, on white bread	33.3

Food Code	Main Food Description	MK-7 Content (µg/100 g)
14640160	Grilled cheese sandwich, reduced fat American cheese, on wheat bread	33.3
14640165	Grilled cheese sandwich, reduced fat American cheese, on whole wheat bread	33.3
14640185	Grilled cheese sandwich, reduced fat Cheddar cheese, on white bread	33.3
14640190	Grilled cheese sandwich, reduced fat Cheddar cheese, on wheat bread	33.3
14640195	Grilled cheese sandwich, reduced fat Cheddar cheese, on whole wheat bread	33.3
81104010	Margarine-oil blend, tub, light	66.7
81104020	Margarine-oil blend, stick, light	66.7
27446225	Chicken or turkey salad, made with light mayonnaise	66.7
27450061	Tuna salad, made with light mayonnaise	66.7
32103015	Egg salad, made with light mayonnaise	66.7
58148111	Macaroni or pasta salad, made with light mayonnaise	66.7
71601015	Potato salad with egg, made with light mayonnaise	66.7
71603015	Potato salad, made with light mayonnaise	66.7
83204000	Mayonnaise, light	66.7
83204030	Mayonnaise, reduced fat, with olive oil	66.7
83300700	Mayonnaise, fat free	66.7
82104000	Olive oil	66.7
11459990	Frozen yogurt, NFS	11.1
11460000	Frozen yogurt, vanilla	11.1
11460100	Frozen yogurt, chocolate	11.1
11460500	Frozen yogurt, soft serve, vanilla	11.1
11460510	Frozen yogurt, soft serve, chocolate	11.1
11461200	Frozen yogurt sandwich	11.1
11461210	Frozen yogurt bar, vanilla	11.1
11461220	Frozen yogurt bar, chocolate	11.1
11461250	Frozen yogurt cone, chocolate	11.1
11461260	Frozen yogurt cone, vanilla	11.1
11461300	Frozen yogurt cone, vanilla, waffle cone	11.1
11461320	Frozen yogurt cone, chocolate, waffle cone	11.1
13110000	Ice cream, NFS	7.7
13110100	Ice cream, vanilla	7.7
13110102	Ice cream, vanilla, with additional ingredients	7.7
13110110	Ice cream, chocolate	7.7
13110112	Ice cream, chocolate, with additional ingredients	7.7
13110200	Ice cream, soft serve, vanilla	7.7
13110210	Ice cream, soft serve, chocolate	7.7
13110460	Gelato, vanilla	7.7
13110470	Gelato, chocolate	7.7
13120050	Ice cream bar, vanilla	7.7
13120100	Ice cream bar, vanilla, chocolate coated	7.7
13120110	Ice cream candy bar	7.7
13120140	Ice cream bar, chocolate	7.7
13120500	Ice cream sandwich, vanilla	7.7
13120510	Ice cream sandwich, chocolate	7.7

Food Code	Main Food Description	MK-7 Content (µg/100 g)
13120550	Ice cream cookie sandwich	7.7
13120730	Ice cream cone, scooped, vanilla	7.7
13120735	Ice cream cone, scooped, vanilla, waffle cone	7.7
13120740	Ice cream cone, NFS	7.7
13120770	Ice cream cone, scooped, chocolate	7.7
13120775	Ice cream cone, scooped, chocolate, waffle cone	7.7
13120782	Ice cream cone, soft serve, vanilla	7.7
13120784	Ice cream cone, soft serve, chocolate	7.7
13120786	Ice cream cone, soft serve, vanilla, waffle cone	7.7
13120788	Ice cream cone, soft serve, chocolate, waffle cone	7.7
13120790	Ice cream cone, vanilla, prepackaged	7.7
13120792	Ice cream cone, chocolate, prepackaged	7.7
13120800	Ice cream soda, flavors other than chocolate	7.7
13120810	Ice cream soda, chocolate	7.7
13121000	Ice cream sundae, NFS	7.7
13121100	Ice cream sundae, fruit topping	7.7
13121120	Banana split	7.7
13121300	Ice cream sundae, hot fudge topping	7.7
13121400	Ice cream sundae, caramel topping	7.7
13126000	Ice cream, fried	7.7
13130100	Light ice cream, NFS	7.7
13130300	Light ice cream, vanilla	7.7
13130310	Light ice cream, chocolate	7.7
13130700	Soft serve, blended with candy or cookies, from fast food	7.7
13135000	Light ice cream sandwich, vanilla	7.7
13135010	Light ice cream sandwich, chocolate	7.7
13140000	Light ice cream bar, vanilla	7.7
13140100	Light ice cream bar, vanilla, chocolate coated	7.7
13140115	Light ice cream bar, chocolate	7.7
13142100	Light ice cream cone, vanilla, prepackaged	7.7
13142110	Light ice cream cone, chocolate, prepackaged	7.7
53710400	Cereal or granola bar (General Mills Fiber One Chewy Bar)	25
53710500	Cereal or granola bar (Kellogg's Nutri-Grain Cereal Bar)	25
53710502	Cereal or granola bar (Kellogg's Nutri-Grain Yogurt Bar)	25
53710504	Cereal or granola bar (Kellogg's Nutri-Grain Fruit and Nut Bar)	25
53710600	Milk 'n Cereal bar	25
53710700	Cereal or granola bar (Kellogg's Special K bar)	25
53710800	Cereal or granola bar (Kashi Chewy)	25
53710802	Cereal or granola bar (Kashi Crunchy)	25
53710810	Cereal or granola bar (KIND Fruit and Nut Bar)	25
53710900	Cereal or granola bar (General Mills Nature Valley Chewy Trail Mix)	25
53710902	Cereal or granola bar, with yogurt coating (General Mills Nature Valley Chewy Granola Bar)	25
53710904	Cereal or granola bar (General Mills Nature Valley Sweet and Salty Granola Bar)	25

Food Code	Main Food Description	MK-7 Content (µg/100 g)
53710906	Cereal or granola bar (General Mills Nature Valley Crunchy Granola Bar)	25
53711000	Cereal or granola bar (Quaker Chewy Granola Bar)	25
53711002	Cereal or granola bar (Quaker Chewy 90 Calorie Granola Bar)	25
53711004	Cereal or granola bar (Quaker Chewy 25% Less Sugar Granola Bar)	25
53711006	Cereal or granola bar (Quaker Chewy Dipps Granola Bar)	25
53711100	Cereal or granola bar (Quaker Granola Bites)	25
53712000	Snack bar, oatmeal	25
53712100	Cereal or Granola bar, NFS	25
53712200	Cereal or granola bar, lowfat, NFS	25
53712210	Cereal or granola bar, nonfat	25
53713000	Cereal or granola bar, reduced sugar, NFS	25
53713010	Cereal or granola bar, fruit and nut	25
53713100	Cereal or granola bar, peanuts , oats, sugar, wheat germ	25
53714200	Cereal or granola bar, chocolate coated, NFS	25
53714210	Cereal or granola bar, with coconut, chocolate coated	25
53714220	Cereal or granola bar with nuts, chocolate coated	25
53714230	Cereal or granola bar, oats, nuts, coated with non-chocolate coating	25
53714250	Cereal or granola bar, coated with non-chocolate coating	25
53714300	Cereal or granola bar, high fiber, coated with non-chocolate yogurt coating	25
53714400	Cereal or granola bar, with rice cereal	25
53714500	Breakfast bar, NFS	25
53714510	Breakfast bar, date, with yogurt coating	25
53714520	Breakfast bar, cereal crust with fruit filling, lowfat	25
56104000	Pasta, vegetable, cooked	7.1
56112000	Noodles, cooked	7.1
56113000	Noodles, whole grain, cooked	7.1
56113990	Noodles, vegetable, cooked	7.1
56116990	Long rice noodles, made from mung beans, cooked	7.1
56117090	Rice noodles, cooked	7.1
56130000	Pasta, cooked	7.1
56132990	Pasta, whole grain, cooked	7.1
56140100	Pasta, gluten free	7.1
58122210	Gnocchi, cheese	7.1
58122220	Gnocchi, potato	7.1
58130011	Lasagna with meat	7.1
58130013	Lasagna with meat, canned	7.1
58130014	Lasagna with meat, from restaurant	7.1
58130016	Lasagna with meat, frozen	7.1
58130020	Lasagna with meat and spinach	7.1
58130140	Lasagna with chicken or turkey	7.1
58130150	Lasagna, with chicken or turkey, and spinach	7.1
58130310	Lasagna, meatless	7.1
58130320	Lasagna, meatless, with vegetables	7.1
58131100	Ravioli, NS as to filling, no sauce	7.1

Food Code	Main Food Description	MK-7 Content (µg/100 g)
58131110	Ravioli, NS as to filling, with tomato sauce	7.1
58131120	Ravioli, NS as to filling, with cream sauce	7.1
58131310	Ravioli, meat-filled, no sauce	7.1
58131320	Ravioli, meat-filled, with tomato sauce or meat sauce	7.1
58131323	Ravioli, meat-filled, with tomato sauce or meat sauce, canned	7.1
58131330	Ravioli, meat-filled, with cream sauce	7.1
58131510	Ravioli, cheese-filled, no sauce	7.1
58131520	Ravioli, cheese-filled, with tomato sauce	7.1
58131523	Ravioli, cheese-filled, with tomato sauce, canned	7.1
58131530	Ravioli, cheese-filled, with meat sauce	7.1
58131535	Ravioli, cheese-filled, with cream sauce	7.1
58131590	Ravioli, cheese and spinach-filled, no sauce	7.1
58131600	Ravioli, cheese and spinach-filled, with cream sauce	7.1
58131610	Ravioli, cheese and spinach filled, with tomato sauce	7.1
58133110	Manicotti, cheese-filled, no sauce	7.1
58133120	Manicotti, cheese-filled, with tomato sauce, meatless	7.1
58133130	Manicotti, cheese-filled, with meat sauce	7.1
58133140	Manicotti, vegetable- and cheese-filled, with tomato sauce, meatless	7.1
58134110	Stuffed shells, cheese-filled, no sauce	7.1
58134120	Stuffed shells, cheese-filled, with tomato sauce, meatless	7.1
58134130	Stuffed shells, cheese-filled, with meat sauce	7.1
58134160	Stuffed shells, cheese- and spinach- filled, no sauce	7.1
58134210	Stuffed shells, with chicken, with tomato sauce	7.1
58134310	Stuffed shells, with fish and/or shellfish, with tomato sauce	7.1
58134610	Tortellini, meat-filled, with tomato sauce	7.1
58134613	Tortellini, meat-filled, with tomato sauce, canned	7.1
58134620	Tortellini, cheese-filled, meatless, with tomato sauce	7.1
58134623	Tortellini, cheese-filled, meatless, with tomato sauce, canned	7.1
58134640	Tortellini, cheese-filled, meatless, with vinaigrette dressing	7.1
58134650	Tortellini, meat-filled, no sauce	7.1
58134660	Tortellini, cheese-filled, with cream sauce	7.1
58134680	Tortellini, cheese-filled, no sauce	7.1
58134710	Tortellini, spinach-filled, with tomato sauce	7.1
58134720	Tortellini, spinach-filled, no sauce	7.1
58134810	Cannelloni, cheese- and spinach-filled, no sauce	7.1
58140110	Spaghetti with corned beef, Puerto Rican style	7.1
58140310	Macaroni with tuna, Puerto Rican style	7.1
58145110	Macaroni or noodles with cheese	7.1
58145111	Macaroni or noodles with cheese, from restaurant	7.1
58145112	Macaroni or noodles with cheese, made from packaged mix	7.1
58145113	Macaroni or noodles with cheese, canned	7.1
58145117	Macaroni or noodles with cheese, Easy Mac type	7.1
58145119	Macaroni or noodles with cheese, made from reduced fat packaged mix	7.1
58145120	Macaroni or noodles with cheese and tuna	7.1

Food Code	Main Food Description	MK-7 Content (µg/100 g)
58145135	Macaroni or noodles with cheese and meat	7.1
58145136	Macaroni or noodles with cheese and meat, prepared from Hamburger Helper mix	7.1
58145140	Macaroni or noodles with cheese and tomato	7.1
58145160	Macaroni or noodles with cheese and frankfurters or hot dogs	7.1
58145170	Macaroni or noodles with cheese and egg	7.1
58145190	Macaroni or noodles with cheese and chicken or turkey	7.1
58145300	Macaroni or noodles with cheese, whole grain	7.1
58146120	Pasta with tomato-based sauce, cheese and meat	7.1
58146150	Pasta with tomato-based sauce and cheese	7.1
58146160	Pasta with vegetables, no sauce or dressing	7.1
58146210	Pasta with sauce, NFS	7.1
58146215	Pasta with sauce, meatless, school lunch	7.1
58146221	Pasta with tomato-based sauce, restaurant	7.1
58146223	Pasta with tomato-based sauce, ready-to-heat	7.1
58146301	Pasta with tomato-based sauce, and added vegetables, restaurant	7.1
58146303	Pasta with tomato-based sauce, and added vegetables, ready-to-heat	7.1
58146315	Pasta with sauce and meat, from school lunch	7.1
58146321	Pasta with tomato-based sauce and meat, restaurant	7.1
58146323	Pasta with tomato-based sauce and meat, ready-to-heat	7.1
58146331	Pasta with tomato-based sauce, meat, and added vegetables, restaurant	7.1
58146333	Pasta with tomato-based sauce, meat, and added vegetables, ready-to-heat	7.1
58146341	Pasta with tomato-based sauce and poultry, restaurant	7.1
58146343	Pasta with tomato-based sauce and poultry, ready-to-heat	7.1
58146351	Pasta with tomato-based sauce, poultry, and added vegetables, restaurant	7.1
58146353	Pasta with tomato-based sauce, poultry, and added vegetables, ready-to-heat	7.1
58146361	Pasta with tomato-based sauce and seafood, restaurant	7.1
58146363	Pasta with tomato-based sauce and seafood, ready-to-heat	7.1
58146371	Pasta with tomato-based sauce, seafood, and added vegetables, restaurant	7.1
58146373	Pasta with tomato-based sauce, seafood, and added vegetables, ready-to-heat	7.1
58146381	Pasta with cream sauce, restaurant	7.1
58146383	Pasta with cream sauce, ready-to-heat	7.1
58146391	Pasta with cream sauce and added vegetables, restaurant	7.1
58146393	Pasta with cream sauce and added vegetables, ready-to-heat	7.1
58146401	Pasta with cream sauce and meat, restaurant	7.1
58146403	Pasta with cream sauce and meat, ready-to-heat	7.1
58146411	Pasta with cream sauce, meat, and added vegetables, restaurant	7.1
58146413	Pasta with cream sauce, meat, and added vegetables, ready-to-heat	7.1
58146421	Pasta with cream sauce and poultry, restaurant	7.1
58146423	Pasta with cream sauce and poultry, ready-to-heat	7.1
58146431	Pasta with cream sauce, poultry, and added vegetables, restaurant	7.1
58146433	Pasta with cream sauce, poultry, and added vegetables, ready-to-heat	7.1
58146441	Pasta with cream sauce and seafood, restaurant	7.1
58146443	Pasta with cream sauce and seafood, ready-to-heat	7.1
58146451	Pasta with cream sauce, seafood, and added vegetables, restaurant	7.1

Food Code	Main Food Description	MK-7 Content (µg/100 g)
58146453	Pasta with cream sauce, seafood, and added vegetables, ready-to-heat	7.1
58146601	Pasta, whole grain, with tomato-based sauce, restaurant	7.1
58146603	Pasta, whole grain, with tomato-based sauce, ready-to-heat	7.1
58146611	Pasta, whole grain, with tomato-based sauce and added vegetables, restaurant	7.1
58146613	Pasta, whole grain, with tomato-based sauce and added vegetables, ready-to-heat	7.1
58146621	Pasta, whole grain, with tomato-based sauce and meat, restaurant	7.1
58146623	Pasta, whole grain, with tomato-based sauce and meat, ready-to-heat	7.1
58146631	Pasta, whole grain, with tomato-based sauce, meat, and added vegetables, restaurant	7.1
58146633	Pasta, whole grain, with tomato-based sauce, meat, and added vegetables, ready-to-heat	7.1
58146641	Pasta, whole grain, with tomato-based sauce and poultry, restaurant	7.1
58146643	Pasta, whole grain, with tomato-based sauce and poultry, ready-to-heat	7.1
58146651	Pasta, whole grain, with tomato-based sauce, poultry, and added vegetables, restaurant	7.1
58146653	Pasta, whole grain, with tomato-based sauce, poultry, and added vegetables, ready-to-heat	7.1
58146661	Pasta, whole grain, with tomato-based sauce and seafood, restaurant	7.1
58146663	Pasta, whole grain, with tomato-based sauce and seafood, ready-to-heat	7.1
58146671	Pasta, whole grain, with tomato-based sauce, seafood, and added vegetables, restaurant	7.1
58146673	Pasta, whole grain, with tomato-based sauce, seafood, and added vegetables, ready-to-heat	7.1
58146681	Pasta, whole grain, with cream sauce, restaurant	7.1
58146683	Pasta, whole grain, with cream sauce, ready-to-heat	7.1
58146691	Pasta, whole grain, with cream sauce, and added vegetables, restaurant	7.1
58146693	Pasta, whole grain, with cream sauce, and added vegetables, ready-to-heat	7.1
58146701	Pasta, whole grain, with cream sauce and meat, restaurant	7.1
58146703	Pasta, whole grain, with cream sauce and meat, ready-to-heat	7.1
58146711	Pasta, whole grain, with cream sauce, meat, and added vegetables, restaurant	7.1
58146713	Pasta, whole grain, with cream sauce, meat, and added vegetables, ready-to-heat	7.1
58146721	Pasta, whole grain, with cream sauce and poultry, restaurant	7.1
58146723	Pasta, whole grain, with cream sauce and poultry, ready-to-heat	7.1
58146731	Pasta, whole grain, with cream sauce, poultry, and added vegetables, restaurant	7.1
58146733	Pasta, whole grain, with cream sauce, poultry, and added vegetables, ready-to-heat	7.1
58146741	Pasta, whole grain, with cream sauce and seafood, restaurant	7.1
58146743	Pasta, whole grain, with cream sauce and seafood, ready-to-heat	7.1
58146751	Pasta, whole grain, with cream sauce, seafood, and added vegetables, restaurant	7.1
58146753	Pasta, whole grain, with cream sauce, seafood, and added vegetables, ready-to-heat	7.1
58147110	Pasta with tomato-based sauce and beans or lentils	7.1
58147330	Macaroni or noodles, creamed, with cheese	7.1
58147340	Macaroni or noodles, creamed, with cheese and tuna	7.1
58147510	Flavored pasta	7.1
58301050	Lasagna with cheese and meat sauce, diet frozen meal	7.1

Food Code	Main Food Description	MK-7 Content (µg/100 g)
58301110	Vegetable lasagna, frozen meal	7.1
58302000	Macaroni and cheese, diet frozen meal	7.1
58304010	Spaghetti and meatballs dinner, NFS, frozen meal	7.1
58304050	Spaghetti with meat and mushroom sauce, diet frozen meal	7.1
58304060	Spaghetti with meat sauce, diet frozen meal	7.1
58304200	Ravioli, cheese-filled, with tomato sauce, diet frozen meal	7.1
58305250	Pasta with vegetable and cheese sauce, diet frozen meal	7.1
58106200	Pizza, cheese, from frozen, thin crust	18.1
58106205	Pizza, cheese, from frozen, thick crust	18.1
58106210	Pizza, cheese, from restaurant or fast food, NS as to type of crust	18.1
58106220	Pizza, cheese, from restaurant or fast food, thin crust	18.1
58106225	Pizza, cheese, from restaurant or fast food, medium crust	18.1
58106230	Pizza, cheese, from restaurant or fast food, thick crust	18.1
58106233	Pizza, cheese, stuffed crust	18.1
58106234	Pizza, cheese, from school lunch, medium crust	18.1
58106235	Pizza, cheese, from school lunch, thin crust	18.1
58106236	Pizza, cheese, from school lunch, thick crust	18.1
58106250	Pizza, extra cheese, thin crust	18.1
58106260	Pizza, extra cheese, thick crust	18.1
58106300	Pizza, cheese, with vegetables, from frozen, thin crust	18.1
58106305	Pizza, cheese with vegetables, from frozen, thick crust	18.1
58106320	Pizza, cheese, with vegetables, from restaurant or fast food, thin crust	18.1
58106325	Pizza, cheese, with vegetables, from restaurant or fast food, medium crust	18.1
58106330	Pizza, cheese, with vegetables, from restaurant or fast food, thick crust	18.1
58106345	Pizza with cheese and extra vegetables, thin crust	18.1
58106347	Pizza with cheese and extra vegetables, medium crust	18.1
58106350	Pizza with cheese and extra vegetables, thick crust	18.1
58106358	Pizza, cheese, with fruit, thin crust	18.1
58106359	Pizza, cheese, with fruit, medium crust	18.1
58106360	Pizza, cheese, with fruit, thick crust	18.1
58106512	Pizza with pepperoni, from frozen, thin crust	18.1
58106514	Pizza with pepperoni, from frozen, medium crust	18.1
58106516	Pizza with pepperoni, from frozen, thick crust	18.1
58106540	Pizza with pepperoni, from restaurant or fast food, NS as to type of crust	18.1
58106550	Pizza with pepperoni, from restaurant or fast food, thin crust	18.1
58106555	Pizza with pepperoni, from restaurant or fast food, medium crust	18.1
58106560	Pizza with pepperoni, from restaurant or fast food, thick crust	18.1
58106565	Pizza with pepperoni, stuffed crust	18.1
58106570	Pizza with pepperoni, from school lunch, thin crust	18.1
58106578	Pizza, with pepperoni, from school lunch, medium crust	18.1
58106580	Pizza with pepperoni, from school lunch, thick crust	18.1
58106602	Pizza with meat other than pepperoni, from frozen, thin crust	18.1
58106604	Pizza with meat other than pepperoni, from frozen, medium crust	18.1
58106606	Pizza with meat other than pepperoni, from frozen, thick crust	18.1

Food Code	Main Food Description	MK-7 Content (µg/100 g)
58106610	Pizza with meat other than pepperoni, from restaurant or fast food, NS as to type of crust	18.1
58106620	Pizza with meat other than pepperoni, from restaurant or fast food, thin crust	18.1
58106625	Pizza with meat other than pepperoni, from restaurant or fast food, medium crust	18.1
58106630	Pizza with meat other than pepperoni, from restaurant or fast food, thick crust	18.1
58106633	Pizza, with meat other than pepperoni, stuffed crust	18.1
58106634	Pizza, with meat other than pepperoni, from school lunch, medium crust	18.1
58106635	Pizza, with meat other than pepperoni, from school lunch, thin crust	18.1
58106636	Pizza, with meat other than pepperoni, from school lunch, thick crust	18.1
58106650	Pizza with extra meat, thin crust	18.1
58106655	Pizza with extra meat, medium crust	18.1
58106660	Pizza with extra meat, thick crust	18.1
58106700	Pizza with meat and vegetables, from frozen, thin crust	18.1
58106702	Pizza with meat and vegetables, from frozen, medium crust	18.1
58106705	Pizza with meat and vegetables, from frozen, thick crust	18.1
58106720	Pizza with meat and vegetables, from restaurant or fast food, thin crust	18.1
58106725	Pizza with meat and vegetables, from restaurant or fast food, medium crust	18.1
58106730	Pizza with meat and vegetables, from restaurant or fast food, thick crust	18.1
58106736	Pizza with extra meat and extra vegetables, thin crust	18.1
58106737	Pizza with extra meat and extra vegetables, thick crust	18.1
58106738	Pizza with extra meat and extra vegetables, medium crust	18.1
58106750	Pizza with meat and fruit, thin crust	18.1
58106755	Pizza with meat and fruit, medium crust	18.1
58106760	Pizza with meat and fruit, thick crust	18.1
58106820	Pizza with beans and vegetables, thin crust	18.1
58106830	Pizza with beans and vegetables, thick crust	18.1
58107050	Pizza, no cheese, thin crust	18.1
58107100	Pizza, no cheese, thick crust	18.1
58107205	White pizza, cheese, thin crust	18.1
58107207	White pizza, cheese, thick crust	18.1
58107212	White pizza, cheese, with vegetables, thin crust	18.1
58107214	White pizza, cheese, with vegetables, thick crust	18.1
58107222	White pizza, cheese, with meat, thin crust	18.1
58107224	White pizza, cheese, with meat, thick crust	18.1
58107232	White pizza, cheese, with meat and vegetables, thin crust	18.1
58107234	White pizza, cheese, with meat and vegetables, thick crust	18.1
58108000	Calzone, with cheese, meatless	18.1
58108010	Calzone, with meat and cheese	18.1
58108050	Pizza rolls	18.1
58109015	Pizza, cheese, whole wheat thin crust	18.1
58109020	Pizza, cheese, whole wheat thick crust	18.1
58109030	Pizza, with meat, whole wheat thin crust	18.1
58109040	Pizza, with meat, whole wheat thick crust	18.1
58109050	Pizza, cheese and vegetables, whole wheat thin crust	18.1

Food Code	Main Food Description	MK-7 Content (µg/100 g)
58109060	Pizza, cheese and vegetables, whole wheat thick crust	18.1
58109100	Pizza, cheese, gluten-free thin crust	18.1
58109110	Pizza, cheese, gluten-free thick crust	18.1
58109120	Pizza, with meat, gluten-free thin crust	18.1
58109130	Pizza, with meat, gluten-free thick crust	18.1
58109140	Pizza, cheese and vegetables, gluten-free thin crust	18.1
58109150	Pizza, cheese and vegetables, gluten-free thick crust	18.1
11100000	Milk, NFS	4.2
11111000	Milk, whole	4.2
11111100	Milk, low sodium, whole	4.2
11111150	Milk, calcium fortified, whole	4.2
11111160	Milk, calcium fortified, low fat (1%)	4.2
11111170	Milk, calcium fortified, fat free (skim)	4.2
11112110	Milk, reduced fat (2%)	4.2
11112120	Milk, acidophilus, low fat (1%)	4.2
11112130	Milk, acidophilus, reduced fat (2%)	4.2
11112210	Milk, low fat (1%)	4.2
11113000	Milk, fat free (skim)	4.2
11114300	Milk, lactose free, low fat (1%)	4.2
11114320	Milk, lactose free, fat free (skim)	4.2
11114330	Milk, lactose free, reduced fat (2%)	4.2
11114350	Milk, lactose free, whole	4.2
11115000	Buttermilk, fat free (skim)	4.2
11115100	Buttermilk, low fat (1%)	4.2
11115200	Buttermilk, reduced fat (2%)	4.2
11115300	Buttermilk, whole	4.2
11115400	Kefir, NS as to fat content	4.2
11116000	Goat's milk, whole	4.2
11210050	Milk, evaporated, NS as to fat content	4.2
11211050	Milk, evaporated, whole	4.2
11211400	Milk, evaporated, reduced fat (2%)	4.2
11212050	Milk, evaporated, fat free (skim)	4.2
11220000	Milk, condensed, sweetened	4.2
12100100	Cream, NS as to light, heavy, or half and half	66.7
12110100	Cream, light	66.7
12120100	Cream, half and half	66.7
12120106	Cream, half and half, flavored	66.7
12120110	Cream, half and half, fat free	66.7
12130100	Cream, heavy	66.7
11400000	Yogurt, NFS	5.9
11400010	Yogurt, Greek, NS as to type of milk or flavor	5.9
11410000	Yogurt, NS as to type of milk or flavor	5.9
11411010	Yogurt, NS as to type of milk, plain	5.9
11411100	Yogurt, whole milk, plain	5.9

Food Code	Main Food Description	MK-7 Content (µg/100 g)
11411200	Yogurt, low fat milk, plain	5.9
11411300	Yogurt, nonfat milk, plain	5.9
11411390	Yogurt, Greek, NS as to type of milk, plain	5.9
11411400	Yogurt, Greek, whole milk, plain	5.9
11411410	Yogurt, Greek, low fat milk, plain	5.9
11411420	Yogurt, Greek, nonfat milk, plain	5.9
11430000	Yogurt, NS as to type of milk, fruit	5.9
11431000	Yogurt, whole milk, fruit	5.9
11432000	Yogurt, low fat milk, fruit	5.9
11433000	Yogurt, nonfat milk, fruit	5.9
11433990	Yogurt, Greek, NS as to type of milk, fruit	5.9
11434000	Yogurt, Greek, whole milk, fruit	5.9
11434010	Yogurt, Greek, low fat milk, fruit	5.9
11434020	Yogurt, Greek, nonfat milk, fruit	5.9
11434090	Yogurt, NS as to type of milk, flavors other than fruit	5.9
11434100	Yogurt, whole milk, flavors other than fruit	5.9
11434200	Yogurt, low fat milk, flavors other than fruit	5.9
11434300	Yogurt, nonfat milk, flavors other than fruit	5.9
11435000	Yogurt, Greek, NS as to type of milk, flavors other than fruit	5.9
11435010	Yogurt, Greek, whole milk, flavors other than fruit	5.9
11435020	Yogurt, Greek, low fat milk, flavors other than fruit	5.9
11435030	Yogurt, Greek, nonfat milk, flavors other than fruit	5.9
11435100	Yogurt, Greek, with oats	5.9
11446000	Yogurt parfait, low fat, with fruit	5.9
11436000	Yogurt, liquid	11.1
61201020	Grapefruit juice, 100%, NS as to form	4.2
61201220	Grapefruit juice, 100%, canned, bottled or in a carton	4.2
61201225	Grapefruit juice, 100%, with calcium added	4.2
61201620	Grapefruit juice,100%, frozen, reconstituted	4.2
61210000	Orange juice, 100%, NFS	4.2
61210220	Orange juice, 100%, canned, bottled or in a carton	4.2
61210250	Orange juice, 100%, with calcium added, canned, bottled or in a carton	4.2
61210620	Orange juice, 100%, frozen, reconstituted	4.2
61210720	Orange juice, 100%, frozen, not reconstituted	4.2
61210820	Orange juice, 100%, with calcium added, frozen, reconstituted	4.2
61213220	Tangerine juice, 100%	4.2
61213800	Fruit juice blend, citrus, 100% juice	4.2
61213900	Fruit juice blend, citrus, 100% juice, with calcium added	4.2
64100100	Fruit juice, NFS	4.2
64100110	Fruit juice blend, 100% juice	4.2
64100200	Cranberry juice blend, 100% juice	4.2
64100220	Cranberry juice blend, 100% juice, with calcium added	4.2
64101010	Apple cider	4.2
64104010	Apple juice, 100%	4.2

Food Code	Main Food Description	MK-7 Content (µg/100 g)
64104030	Apple juice, 100%, with calcium added	4.2
64104600	Blackberry juice, 100%	4.2
64104610	Blueberry juice	4.2
64105400	Cranberry juice, 100%, not a blend	4.2
64116020	Grape juice, 100%	4.2
64116060	Grape juice, 100%, with calcium added	4.2
64120010	Papaya juice, 100%	4.2
64121000	Passion fruit juice, 100%	4.2
64124020	Pineapple juice, 100%	4.2
64126000	Pomegranate juice, 100%	4.2
64132010	Prune juice, 100%	4.2
64132500	Strawberry juice, 100%	4.2
64133100	Watermelon juice, 100%	4.2
92510720	Fruit punch, made with fruit juice and soda	4.2
92510730	Fruit punch, made with soda, fruit juice, and sherbet or ice cream	4.2
95342000	Fruit juice, acai blend	4.2
73105000	Beet juice	4.2
73105010	Carrot juice, 100%	4.2
74301100	Tomato juice, 100%	4.2
74301150	Tomato juice, 100%, low sodium	4.2
74302000	Tomato juice cocktail	4.2
74303000	Tomato and vegetable juice, 100%	4.2
74303100	Tomato and vegetable juice, 100%, low sodium	4.2
75132000	Mixed vegetable juice	4.2
75132100	Celery juice	4.2
75200700	Aloe vera juice drink	4.2
78101000	Vegetable and fruit juice, 100% juice, with high vitamin C	4.2

APPENDIX C
Representative Food Codes for the Background Diet Levels of Vitamin K Isomers (2017-2018 NHANES Data)