Report of the Scientific Committee for Animal Nutrition
on the classification of vitamins
in the Annex to Council Directive 70/524/EEC
concerning additives in animal feedingstuffs
(Opinion expressed on 18 March 1994)

TERMS OF REFERENCE (June 1991)

The Commission requested the SCAN to provide its advice for the preparation of a definitive list of vitamins and vitamin-like substances for use within the frameworks of the Annexes to Council Directive 70/524/EEC[1] concerning additives in animal feedingstuffs, as amended by Council Directive 84/587/EEC of 29 November 1984[2,] and more specifically,

1. How could be reorganised chapter H "Vitamins provitamins and chemically well defined substances having a similar effect" of the Annex I and in doing so,

2. Which substances could be included in this Chapter?

BACKGROUND

The Commission, at the request of the member States, is drafting a proposal for the reorganisation of Chapter H Council Directive 70/524/EEC concerning additives in animal feedingstuffs. In accordance to this directive, the use and labelling of vitamin-additives in animal feedingstuffs must fulfil the following prerequisites:

- The conditions of the Article 7 (Efficacy, Safety for human being and environment, control) also apply as is the case of the necessity of submitting a dossier (Article 9).

- Only the chemical form indicated in the annex may be indicated in the label.

- If total vitamin content is indicated in the label, this must include also that of natural origin.

- Article 12 fixes maximum levels for Vitamin D, and since 18.05.1991 maximum levels apply provisionally to Vitamin A.

- The MS's must control manufacturers of vitamins and premix, these must fulfil the minimum conditions set in Annex III

For the marketing of vitamin-additives, the labelling provisions of Article 14 makes it compulsory to indicate

- the level and expiring date of alpha-tocopherol (Article 14.1 B, a),

1 O.J. No. L270 (14.12.70) p.1
2 O.J. No. L319 (08.12.84) p.13

- the active substance and expiring date for other vitamins (Article 14.1 B, c),

- if the vitamin additive is sold in the form of premixtures the label must also indicate "to be used exclusively for manufacturers of premixtures" (Article 14.1 B, e).

Article 15 makes it compulsory to label alpha-tocopherol levels and expiring date for vitamin E (Article 15.1 B, d) while for other vitamins, provitamins and substances having similar effect, the specific name in accordance with Annexes I and II must be indicated, the active substance level and expiring date (Article 15.1 B, e). The expiring date shown on the label must be one single date: namely the deadline that will be reached first.

Feedingstuffs can be marketed only if the label fixing responsibilities on the producer, packer, importer, seller or distributor, indicates levels and expiring dates of alpha-tocopherol or specific name, active substance level, and expiring date for other vitamins (Article 16.1 d & e). In this respect vitamins other than A, D, & E, provitamins and additives having a similar effect may be indicated if the amounts of these substances can be determined by official methods of analysis. In this case, the name of the active substance level and expiring date must also be given.

It must be clearly printed in the label, container or in the package, the level added (Article 16.5 b) EEC number or trade name (Article 16.5 c) and expiring date, namely the deadline which will be reached first (Article 16.6). Any other references shall be prohibited by Member States.

Concerning the measures to ensure that additive or premixes are officially checked in respect of the identity, the manufacturers must inform the authorities and margins of tolerance may be fixed to be allowed where there is discrepancy between official check and stated content of the additive.

OPINION OF THE COMMITTEE

The attached Appendix 1 represents the responses of the Scientific Committee for Animal nutrition (SCAN) to the Commission's request for SCAN to consider the preparation of a definitive list of vitamins and vitamin-like substances for use within the frameworks of Annexes to Council Directive 70/524/EEC[3].

In forming its views SCAN has taken cognisance of points the have been raised by national experts and by those representing the industry and is of the opinion that the list represents the most appropriate categorisation that can be derived taking into account the present state of knowledge.

In coming to its conclusions SCAN has encountered a number of areas that may require further consideration in the light of additional information and it may therefore be necessary to further review the detail of the classification at intervals in the future. The following points should be noted specifically:

3 O.J. No L270 (14.12.70) p.1

1. With a few minor exceptions SCAN is unaware of any problems which have arisen through the traditional approach to the classification of vitamins and it has therefore been content to recommend that approach should be continued. This allows the main vitamin substances whether derived from natural sources or by chemical synthesis to be classified by chemistry and function in a way that will be understood generally both by the technical and non-technical users of the classification.

   With regard to the vitamin-like substances that have been classified as "Cofactors and Substances with a similar Biological Activity" the position is more problematic. There are a number of substances which are added to feeds and for which cofactor-like responses could possibly be claimed. Some of these are already dealt with as feed additives under Council Directive 70/524/eec whilst for others the evidence of their activity and more of action is limited or lacking. SCAN's listing has therefore been conservative and it should be recognised that further research may result in the discovery of co-factors that are not included in the present list.

   Conversely, SCAN is aware of some commercial applications of "Co-factors and Substances with Similar Biological Activity" that may go beyond that which may be fully substantiated scientifically given the substances characteristics and known the mode of activity.

   It has therefore been recommended that these substances should be kept under particular scrutiny and that the firms interested in their sale should document, in a preliminary form, the activity and the efficacy of their products for the purposes claimed.

2. Alongside the classification of the major groups of vitamins and vitamin-like substances SCAN has considered the specific chemical substances that should be listed within each group. In doing this the approach has been to favour the common chemical names through which the materials are known rather than using the strict chemical nomenclature, and associated chemical formulae, the benefit of the approach adopted in terms of familiarity to the industry is clear. However, there may be an argument for a more precise chemical definition by formulae where substances can be purchased in no-hydrated or hydrated forms and it is recommended that this is kept under review.

   At present there is no evidence of confusion in the market arising from any lack of definition in the specification of substances, whether they are derived from natural sources or by chemical synthesis.

3. In selecting the specific substances to be included in the "within additive" listing SCAN has been influenced by a number of considerations. It was concluded that there were drawbacks and potential dangers in listing all known or potential forms of the active chemical and the approach adopted has therefore been to identify those which in use presently and for which there is a body of scientific evidence of utility, efficacy and safety within known field and limits of dosage. In coming to conclusions on the substances it should be said that, whilst there is no general cause for concern, there are areas in which information is limited and further scientific research is required. For

example, there is a need for further work on the relative biological activities of different forms of active substances.

4. In foreseeing the future entry of any new substances to the "within additive" listing SCAN is concerned that there should not be an unreasonable restriction on the use of new forms of well documented Additives. Minor changes in the chemical form of a substance, such as the replacement of a sodium salt by a potassium salt, which are unlikely to have significant implications for the efficacy or safety should be subject to a system of accelerated approval. On the other hand, substantial alterations in the form of the Additive may have important implications for biological activities, and where this is the case a fuller system of approval will be required.

   There is a specific concern where the Additive substances may occur in different isomeric forms and where only one isomeric form has the additive activity. In these cases new processes of industrial manufacture may produce lower-cost, isomeric mixtures but because of the metabolic influences of non-active isomer the biological potency of the mixed isomer may be less than implied by its content of the active isomer.

   Additionally, it is important to ensure that the inclusions in the diet of new isomeric or innovative forms of Additive that are untried in terms of long established nutritional practice have no adverse health and safety implications for animals or man.

   Innovative forms of Additive may include derivations of vitamins which correspond in molecular composition and structure to the metabolic substances that are synthesised from vitamins in the body. In some cases these synthesised substances are potent regulators of metabolism and may raise particular considerations about their addition to the diet.

5. In considering the provisions on Appendix I under the column "Species or category of animal", "Maximum age", "Maximum content of complete feedingstuffs or of the daily ration" and "Other provisions" SCAN has recognised that there are elements of terminology etc. that must conform to that in existing legal provisions in the member States. However, it would draw attention to the need for definitions and categories to be improved in their precision, to avoid possibility of confusion and of interpretation at member states level.

   Similarly, there is a continuing requirement for improved scientific information on the most appropriated levels of Additive inclusion in the diet and for improved analytical methods for monitoring and statutory purposes. Specifically, in relation to Vitamin A, SCAN finds no case for departing from its earlier opinion also published in this series of reports, but would again draw the attention to the high levels of vitamin A that may occur naturally in the livers of grazing animals and which are not due to vitamin A supplementation of the diet.

6. Under the additive category of "Essential Fatty Acids", SCAN notes and is supportive of the trend for the specialist manufacturers increasingly to provide specific information on the individual fatty acid contents of additives mixtures. As scientific information o, the specific effects of fatty acids accumulates the case for more detailed information on fatty acids composition may be strengthened.

EEC No	Group	Additive	Chemical formula, description	Species or category of animal	Maximum Age	Maximum content /kg of complete feedingstuff	Other provisions
	H. Vitamins, provitamins and chemically well-defined substances having a similar effect						
	A. VITAMINS AND PROVITAMINS					p	Reference standard: 1 μg retinol
E 672	1. Vitamin A		[mol wt: 286.4]				1 I.U.=0.3 μg retinol
		retinol acetate					1 I.U.=0.34 μg retinol acetate
		retinol propionate					1 I.U.=0.36 μg retinol propionate
		retinol palmitate					1 I.U.=0.55 μg retinol palmitate
				Chickens for fattening	-	13.500 I.U.	)
				Turkeys for fattening	-	13.500 I.U.	)
				Lambs for fattening	-	13.500 I.U.	) All compound feedingstuffs except
				Pigs for fattening	-	13.500 I.U.	) compound feedingstuffs for young
				Bovines for fattening	-	13.500 I.U.	) animals
				Rabbits for fattening	-	13.500 I.U.	)
				Calves for fattening	-	25.000 I.U.	) Only milk replacers
				Other species or categories of animals	-	-	)
E 160(a)	2. Beta-carotene	beta-carotene	[mol wt: 536.9]	All	-	-	Reference standard: 1 mg β-carotene
E 670	3. vitamine D2	ergocalciferol	[mol wt: 396.6]				Reference standard: 1 μg ergocalciferol 1 I.U.=0.025 μg
				Pigs	-	2.000 I.U.	)
				Bovines	-	4.000 I.U.	)
				Ovines [goats]	-	4.000 I.U.	)
				Piglets	-	10.000 I.U.	) milk) simultaneous
				Calves	-	10.000 I.U.	) replacers) incorporation with D3
				[Lambs/kids]	-	10.000 I.U.	) only) not permitted
				Equines	-	4.000 I.U.	
				Other spec./categ. of animals (with excep. of poultry, fishes)	-	2.000 I.U.	

EEC No	Group	Additive	Chemical formula, description	Species or category of animal	Maximum age	Maximum content /kg of complete feedingstuff	Other provisions
E 671	4. Vitamin D3	cholecalciferol	[mol wt: 384.6]				Reference standard: 1μg cholecalciferol 1 I.U. = 0.025 μg
				Pigs	-	2.000 I.U.	)
				Bovines	-	4.000 I.U.	)
				Ovines [goats]	-	4.000 I.U.	) simultaneous
				Piglets	-	10.000 I.U.	) milk) incorporation
				Calves	-	10.000 I.U.	) replacers only) with D2
				[Lambs/kids]	-	10.000 I.U.	)) not permitted
				Equines	-	4.000 I.U.	)
				Chickens for fattening	-	5.000 I.U.	)
				Turkeys	-	5.000 I.U.	)
				Other poultry	-	3.000 I.U.	)
				Fishes	-	10.000 I.U.	)
				Other species or categories of animals	-	2.000 I.U.	)
	5. Vitamin E		[mol wt: 430.7]				Reference standard:
		DL-alpha-tocopheryl acetate		All	-	-	1 mg DL-alpha-tocopherol acetate =1 I.U.
		DL-alpha-tocopheryl succinate		All	-	-	1mg= 1.12mg DL-alpha-tocopherol succinate
	6. Vitamin K3						Reference standard: 1 mg de menodione = 1 I.U.
			[mol wt: 172.2]				
		menadione sodium bisulphite (MSB)		All	-	-	1mg=1.60mg MSB
		menadione nicotinamide bisulphite		All	-	-	1mg = 2.19mg MNB
		menodione nicotine acid bisulphite (MNAB)		All	-	-	1mg = 2.19mg MNAB
		menadione dimethyl pyrimidinol bisulphite (MDPB)		All	-	-	1mg = 2.20mg MDPB(4)
		menadione pyrimidinol bisulphite (MPB)		All	-	-	1mg = 4.3 mg MPB

EEC No	Group	Additive	Chemical formula, description	Species or category of animal	Maximum age	Maximum content /kg of complete feedingstuff	Other provisions
	7. Vitamin B1						Reference standard: 1mg thiamine 1 I.U. = 0.003 mg
			[mol wt: 300.8]				
		thiamine hydrochloride		All	-	-	1mg = 1.12mg thiamine HCL
		thiamine mononitrate		All	-	-	1mg = 1.09mg thiamine mononitrate
		thiamine sulphate		All	-	-	1mg = 1.36mg thiamine sulphate
	8. Vitamin B2						Reference standard: 1mg riboflavine
			[mol wt: 376.4]				
E 101		riboflavine		All	-	-	
E 101a		riboflavine-5° - phosphate ester monosodium salt		All	-	-	1mg = 1.37mg riboflavine-s'-phosphate
	9. Vitamin B6						Reference standard: 1mg pyridoxine
			[mol wt: 169.2]				
		pyridoxine hydrochloride		All	-	-	1mg = 1.22mg pyridoxine HCL
	10. Vitamin B12		[mol wt: 1355,4]				Reference standard: 1 μg cyanocabalamin
		cyanocobalamin		All	-	-	
		hydroxycobalamine		All	-	-	1mg hydroxycabalamine = 1.006 mg cyanocobalamine
(E 300)	11. Vitamin C		[mol wt: 176.1]				Reference standard: 1mg L-ascorbic acid
-300		L-ascorbic acid		All	-	-	
-301		sodium L-ascorbate		All	-	-	1mg = 1.12mg sodium L-ascorbate
-302		calcium L-ascorbate		All	-	-	1mg = 2.22mg calcium L-ascorbate
-304		ascorbyl palmitate		All	-	-	1mg = 2.35mg ascorbyl palmitate
		dipotasium L-ascorbyl-sulphate-dihydrate		All	-	-	1mg = 2.08mg
		alpha-glucosid-L-ascorbic acid					1mg = 1.92mg
		ascorbyl-monophosphate-calcium (AMC)		All	-	-	1mg = 2.08mg AMC
		ascorbyl-monophosphate-potassium magnesium		All	-	-	1mg = 1.79mg AMPM


(AMPM)

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		ascorbyl-monophosphate-sodium magnesium (AMSM)		All	-	-	1mg = 2.22mg AMSM
		ascorbyl polyphosphate (AP)		All	-	-	1mg = 6.67mg AP
	12. Pantothenic Acid		[mol wt: 219.2]				Reference standard: 1mg pantothenic acid
		calcium-D-pantothenate		All	-	-	1mg = 1.09mg calcium-D-panthothenate
		sodium-D-pantothenate		All	-	-	1mg = 1.10mg sodium-D-panthothenate
		D-panthothenol		All	-	-	1mg = 0.94mg D-panthenol
	13. Nicotinic Acid	nicotinic acid (niacin)	[mol wt: 123.1]	All	-	-	Reference standard: 1mg nicotinic acid
		nicotinic acid amide (nicotinamide-niacinamide) (NA)	[mol wt: 122.1]	All	-	-	Reference standard: 1mg nicotinamide 1mg = 2.43mg NAA
		nicotinamide ascorbate (NAA)		All	-	-	
	14. Folic Acid		[mol wt: 441.4]				Reference standard: 1mg folic acid
		folic acid		All	-	-	
		sodium folate		All	-	-	1mg = 1,05mg sodium folate
	15. Para Amino Benzoic Acid (PABA)		[mol wt: 137.1]				Reference standard: 1mg p-amino benzoic acid
		p-amino benzoic acid		All	-	-	
	16. Biotin		[mol wt: 244.3]				Reference standard: 1mg D-(+)-biotin
		D-(+)-biotin		All	-	-	
	17. Choline		[mol wt: 121.18]				Reference standard: 1mg choline hydroxid
		choline chloride		All	-	-	1mg = 1.15mg choline chloride
		choline dihydrogen citrate (CDC)		All	-	-	1mg = 2.44mg CDC
		choline bitartrate		All	-	-	1mg = 2.08mg choline bitartrate

EEC No	Group	Additive	Chemical formula, description	Species or category of animal	Maximum age	Maximum content /kg of complete feedingstuff	Other provisions
	B. COFACTORS AND SUBSTANCES WITH A SIMILA BIOLOGICAL ACTIVITY						
	1. Inositol		[mol wt: 180.2]				Reference standard: 1mg inositol
		inositol		All	-	-	
	2. L-Carnitine		[mol wt: 161.2]				Reference standard: 1mg L-carnitine
		L-carnitine		All	-	-	
		L-carnitine-L-tartrate (LCL		All	-	-	1mg = 1.47mg de LCLT
	3. Betaine		[mol wt: 117.1]				Reference standard: 1mg betaine
		betaine anhydre		All	-	-	1mg = 1.31mg betaine HCL
		betaine hydrochloride		All	-	-	1mg = 1.15mg betaine MH
		betaine monohydrate		All	-	-	
	4. Tourine		[mol wt: 125.1]				Reference standard: 1mg tourine
		tourine					
	5. Essential Fatty Acids						
		Ω-3 fatty acids		All	-	-	
		Ω-6 fatty acids		All	-	-	