

Maisons-Alfort, 1 March 2010

OPINION

of the French Food Safety Agency on the update of French population reference intakes (ANCs) for fatty acids

THE DIRECTOR GENERAL

1. REVIEW OF THE REQUEST

The French Food Safety Agency (AFSSA) issued an internal request on 27 October 2005 to update French population reference intakes (Apports nutritionnels conseillés: ANCs) for fatty acids.

2. BACKGROUND

The ANCs for fatty acids (FAs) were defined by AFSSA in 2001. The following were proposed for adults:

- an intake range for total FAs;
- for polyunsaturated fatty acids (PUFAs), values for linoleic acid (C18:2n-6), alpha-linolenic acid (C18:3n-3) and the long-chain PUFA group (LC-PUFAs, ≥ 20 carbons), while also defining a value for docosahexaenoic acid (DHA; C22:6n-3).

The scientific data acquired since 2001 raise questions about the need to:

- make a recommendation for eicosapentaenoic acid (EPA; C20:5n-3), reassess the recommendation for DHA, and make a recommendation that covers both;
- reassess the recommendation for linoleic acid;
- reassess the proportion of total saturated FAs in energy intake and the need to distinguish between recommendations for different saturated FAs.

3. METHOD OF EXPERT ASSESSMENT

Collective expert assessment was provided by the “*Actualisation des Apports Nutritionnels Conseillés en acides gras*” [Updating of French population reference intakes for fatty acids] working group whose Opinion was adopted by the Scientific Panel (Comité d'experts spécialisé: CES) on ‘Human Nutrition’, which met on 25 June and 29 October 2009.

There are many FAs involving multiple functions. Among the PUFAs, some are known as ‘essential’ precursors (linoleic, C18:2n-6 and alpha-linolenic, C18:3n-3 acids) because they are essential for growth and physiological functions, and cannot be synthesised by humans. Derivatives of these essential precursors are called ‘conditionally essential’ since humans and animals can synthesise them (contingent on having essential precursor FAs). Other FAs (other polyunsaturates, monounsaturates, and saturates) are nutrients that can be synthesised *de novo* by the body. These characteristics of FAs bring about complex balances.

The working group has considered the main FAs, including those that humans can synthesise, because all have a biological function.

3.1. Methods for defining ANCs for fatty acids

The ANC is a *reference value* that encompasses the physiological requirements for almost the entire population. The values concern healthy individuals and include the objective of maintaining this good health, which corresponds to the limits of primary prevention. Managing the nutrition of a patient or a subject who has a disease is inherently individual and lies beyond the purview of primary prevention; it is therefore outside the scope of the ANCs.

For the essential and 'conditionally essential' FAs, the physiological requirements correspond to a necessary intake for:

- avoiding any dietary deficit of essential FAs and ensuring proper functioning of the entire body, particularly brain development and function; these are *minimum physiological requirements*;
- ensuring preventive roles in physiopathological terms; these are *optimum physiological requirements* (primary prevention). The following disorders will be considered: metabolic syndrome, diabetes, obesity, cardio-vascular diseases, cancers (breast and colon, in particular) and other diseases such as age-related macular degeneration (AMD).

The method for setting the ANCs for these essential and 'conditionally essential' FAs includes the following steps:

- estimation of the minimum physiological requirement;
- identification of data enabling adapting the minimum physiological requirement for each of the disorders listed above, for the purpose of defining an optimum physiological requirement (prevention);
- integration and synthesis of all the physiological and physiopathological considerations available for defining ANCs.

Due to a lack of sufficient data, the minimum physiological requirement has not been established for non-essential FAs. ANCs have thus been established taking into account physiopathological considerations and the need for balance among the different FAs, within the limit of requirements of total lipids.

3.2. Overview of the literature

Considering that much of the data on nutrition have been and continue to be gathered primarily in animals, the working group has included studies ranging from *in vitro* models to animal models and epidemiological intervention studies in humans, to provide the most comprehensive support for establishing ANCs for FAs. The bibliography used concerns studies published up to August 2009. This Opinion includes the key points from a full report that will provide all the rationale from the literature forming the basis of AFSSA's recommendations.

4. DETERMINATION OF ANCS

4.1. In adults

4.1.1. Determination of the proportion of total lipids in energy intake (Table 1)

This value is inseparable from those of proteins and carbohydrates. The available data have led to the definition of a physiological requirement of total FAs of 30% of energy intake (EI). Indeed, in Western countries a lipid intake below 30% of EI results in a significant reduction in intake of PUFAs (DHA), falling below dietary needs. In primary prevention, the available data clearly indicate that the total amount of energy, and not the dietary lipid content, is generally correlated with the risk of disorders such as metabolic syndrome, diabetes, obesity, cardiovascular diseases, cancers and AMD. They also indicate that the sharp decrease in the proportion of lipids below 35% of EI, in favour of carbohydrates, does not result in any added benefit in terms of reducing the risk of the pathologies mentioned and could sometimes induce deleterious

effects Thus, after considering minimum and optimum physiological requirements, a total lipid intake of 35 to 40% of EI is recommended in adults for an energy intake of nearly 2000 kcal.

4.1.2.Determination of ANCs for the different fatty acids (Table 1)

The ANCs, shown in Table 1, are established for adult subjects (men or women) for an energy intake of 2000 kcal. The table shows the minimum physiological requirement (limited to essential FAs), estimated optimum physiological requirements, in terms of prevention for each disorder, and finally the ANC.

Lacking specific data, the estimated physiological requirements also apply to elderly subjects.

In view of recent data, the biochemical classification of FAs, namely as 'polyunsaturated, monounsaturated and saturated', no longer corresponds to the diversity of FAs, the accuracy of the studies, the specificity of functions and effects, and is of little relevance for public health. Thus, in this Opinion, the essential FAs are distinguished from the non-essential FAs (Table 1).

➤ Essential fatty acids

Given the scientific data available, the assessment of physiological requirements in adult men and women is confined to three essential FAs: linoleic acid (C18:2n-6), alpha-linolenic acid (C18:3n-3) and one of its derivatives, DHA (docosahexaenoic acid, C22:6n-3). The essential nature of DHA is related to its low formation by conversion of alpha-linolenic acid and has led to the definition of a minimum physiological requirement.

- *Linoleic acid (C18:2n-6)*

Recommendations for this FA have steadily increased since being established as essential. Subsequently an international debate arose, suggesting that the proposed needs were overestimated in epidemiological studies due to a lack of accurate measurements of n-3 PUFA intakes, and in clinical studies due to the lack of n-3 PUFA intakes. However, in animals, the addition of alpha-linolenic acid to diets deficient in linoleic acid reduced the specific requirement of linoleic acid by limiting the signs of deficiency and the observed impairment of growth. The need to specify the minimum physiological requirement of linoleic acid is also aiming to limit the imbalance between the two PUFA families when consumption of n-3 PUFAs is low (alpha-linolenic precursor and long-chain derivatives). Indeed, this imbalance is detrimental to the synthesis and availability of n3 LC-PUFAs (EPA and DHA) and to their incorporation into the tissues, which could accentuate physiological disturbances and contribute to the occurrence of pathologies such as neuropsychiatric disorders, cardiovascular diseases, inflammatory diseases, diabetes and obesity. In this context, a linoleic acid/alpha-linolenic acid ratio below 5 is generally accepted.

Finally, on the basis of the available data, the minimum physiological requirement of linoleic acid is estimated at 2% of EI, which is equivalent to 4.4 g/day for an energy intake of 2000 kcal/day. AFSSA established the ANC at 4% of EI. This value reflects both the importance of achieving a total for PUFAs that contributes to cardiovascular prevention and limiting intakes to maintain a linoleic acid/alpha-linolenic acid ratio below 5, and thereby prevent disease, studied on the basis of risk biomarkers, or at times using incidence data as in the case of AMD.

- *Alpha-linolenic acid (C18:3n-3)*

As an n-3 family precursor, the essential nature of this FA relates to its role in proper cerebral and visual function. It has been shown recently that in humans, alpha-linolenic acid is very well catabolised and can be converted into DHA to a limited extent, but undergoes lesser catabolism in rodents. Therefore it is appropriate, to cover the needs of almost the entire population, to define a minimum physiological requirement for humans that is higher than the value resulting from animal studies in rodents. On the basis of the available data, the minimum physiological requirement of alpha-linolenic acid is estimated at 0.8% of EI for adults, which is equivalent to 1.8 g/day for an energy intake of 2000 kcal/day.

The ANC is set at 1% of EI given the favourable data derived from numerous observational epidemiological studies in the cardiovascular field, and the need to reach a total of n-3 + n-6 PUFAs conducive to cardiovascular prevention and to strictly maintain a linoleic acid/alpha-linolenic acid ratio lower than 5.

The linoleic acid/alpha-linolenic acid ratio is of less significance currently since the physiological requirements for linoleic and alpha-linolenic acids are well established and covered, and the intakes of EPA and DHA are assured. However, this ratio may remain a practical benchmark in terms of overall diet. It also retains its importance if there is any imbalance due to a deficiency of alpha-linolenic acid intake and/or an excess intake of linoleic acid, and even more still if there is an additional deficiency of EPA and DHA intakes.

- *Docosahexaenoic acid (DHA; C22:6n-3)*

This n-3 PUFA is a major constituent of cerebral and visual structure and function. The new data, specifically those related to the very low conversion of alpha-linolenic acid into DHA, now clearly demonstrated, has led to the minimum physiological requirement being set at 250 mg/day for an adult (or 0.113% of energy), a value twice as high as that suggested in 2001. The data in the literature related to the prevention of different risks generally indicate values of around 500 mg/day, for the sum of EPA+DHA, due to the consumption and use of fish and fish oil (sources that contain EPA+DHA in close enough proportions) in epidemiological and clinical studies. Thus, AFSSA has established an ANC of 250 mg/day for DHA.

- **Non-essential fatty acids**

- *Eicosapentaenoic acid (EPA; C20:5n-3)*

The functions that this n-3 PUFA carries out are essential (precursor of a family of eicosanoids) but currently there is insufficient data for considering it to be absolutely essential and for defining a minimum physiological requirement. Indeed, the conversion of alpha-linolenic acid into EPA is significant since the intakes of alpha-linolenic acid (and of linoleic acid, for competing reasons) are adequate. However, in terms of risk prevention, an ANC for EPA has been defined on the basis of bibliographic data that often group together EPA+DHA. Thus, an ANC of 250 mg/day is defined for EPA using prevention data, by subtracting from the combined value of 500 mg/day for EPA+DHA.

- *Saturated fatty acids*

Saturated FAs cannot be regarded as a unit because they differ in their structure, their metabolism, their cell functions and even their deleterious effects in case of excess.

From now on it is advisable to distinguish the subgroup of 'lauric, myristic, and palmitic acids' which is atherogenic in the event of excess.

Based on observation studies and not formal intervention studies, AFSSA established a maximum intake of 8% of EI for this subgroup.

Other saturated FAs, particularly the short and medium chains, have no known harmful effect and some of them even have rather beneficial effects. However, at present, it is not possible to establish recommendations for them and AFSSA considers it prudent to maintain an intake of total saturated FAs lower than 12% of EI.

- *Oleic acid (C18:1n-9)*

Oleic acid is now properly identified within the heterogeneous 'monounsaturates' group, within which oleic acid is the predominant component in the diet.

The ANC for oleic acid is expressed as a range from 15 to 20% of EI. The lower intake limit is based on the risk related to the substitution of oleic acid by saturated FAs which are 'atherogenic in excess'. As for the upper intake limit, it is suggested by epidemiological and clinical data on cardiovascular risk factors.

- *Other non-essential fatty acids*

This group includes a varied set of FAs (polyunsaturated, monounsaturated, *trans* and conjugated), each present in very low amounts but whose total accounts for about 2% of EI. They may play major physiological roles such as arachidonic acid (C20:4n-6), a precursor of a family of eicosanoids, also provided by the active conversion of linoleic acid, or potentially important physiological roles like certain n-3 PUFAs (stearidonic acid C18:4n-3 and especially docosapentaenoic acid C22:5n-3) which are convertible into EPA or DHA. This is also true for some conjugated FAs such as ruminic acid.

For all of the FAs, the available data are insufficient for defining a physiological requirement and an ANC.

4.2. Pregnant and lactating women, infants, children and adolescents

4.2.1. Determination of ANCs for pregnant and lactating women (Table 2)

The level of precursor and long-chain PUFAs of the n-6 and n-3 series in the maternal diet primarily influences the development of the brain in newborns (during pregnancy and lactation) and the health of the mother (during pregnancy).

Concerning DHA, the recommended intakes are based on epidemiological and clinical studies that have assessed the effects of dietary intake of DHA and/or EPA on the parameters of pregnancy and on the visual and cognitive development of the young child. They are also based on the value and the arguments advanced for adult men or women, in terms of disease prevention.

Concerning the precursor PUFAs and all other FAs, the ANC values proposed for adult subjects in terms of disease prevention apply, due to a lack of specific experimental data in pregnant and lactating women.

4.2.2. Determination of ANCs for the newborn/infant up to age 6 months (Table 3)

Concerning linoleic acid, several groups of experts and various regulations, including those in France, have proposed recommendations establishing a minimum intake of 2.7% of EI. AFSSA adopted this value as the ANC for linoleic acid.

With respect to the ANC for alpha-linolenic acid, AFSSA maintains a minimum value of 0.45% of energy (or 1% of the total FAs of the lipid content of milk), 1.5% representing a value beyond which there is no additional nutritional value. Consistent with various current international recommendations, the ANC for DHA is established at 0.32% of total FAs. In addition, DHA intake must be balanced with that of arachidonic acid (0.5% of total FAs) to avoid a deficiency of the latter in infants. Lastly, EPA intake must be lower than that of DHA.

4.2.3. Determination of ANCs for the infant of more than 6 months, child and adolescent (Table 4)

The proportion of energy intake that lipids represent in toddlers up to 3 years, as for infants, is 45 to 50% of EI, which then decreases to 35-40% in children and adolescents. In this last age group, the recommendations are those for adult men and women because they are based on disease prevention considerations.

The values of alpha-linolenic and linoleic acid proposed for infants of less than 6 months also apply for infants aged 6 months to one year and toddlers (1 to 3 years). Adult ANCs apply for children aged 3 to 9 years and adolescents, which are 4% and 1% for linoleic and alpha-linolenic acid, respectively.

An ANC of 70 mg per day of DHA, for infants over 6 months and toddlers, should ensure continuous accumulation of this PUFA in the cerebral membranes. For adolescents, the proposed ANC corresponds to that for adults (250 mg of DHA per day and 500 mg for EPA+DHA). For children over 3 years, the accepted ANC is 125 mg per day for DHA and 250 mg for EPA+DHA, given the reduction by half of energy intakes compared with those for adolescents.

5. CONCLUSION

The innovative nature of this assessment lies in the fact that the ANC of each fatty acid studied has been established from minimum physiological requirements and by considering the physiopathological aspects.

Thus, the scientific data acquired since the previous assessment of ANCs (2001) have led to:

- setting an ANC for linoleic acid resulting from both the importance of reaching a total PUFA that promotes cardiovascular prevention, and limiting intake to maintain a linoleic acid/alpha-linolenic acid ratio of less than 5;

- revising the ANC for alpha-linolenic acid upward with the aim of preventing cardiovascular diseases;
- raising the ANC value for DHA, because of its very low rate of conversion from alpha-linolenic acid, which is now clearly documented;
- defining an ANC for EPA, based on prevention data, for cardiovascular diseases in particular;
- distinguishing, among the saturated fatty acids, the subgroup of 'lauric, myristic and palmitic acids' considered to be atherogenic in excess, and establishing a maximum value for this subgroup that is not to be exceeded;
- assigning an ANC for oleic acid and not for MUFA;
- changing the proportion of total lipids in total energy intake, with respect to overall balance between macronutrients and data related to preventing metabolic syndrome and cardiovascular risk; thus, to the extent that energy balance is achieved, this share may reach 40% of energy intake without being suggestive of a risk of the diseases under consideration, as part of primary prevention.

The values proposed for ANCs account for different conditions for each FA considered, this depending on the physiopathological data available and the essential or non-essential nature of the FAs. However, dietary lipids are not limited to the FAs for which an ANC can be established and many other FAs are likely to be of interest, as future research should demonstrate.

The ANCs are benchmarks for health and nutrition professionals. They are likely to be compared with actual French consumption data and translated into dietary guidelines for the population. However, at this time it is possible to recommend a varied lipid diet, including fats from animal and vegetable sources, within the boundaries of recommended energy intakes.

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KEY WORDS

(lipids, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, adults, pregnant and lactating women, infants, children and adolescents, requirements, prevention)

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Table 1: Table of recommendations for an adult consuming a 2000 kcal diet

Apart from those for EPA and DHA, the values are expressed as a **percentage of the non-alcohol energy intake**, which will be referred to simply as 'energy intake' (EI). In the case of DHA (docosahexaenoic acid, C22:6n-3) and EPA (eicosapentaenoic acid, C20:5n-3), the values are expressed in milligrams insofar as the available studies have used this unit.

		MINIMUM PHYSIO- LOGICAL REQUIRE- MENT*	PREVENTION OF RISK					ANC 2010
			Metabolic syndrome - Diabetes - Obesity	Cardiovascular diseases	Cancers: breast and colon**	Neuro- psychiatric disorders	Other pathologies: AMD***	
Total lipids ^a		30 ^b	30-40	35-40 ^c	35-40	35-40 ^d	<40	35-40 ^c
Essential FAs	Linoleic acid C18:2n-6	2	2 ^e	5	2 ^e	2 ^e	≤4 ^f	4 ^g
	α-linolenic acid C18:3n-3	0.8	0.8 ^e	1 ^h	0.8 ^e	0.8 ^e	0.8 ^e	1 ^h
	Docosahexaenoic acid DHA, C22:6n-3	250 mg	500 mg	500-750 mg ⁱ	500mg	≥ 200-300 mg	500 mg	250 mg
Eicosapentaenoic acid EPA, C20:5n-3	-	250 mg ^j						
Non-essential FAs	Lauric acid (C12:0) + Myristic acid (C14:0) + Palmitic acid (C16:0)	-	-	≤8 ^h	-	-	-	≤ 8
	Total Saturated Fatty Acids	-	- ^k	≤12	≤12 ^l	-	-	≤12
	Oleic acid C18:1n-9	-	-	≤20 ^m	-	-	-	15-20
	Other non-essential FAs ⁿ	-	-	-	-	-	-	-

* Corresponds to the fatty acids at an intake level necessary to avoid any essential fatty acid dietary deficiency syndrome. These recommendations ensure the proper function of the entire body, particularly cerebral development and function.

** Among the cancers studied, only studies related to breast and colon cancers enable recommendations to be established.

*** Among the diseases studied, only studies related to AMD enable recommendations to be established.

«-» There are insufficient bibliographic data to reach conclusions.

^a The values apply only to energy intake close to 2000 kcal and when energy balance is achieved.

^b A minimum requirement of 30% seems desirable for ensuring a minimum intake of essential PUFAs. In addition, there is no benefit to dropping below 30%

^c For intakes of less than 35%, there is no established benefit to cardiovascular health.

^d The values proposed for preventing the risk of cardiovascular diseases and metabolic syndrome may apply in the absence of specific data, given the possibility of a link to disease.

^e In the absence of specific data, the physiological requirement applies.

^f On the basis of observational studies which show that excessive intakes of linoleic acid (greater than 2.5% or 5.5%, according to the studies) are associated with a loss of beneficial effects of LC n-3 PUFAs. Therefore, the value of 4% was selected with care.

^g The ANC accounts for the fact that a certain number of data suggest a maximum limit for linoleic acid intake.

^h This fact is inferred from observational epidemiological studies and not from formal intervention studies

ⁱ Requirements for EPA+DHA can reach 750 mg for subjects at high cardiovascular risk (secondary prevention).

^j The data often group the effects of EPA+DHA together, thus the value of 250 mg is obtained by subtraction.

^k Consistent clinical data are lacking.

^l Data are restricted to breast cancer.

^m Based on a combination of epidemiological studies and clinical data suggesting an intake limit value.

ⁿ 'Other non-essential FAs' represent a group of fatty acids consumed in low amounts for which there are currently no definable ANCs. These fatty acids, which represent about 2% of EI, include in particular monounsaturated fatty acids (16:1n-7, 18:1n-7; 22:1n-9...), PUFAs (18:3n-6, 20:3n-6, 20:4n-6; 18:4n-3, 20:4n-3, 22:5n-3...) and *trans* and conjugated fatty acids (18:2n-7*t*; 18:2n-7 *9c,11*t**). Regarding *trans* FAs, it should be remembered that their maximum intake level is limited to 2% (AFSSA 2005).

Table 2: French population reference intakes (ANCs) of precursor and long-chain polyunsaturated fatty acids for pregnant women consuming 2050 Kcal and for lactating women consuming 2250 Kcal, with 35-40% of the energy intake in the form of lipids.

	Linoleic acid (18:2n-6)	Alpha-linolenic acid (18:3n-3)	Arachidonic acid (20:4n-6)	Docosahexaenoic acid (22:6n-3)	Long-chain n-3 PUFAs (EPA+DHA)
Pregnant women	4.0% EI	1.0% EI	- ^a	250 mg	500 mg ^b
Lactating women	4.0% EI	1.0% EI	- ^a	250 mg	500 mg ^b

Values are expressed as a % of energy intake (EI) or in mg.

^a There are no data to justify recommendations.

^b These values are based on considerations that apply to adults.

Table 3: French population reference intakes (ANCs) of precursor and long-chain polyunsaturated fatty acids for newborns/infants

	Linoleic acid (18:2n-6)	Alpha-linolenic acid (18:3n-3)	Arachidonic acid (20:4n-6)	Docosahexaenoic acid (22:6n-3)	Long-chain n-3 PUFAs (EPA+DHA)
Newborn/infant (first 6 months)	2.7% EI	0.45% EI	0.5% TFA	0.32% TFA	EPA < DHA

Values are expressed as a % of energy intake (EI) or as a percentage of total fatty acids (TFA) for milk contributing, per 100 mL reconstituted, 70 kcal and 3.4 g of total lipids

Table 4: French population reference intakes (ANCs) of precursor and long-chain polyunsaturated fatty acids for infants over 6 months, children and adolescents

	Linoleic acid (18:2n-6)	Alpha-linolenic acid (18:3n-3)	Arachidonic acid (20:4n-6)	Docosahexaenoic acid (22:6n-3)	Long-chain n-3 PUFAs (EPA+DHA)
Infants (6 months to 1 year)	2.7% EI	0.45% EI	- ^a	70 mg ^b	- ^c
Toddlers (1 to 3 years)	2.7% EI	0.45% EI	- ^a	70 mg ^b	- ^c
Children (3 to 9 years)	4.0% EI	1.0% EI	- ^a	125 mg ^b	250 mg ^b
Adolescents (10 to 18 years)	4.0% EI	1.0% EI	- ^a	250 mg ^b	500 mg ^b

Values are expressed as a % of energy intake (EI) or in mg.

^a There are no data to justify recommendations.

^b The variability of the daily energy intake amount does not enable expression of ANCs as a % of energy.

^c There are no data for establishing requirements for EPA or EPA+DHA.