Scientific **A**dvisory **C**ommittee on **N**utrition

Subgroup on Vitamin A

Paper for Discussion:

The Food Standards Agency have asked SACN to review current advice to consumers on vitamin A (retinol) intake with particular reference to liver.

Please see the attached paper for discussion.

Background

CURRENT ADVICE ON INTAKES OF VITAMIN A

1. In 1990, the Department of Health issued advice to pregnant women or women thinking of becoming pregnant not to take any supplement containing vitamin A at any level or to eat liver or liver products unless advised to do so by their general practitioner. This advice was issued because of the risk of teratogenic effects of vitamin A to the unborn child (Department of Health, 1990).

THE EXPERT GROUP ON VITAMINS AND MINERALS ADVICE ON VITAMIN A

2. In May 2003, the Expert Group on Vitamins and Minerals (EVM) reported on the safety in long-term use of vitamin and mineral supplements sold under food law, recommending maximum advisable levels of intake. For vitamin A, a Guidance Level for total retinol intake of 1500µgRE/day was set. This level was agreed due to emerging evidence that intakes above this level may increase the risk of bone fracture.

3. The risk assessment for vitamin A from the EVM report is attached (Annex 1), as are the papers considered by the group on bone toxicity (Annex 2). Two additional papers, not considered in the EVM risk assessment, on the possible adverse effects of vitamin A on bone are also attached (Annex 3) and are summarised below.

Kawahara et al, 2002

4. This paper describes a prospective, randomised, single-blind study of vitamin A supplementation in 80 healthy men aged 18-58 years. Half the subjects received 7576µg (25,000 IU) of retinol palmitate daily with their evening meal, the other half received a placebo. Serum bone specific alkaline phosphatase (BSAP) and N-telopeptide of type I collagen (NTx) was measured at 2, 4 and 6 weeks of supplementation. Serum osteocalcin (Oc) was measured at baseline and after 6 weeks of supplementation. Over the course of the study there was no change in BSAP, NTx or Oc in either the placebo or supplemented group. The researchers concluded that short-term vitamin A supplementation did not affect markers of bone turnover in healthy men but the long-term effects were unknown.

5. This study was not included in the EVM risk assessment because it was of short duration and used biomarkers of bone resorption and formation that were not measured in any of the other studies considered by the EVM. The results could not be related to the other studies that were assessed.

Michaëlsson et al., 2003

6. 2322 men, aged between 49-51 years, were enrolled in a population-based, longitudinal cohort study. Serum retinol and beta-carotene was assessed at enrollment. These men were followed up for 30 years and in this time there were 266 reported fractures. Cox regression analysis was used to determine the risk of fracture according to the serum retinol. Those men with the highest serum retinol were found to be at the highest risk of fracture. The risk was concentrated in the highest quintile of serum retinol, the relative risk for all fractures in the highest quintile compared to the middle quintile was 1.64 (95% CI, 1.12-2.41). In addition, one-week dietary records were obtained from about half of the study population 20 years after commencement of the study. The highest quintile for estimated retinol intake (>1.5mg/day) was associated with an energy-adjusted rate ratio of 2.0 (95%CI, 1.00 to 3.00) for any fracture, as compared with the lowest quintile (<0.53mg/day). The authors reported that there was a weak association between dietary vitamin A intake and serum retinol 20 years earlier (r=0.05, P=0.08).

7. This paper is recorded in the EVM report as having been published after the cut off date however it is stated that this paper would have contributed to the risk assessment.

Intake of vitamin A in Great Britain

8. Information on the vitamin A intake of the British population is presented below and is taken from the National Diet and Nutrition Survey (NDNS) series. The emphasis in data presented is on high vitamin A consumers. Vitamin A deficiency is uncommon in Great Britain.

Methodological note

9. NDNS make use of 7-day diaries (4-day in the elderly) of food intake. As the recording of these diaries is restricted to a short continuous time period, the habitual intake of rarely consumed foods may be over- or under- estimated at an individual level (even though estimates of population mean intake ought to be reliable). The retinol content of one or two rarely consumed foods (i.e. liver and liver products) is particularly high. Consumption or lack of consumption of these foods during the diary recording period will therefore have a large impact on retinol intake and may result in retinol intake appearing to be atypically high for some individuals, while it will be atypically low for others. If longer runs of data were available, it might be expected that the same population mean level of retinol intake would be somewhat more evenly distributed amongst the population. This would apply more strongly where a 4-day diary, rather than a 7-day diary, has been used to record food intake.

10. In the following analysis of NDNS data, ‘liver’ includes liver sausage and liver pâté.

Adults Aged 19-64 Years

11. According to the NDNS (Henderson *et al*, 2003), 15% of men and 9% of women had intakes during the diary period that exceed the EVM's Guidance Level for vitamin A of 1500µg/day. Analysis of the data by age shows an age related trend, 1% of men and 3% of women in the 19 -24 age group exceed the Guidance Level as compared to 24% of men and 17% of women in the 50 – 64 year age group.

12. Liver was a major source of vitamin A for people with vitamin A intakes greater than 1500µg/day. For this group liver contributes 50% and 40% of vitamin A intake for men and women respectively. Male liver consumers had an average vitamin A intake of 2945µg/day with 2071µg/day coming from liver alone. Consumers of liver (in the diary week) made up 10% of the NDNS sample and among these 76% of men and 56% of women exceeded 1500µg/day.

13. The contribution of dietary supplements to the vitamin A intakes of those exceeding 1500µg/day was 16% for men and 26% for women. This is less than the contribution for liver. Over all, dietary supplements containing vitamin A were consumed (in the diary week) by 20% of the NDNS sample and among these 41% men and 26% of women had vitamin A intakes that exceeded 1500µg/day.

14. Of the 567 males and 712 females who reported neither consuming liver nor supplements containing vitamin A, 3% and 1% respectively exceeded the EVM Guidance Level.

Young People Aged 4-18 Years

15. The EVM Guidance Level was set for adults, no levels were provided for children. However, the EVM made the general comment that Safe Upper Levels could be applied to children by scaling for body weight or body surface area as appropriate, unless it is specifically indicated that children are particularly vulnerable to the effect concerned or have a greater requirement. Therefore, it was thought prudent to scale down the EVM Guidance Level proportionately for different ages of children. The method used in The Opinion of the Scientific Committee on Food on the Tolerable Upper Intake of Preformed Vitamin A (Annex 4) corrected for differences in basal metabolic rate compared to adults using scaling according to body surface area (body weight$^{0.75}$). This method of calculation was applied to the EVM Guidance Level and Table 1 gives the Guidance Levels suggested for each age group. This method of calculation gives a Guidance Level for 4-6 years that is very close to the RNI.

Table 1: Estimated Guidance Levels for Children of Different Ages Compared to the RNI

Age group (years)	Guidance Level (µg/day)	RNI (µg/day)
4-6	550	400
7-10	750	500
11-14	1000	600
15-18	1300	700/600 (males/females)

16. It is more difficult to make comparisons in children when the calculated thresholds (which are only approximate) vary with age. The NDNS for Young People Aged 4-18 Years (Gregory *et al*, 2000) shows a downward trend with age for children, 35% of boys and 32% of girls aged 4-6 years exceeding the suggested Guidance Level compared to 4% of boys and 3% of girls aged 15-18 years.

17. The small number of older children in the 11-14 and 15-18 age groups that exceed the suggested Guidance Levels makes it difficult to draw conclusions on the contribution of foods to high intakes.

18. In the younger age groups, 34% of 4-6 year olds and 16% of 7-10 year olds exceed the suggested Guidance Level during the diary period. Liver makes a contribution to the intakes of those who exceed the suggested Guidance Level. Average percentage contribution of liver to vitamin A was about 12% in high vitamin A consumers and 0.5% in low vitamin A consumers. Of children aged 4-10 years that were liver consumers, 68% exceeded the suggested Guidance Level for their age group. Of those children that used vitamin A containing supplements in this age group, 77% exceeded the suggested Guidance Level for their age group.

19. Supplements contributed to vitamin A intake in high consumers across all age groups with 66% of boys and 63% of girls that took supplements containing vitamin A during the diary week exceeding the suggested Guidance Level for their age group.

Older People Aged 65 Years and Over

20. Data from the NDNS of adults aged 65 years and over (Finch *et al*, 1998) suggest that 17% of men and 14% of women 65 years and older (excluding those in residential care) in Great Britain have vitamin A intakes above 1500µg/day. For both men and women with intakes over 1500µg/day, liver contributed over 65% of vitamin A intake. Among those who consumed liver during the recording period, 84% of men and 81% of women had intakes that exceeded the EVM Guidance Level.

21. However, dietary supplements also contribute to excess vitamin A intakes in this group. Supplements accounted for approximately 10% for men and 11% for women of vitamin A exposure among those with intakes exceeding the EVM Guidance Level. Among those taking dietary supplements containing vitamin A (during the 4-day diary period) 53% men and 37% of women had vitamin A intakes that exceeded 1500µg/day.

Summary

22. A significant proportion of the population are likely to be exceeding the EVM Guidance Level for vitamin A intake of 1500µg/day. Older age groups are more likely to exceed this level than younger age groups of the population (with the exception of 4-10 year olds). This is of particular concern as older adults are at increased risk of fracture from osteoporosis. High levels of vitamin A maybe compounding this risk.

23. A high proportion of those that exceed the Guidance Level are liver consumers. Dietary supplements also contribute significantly to the vitamin A intakes of consumers that exceed 1500µg/day.

24. The NDNS data, across all population groups, indicates that people living in households that receive benefits are less likely to exceed 1500µg/day than those not receiving benefits.

Terms of reference

25. *In light of the significant number of the population that are currently exceeding the EVM's Guidance Level for vitamin A of 1500µgRE/d, the subgroup's terms of reference are:*

- *To review the current advice to consumers on vitamin A intakes and consumption of liver;*

- *To consider other strategies that might reduce the retinol intake of higher consumers.*

ADDITIONAL INFORMATION:

26. In order to aid the subgroup, information is provided below on the nutritional content of liver, the potential effects of dietary advice to consumers on vitamin A intake and liver consumption and how the level of retinol content of liver may be affected by animal feeding practice.

NUTRITIONAL VALUE OF LIVER AND LIVER PRODUCTS

27. Liver is an extremely rich source of retinol ranging between 25,200µg/100g in calves liver and 10,500µg/100g in chicken liver (McCance and Widdowson 6th Summary Edition, 2002). Liver is a source of other nutrients and some liver products are low cost sources of these nutrients. Liver is rich in iron and other micronutrients. If a suggestion was made to avoid liver in the diet or reduce consumption considerably, careful thought must be given to the effect on other nutrients, particularly iron.

THE POTENTIAL EFFECTS OF DIETARY ADVICE TO REDUCE INTAKES OF VITAMIN A

28. A modelling exercise using NDNS data has been undertaken that explores five potential options for dietary advice that could reduce vitamin A intake. The analysis is presented in Annex 5. As part of the analysis, the effect of reducing liver intake on the intake of iron is considered.

29. The results of the modelling, summarised in Table 2, suggest that the most effective single means of reducing the proportion of the population with intakes of vitamin A above 1500µg/day would be by reducing the consumption of liver. This would only be effective if liver consumption is reduced to below 50g per week. However, to achieve a conspicuous reduction in vitamin A intake then a reduction in liver consumption and eliminating vitamin A in supplements appear to be necessary.

Table 2: Results of modelling, using NDNS data (19-64 years), the potential effects of potential dietary advice on percentage population with high intakes of vitamin A and low intakes of iron

Scenario	Vitamin A intakes above 1500µg/day		Vitamin A intakes below the RNI		Fe intakes below the LRNI	
	Male	Female	Male	Female	Male	Female
Status quo	15.0	8.8	50.3	49.3	0.9	28.8
Reduced Liver (50g/wk), substituting with 50g pork chop	11.8	7.2	50.3	49.3	0.9	29.1
Reduced liver (50g/wk), no substitution.	11.8	7.2	50.3	49.3	0.9	29.1

No liver and no substitution	7.4	5.5	55.3	52.2	0.9	29.3
No vitamin A in supplements	10.7	4.4	55.9	58.6	0.9	28.8
Neither liver nor vitamin A in supplements	2.1	1.0	61.2	61.9	0.9	29.3

RETINOL CONTENT OF LIVER AND ANIMAL FEEDING PRACTICES

30. The retinol content of liver varies between animal. Calves liver contains the highest level of 25,200µg/100g closely followed by pigs liver containing 22,600µg/100g and lambs liver with 19,700µg/100g. The lowest concentration is in chicken liver at 10,500µg/100g. These values were taken from McCance and Widdowson 6th Summary Edition (Food Standards Agency, 2002). It has been shown that levels vary widely between animals both within species as well as between species (Scotter et al, Annex 6).

31. These levels are extremely high and prompted discussion with colleagues in Chemical Contaminants and Animal Feed Division (CCAF) on 15 July. In herbivorous animals, carotenoid in grass and other fodder is converted to retinol. Feeds used to complement or replace such fodder and milk replacers fed to calves from dairy cattle may be supplemented with retinol to ensure that animals' requirements are met. There is a maximum permitted level for retinol that is allowed in animal feeds where it is deliberately added that was agreed in response to similar concerns in the early 1990's. These are set out in the Feeding Stuff Regulations 2000, Schedule 3, Part IV (Annex 7).

32. Recent data (unpublished) from the analysis by Local Authorities of feeding stuffs show that retinol content in animal feeds often exceed these maximum levels. This analysis was not carried out on representative samples from across the UK but provides a useful snapshot. Manufacturers of animal feeds have a practice of 'overage' to ensure that the supplements contain the amount stated on the packet throughout the product's shelf life, this practice also occurs in the human dietary supplement industry.

33. Additionally, there is no maximum level set for feeds intended for dairy cattle and the level set for milk replacement for calves is higher than the level set for other animals. Calves liver contains extremely high levels of retinol. This could be a result of high fetal exposure meaning high retinol stores in the calf at birth, stores which might be further increased by a high level of supplementation in milk replacers.

34. SACN are seeking advice from the Advisory Committee on Animal Feedstuffs on the extent to which supplementation of animal feeds with retinol is affecting the concentration of retinol in animal livers. A paper was presented at the ACAF meeting held on 23 September 2003 (Annex 8) and we have asked that a member of the committee sit on the subgroup. The effects of any potential reductions in

the retinol content of liver on the numbers exceeding the EVM Guidance Level could be modelled using the NDNS data.

LIST OF ANNEXES

Annex 1: Risk Assessment: Vitamin A. Safe Upper Levels for Vitamins and Minerals. Report of the Expert Group on Vitamins and Minerals. May 2003.

Annex 2: Papers on vitamin A and bone toxicity considered by the EVM in their risk assessment:

Ballew C, Galuska D, Gillespie C. (2001) High serum retinyl esters are not associated with reduced bone mineral density in the Third National Health And Nutrition Examination Survey, 1988-1994. *J Bone Miner Res. 16(12):2306-12.*

Feskanich D., Singh V., Willett W.C., Colditz G.A., (2002). Vitamin A intake and hip fractures among postmenopausal women. *Journal of the American Medical Association* **287,** 47-54

Freudenheim J.L., Johnson N.E., Smith E.L., (1986) Relationship between usual nutrient intake and bone mineral content of women 35-65 years of age: longitudinal and cross-sectional analysis. *American Journal of Clinical Nutrition* **44,** 863-876.

Houtkooper L.B., Ritenbaugh C., Aicken M,. Lohman T.G., Going S.B., Weber J.L. (1995). Nutrients and body composition and exercise are related to change in bone mineral density in pre-menopausal women. *Journal of Nutrition* **125,** 1229-1237

Melhus H., Michaëlsson K., Kindmark A., Bergstrom R., Holmberg L., Mallmin H., Wolk A., Ljughall S. (1998). Excessive dietary intake of vitamin A is associated with reduced bone mineral density and increased risk for hip fractures. *Annals of Internal Medicine* **129,** 770-778**.**

Promislow J.H.E., Goodman-Gruen D., Slymen D.J., and Barrett-Connor E. (2002) Retinol intake and bone mineral density in the elderly: The Rancho Bernardo study. *Journal of Bone Mineral Research* **17,** (8), 1349-1358

Sowers M.R., Wallace R.B. (1990) Retinol, supplemental vitamin A and bone status. *Journal of Clinical Epidemiology* **43,** 693-9

Annex 3: Papers on vitamin A and bone toxicity not considered in the EVM risk assessment:

Kawahara T.N., Krueger D.C., Engelke J.A., Harke J.M., and Binkley N.C. (2002) Short-term vitamin A supplementation does not affect bone turnover in men. American Society for Nutritional Sciences

Michaëlsson K., Lithell H., Vessby B., and Melhus H. (2003) Serum retinol levels and the risk of fracture. *The New England Journal of Medicine* 348:287-94

Lips P. (2003) Hypervitaminosis A and fractures. *The New England Journal of Medicine* 348: 347-8

Boucher B.J. (2003) Serum levels and fracture risk. *The New England Journal of Medicine* 348: 1927-8

Annex 4: Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Preformed Vitamin A (retinol and retinyl esters) (2002) European Commission. Brussels.

Annex 5: Using NDNS Data To Predict The Effect Of Dietary Advice That Might Reduce Vitamin A Intake

Annex 6: Scotter M.J., Thorpe S.A., Reynolds S.L., Wilson L.A. and Lewis D.J. (1992) Survey of animal livers for vitamin A content. *Food Additives and Contaminants,* **9**, No 3, 237-242

Annex 7: Excerpt from Feedingstuffs regulations 2000 relating to the addition of fat-soluble vitamins to animal feed.

Annex 8: Paper presented to the Advisory Committee on Animal Feedingstuffs on 23 September 2003

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Gregory J, Foster K, Tyler H and Wiseman M (1990), The Dietary and Nutritional Survey of British Adults, London: HMSO. (ISBN: 0 11 691300 2)

Gregory J R, Collins D L, Davies P S W, Hughes J M and Clarke P C (1995), National Diet and Nutrition Survey: children aged 1½ to 4½ years: Volume 1: Report of the diet and nutrition survey, London: HMSO. (ISBN: 0 11 691611 7)

Finch S, Doyle W, Lowe C, Bates C J, Prentice A, Smithers G and Clarke P C (1998), National Diet and Nutrition Survey: people aged 65 years and over. Volume 1: report of the diet and nutrition survey, London: TSO. (ISBN: 0 11 243019 8)

Gregory J, Lowe S, Bates C J, Prentice A, Jackson L V, Smithers G, Wenlock R and Farron M (2000), National Diet and Nutrition Survey: young people aged 4 to 18 years.

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Henderson L, Gregory J and Swan G (2002), The National Diet and Nutrition Survey: adults aged 19 to 64 years. Volume 1: Types and quantities of foods consumed, London:TSO (ISBN: 0 11 621566 6)

Henderson L, Gregory J, Irving K and Swan G (2003), The National Diet and Nutrition Survey: adults aged 19 to 64 years. Volume 2: Energy, protein, carbohydrate, fat and alcohol intake, London:TSO (ISBN: 0 11 621567 4)

Henderson L, Irving K, Gregory J, Bates, C J, Prentice A, Perks J, Swan G and Farron M (2003), The National Diet and Nutrition Survey: adults aged 19 to 64 years. Volume 3: Vitamin and mineral intake and urinary analytes, London:TSO (ISBN: 0 11 621568 2)

Food Standards Agency (2002) McCance and Widdowson's The Composition of Foods. Sixth Summary Edition. Cambridge: Royal Society of Cambridge.