



**2nd MEETING OF THE SUBGROUP ON VITAMIN A
24 March 2004, FSA, Aviation House, Conference Room 2**

Chair Professor Alan Jackson

Members Professor Peter Aggett
Dr Tim Key
Dr Ann Prentice
Dr Anita Thomas
Dr Anthony Williams
Dr Bruce Cottrill (Advisory Committee on Animal Feedingsuffs)
Dr Cliff Gay (Statistics Branch, FSA)
Dr Ray Smith (Animal Feed Unit, FSA)
Dr Diane Benford (Chemical Safety and Toxicity Division)

Secretariat Dr Alison Tedstone (FSA)
Dr Sheela Reddy (DH)
Ms Lynn Burns (FSA)
Ms Mamta Singh (FSA)

AGENDA ITEM 1 - Chair's welcome and introductions

1. The Chair welcomed members to the 2nd meeting of the SACN Subgroup on Vitamin A and introduced Dr Diane Benford of the FSA's Chemical Safety and Toxicity Division. Dr Benford was part of the Secretariat for the Expert Group on Vitamins and Minerals and had been invited to attend the meeting to explain the basis of setting a Guidance Level for vitamin A.

AGENDA ITEM 2 - Minutes of the last meeting (SACN/VitA/min01/draft)

2. Members were invited to comment on the minutes of the previous meeting. The following changes were agreed:

3. Para 17: The words “fortified food” to be removed from the penultimate line of the paragraph.
4. Para 22: The sentence “There are no recent data on supplement usage in older people from NDNS” to be changed to give the date of the NDNS of older people aged 65 years and over and to state that this is the most recent information on supplement usage in older people.
5. Para 26: “...or might **effect** bone indirectly...” should read “...or might **affect** bone indirectly...”
6. Para 36: The penultimate sentence should read “Studies with ruminants indicate that the higher the concentration of retinol, the less is absorbed **in relative terms.**”
7. Para 44: Should read “ Members requested information on the extent to which retinol and other forms of vitamin A transfer across to the liver.” Also Cottrill had been spelt incorrectly.
8. It was also noted that there was a typing error in Annex 3: Comparisons of UK, US and Scandinavian Diets. The last line of paragraph 4 should read “Adults in the UK also consume more than double the fish...”

ADDITIONAL AGENDA ITEM – correspondence received from Professor David Richardson and Dr Ann Walker (paper tabled)

9. Members were given a brief background of the correspondence between the Secretariat and Professor David Richardson (*dprnutrition LTD*/previously a member of COMA) and Dr Ann Walker (University of Reading).
10. Professor Richardson had contacted the Secretariat regarding the *Scientific Advisory Committee on Nutrition Subgroup on Vitamin A, Paper for Discussion*. Subsequently, Professor Richardson and Dr Walker had submitted a paper to the Secretariat commenting on the vitamin A paper in which they made frequent

references to the “SACN opinion”. The paper had been forwarded to Alan Jackson and other SACN members.

11. The Secretariat had written to Professor Richardson to inform him that the paper he had sent was a misrepresentation of the SACN position as this has not yet been agreed. Professor Richardson’s letter of response was tabled.
12. The main concern expressed in his letter was regarding timing of the release of information on the SACN web site. Premature release of information could lead to misrepresentations of SACN opinion.
13. Members agreed that although publication of papers in a public forum was a procedural process essential for openness, greater clarity might be necessary to limit misinterpretation of the work and opinions of SACN. It was agreed that a clear footer should be used on all future SACN discussion papers.
14. Members agreed that a reply should be sent to Professor Richardson to thank him for his comments and assure him that SACN would discuss the concerns he had raised.

Action: Secretariat

AGENDA ITEM 3 - Additional Background information

Expert Group on Vitamins and Minerals (EVM) Revised Review of Vitamin A (Annex 1)

15. Dr Benford gave a brief background to Annex 1. In summer 2002, the Expert Group had agreed its preliminary conclusions for each nutrient. This was followed by a consultation period of three months, after which the group considered the responses. The report was published in May 2003.
16. Evidence for two separate adverse effects of high intakes of vitamin A, specifically of preformed retinol, was considered. These were teratogenicity and increased risk of fracture. The evidence regarding bone health was not considered

to be robust enough to set a Safe Upper Level. However, taking into account the animal data, the epidemiology data were considered sufficient to set a Guidance Level. It was noted that although the Guidance Level is expressed in $\mu\text{gRE}/\text{day}$ it is based on data on preformed retinol and not on beta-carotene.

17. While a level of certainty can be placed on the teratogenic effects of retinol at supplemental intakes of $3000\mu\text{g}/\text{day}$ and above, there is less confidence in the effects of intakes of $1500\mu\text{g}/\text{day}$ on bone health. Some data suggest that those consuming between $1500\text{-}3000\mu\text{g}/\text{day}$ may be at risk of osteoporotic fracture. There are also data which show no significant association between retinol intakes of $1500\text{-}3000\mu\text{g}/\text{day}$ and risk of osteoporotic fracture.
18. Members questioned the rationale used by the US and the European Scientific Committee on Food (SCF) in considering their recommended tolerable upper level, which had been set at $3000\mu\text{g}/\text{day}$. Dr Benford explained that this figure was set on the basis of evidence for teratogenicity. The US upper level had been set prior to the emergence of some epidemiological evidence for detrimental effects on bone. The SCF did not consider the evidence for effects on bone sufficiently robust to use in setting the Tolerable Upper Level and did not have the option of setting a Guidance Level as used by the EVM.
19. It was also noted that data from NDNS 2001 suggest that retinol intake has decreased since NDNS 1987. To facilitate comparison between the surveys, the Secretariat were requested to tabulate the data on the mean and median retinol intakes from the two surveys as well as the contribution of liver and supplements to these intakes, so that they could be considered later in the meeting.

Action: Secretariat

Pre-publication draft of FSA funded project investigating the association between plasma retinoids and risk of hip fracture (Annex 2)

20. The project had examined data from subjects who had formed the placebo arm of a trial investigating the ability of bisphosphonates to reduce fractures. Blood samples of the placebo group were analysed for retinol, retinyl esters and other

analytes important in bone metabolism. Members were informed that this work had not yet been peer-reviewed.

21. The results from the study showed no relationship between plasma retinol and fracture risk for this group of women, aged over 75 years, in the UK. Members raised several points. These were as follows:

- The range of plasma retinol values was narrower than observed in the NDNS of older people (1994/5). Given the age of the subjects in this study, it may be more appropriate to compare the study group with NDNS subjects aged 75 years and over.
- Concerns were expressed that the criteria for the original study did not exclude women who had already suffered an osteoporotic fracture and may have been particularly old and frail.
- It was not clear whether results had been age-adjusted.
- The ranges of plasma retinol were much lower than in the Scandinavian studies. Members raised the possibility that there may be other differences; for example, the relationship between vitamins A and D, fish consumption, genotype, etc.
- Supplement usage may have changed in the UK in this age group since these subjects were sampled. A similar group sampled now and investigated 10 years on may give a very different picture.

Comparisons of UK, US and Scandinavian Diets (Annex 3)

22. Much of the research suggesting that intakes above 1500µg/day may be detrimental to bone has been carried out either in Scandinavia or in the US. The Subgroup had previously requested information comparing the diets of these countries with that of the UK and this information was summarised in Annex 3.

Differences in the methods for obtaining the information, e.g., classification of food groups, grouping and recruitment of subjects into surveys, were highlighted.. The extent to which the differences between countries are relevant is difficult to ascertain because of the varying methods used.

23. The most striking differences between consumption of various food groups were:
- Consumption of milk is much higher in the UK than in the US, however meat consumption is much less.
 - More fish and seafood is eaten in the UK than in the US but less than in Scandinavia.
 - Cheese consumption is much higher in Scandinavia than either in the US or UK.
24. Total intakes of vitamin A are much higher in the US and Scandinavia. However, in the UK a much greater proportion of total vitamin A intake is from vegetable sources.
25. Members agreed that there were important differences in both nutrient and food intakes between these countries.

Nutritional Aspects of Bone Health, Chapter 17, Vitamin A and Fracture Risk (Annex 4)

26. Members found annex 4, the chapter by Melhus from *Nutritional Aspects of Bone Health* edited by Susan A New and Jean-Phillipe Bonjour (RSC, 2004), helpful and requested the complete list of references cited in the chapter. The chapter highlighted possible mechanisms by which vitamin A could have an effect on bone, including a potential antagonistic effect on vitamin D.
27. It is suggested that retinol interacts with dietary vitamin D rather than that formed in the skin, which may be possible if retinol has its effect at absorption level. Peter Aggett offered to look at the references quoted in the passage relating to the

antagonistic effects of these nutrients, and at other information identified by members, and to prepare a short commentary on the interaction.

Action: Secretariat and Peter Aggett

Intakes and sources of vitamin A statistics in the UK - NDNS Data (Annex 5)

28. Cliff Gay presented annex 5, outlining the calculations used to compensate for the difficulty in estimating habitual vitamin A intake due to the high concentration of retinol in a rarely consumed food, i.e. liver. The adjustment was made using food frequency questionnaire data on the habitual consumption of liver and liver products from the European Prospective Investigation into Cancer (EPIC). The result of the adjustment is to narrow the extremes. When applying this model to the NDNS data for older people 65 years and over, the effect of the adjustment is greater because of the shorter period of four days of weighed dietary intake used in this survey.
29. The validity of this model to normalise habitual liver consumption was discussed. It was agreed that operating within the constraints of the data available and accepting that assumptions had been made, the model provided a more realistic picture of the worse case scenario.
30. It was suggested that the assumptions made in the model could be investigated by comparing NDNS data from 1986/7 with the latest survey. In reality there has been a considerable fall in retinol intake through a fall in liver consumption.
31. It was agreed that all the tables were useful, however the carotenoids should be expressed as *retinol equivalents*. It was agreed that the model should be applied using 1500µg/day preformed retinol in place of the EVM Guidance Level. This would be more appropriate as the available evidence shows that it is preformed retinol that is associated with detrimental effects.
32. The data showed that removing liver had little effect on the numbers of people falling below the LRNI for other nutrients, particularly for iron.

Action: Secretariat

Unpublished data concerning the use of supplements containing vitamin A by pregnant women (Annex 6)

33. Annex 6 provided data from an ongoing study in Aberdeen on the numbers of women taking supplements. It was noted that the number of women taking supplements was high and that 2% were continuing to take vitamin A containing supplements during pregnancy. It was not possible to ascertain whether the women taking retinol-containing supplements were aware that they contained retinol.

Retinol status (Annex 7)

34. Cliff Gay presented annex 7, which outlined the NDNS data on retinol plasma levels. Retinol status is subject to seasonal variation with increased levels in the summer months. Seasonality is an important factor for vitamin D status and the seasonality of retinol may indicate a relationship between vitamins A and D.

35. Members considered whether there were any interactions between retinol and cholesterol. Melhus et al (1998) found that high cholesterol was associated with increased fracture.

Overage in food supplements (Annex 8)

36. The practice of overage, whereby manufacturers add nutrients to products at levels higher than that stated on the label, is used to ensure that retinol levels are at least that quoted on the label throughout the entire shelf life (approximately 3 years). Industry has indicated that this overage ranges between 30-50%.

Review of studies investigating the effects of vitamin A supplementation on hepatic storage in livestock and animals (Annex 9)

37. Dr Bruce Cottrill presented annex 9. All studies considered showed an increase in liver concentration of retinol with increasing vitamin A intake and the existence of

a linear relationship. It was noted that care should be taken when considering these studies as many use levels that are considerably higher than the Maximum Permitted Level¹ (MPL) for animal feeds and the number of studies examined was relatively small.

38. MPLs appear to be high (13500 IU for most complete feeds for most animals) when compared to published estimates of requirements. However, caution needs to be exercised in recommending lower levels of supplementation to ensure no adverse effects on production, reproduction or welfare of farm livestock.
39. Unpublished data from Local Authorities suggest that most complete feed manufacturers claim a retinol content of between 10000 to 11000 IU on their labels. The animal feeds industry also practice overage to ensure this level is present in the product throughout its shelf life. This overage is added to bring the actual content of the product to just below the MPL of 13500 IU.
40. Members agreed it would be useful to further investigate the possibility that reducing the retinol content of liver by reducing retinol intakes of livestock might lower population retinol intakes, especially at the upper end of the distribution. The implications of making such a recommendation were discussed. Industry may be concerned that reduction of retinol levels in feeds may affect production and that such a recommendation may send negative messages to consumers about animal foods. A limitation on the retinol content of liver could be seen as a barrier to trade as much of the meat (including liver and liver products) consumed in the UK is imported.
41. Altering animal feeds to reduce retinol content of liver may have effects on dairy products and eggs. Dr Bruce Cottrill agreed to further investigate the literature on this matter, as low retinol consumers obtain most of their retinol from these sources.

¹ Maximum Permitted Levels for vitamin A in feeds for fattening poultry and livestock are fixed by EC legislation (Directive 70/524/EEC, as amended). They are based on the requirements of the animals, but include a safety margin to allow for variability in the feed and uncertainty about the availability and requirements of the nutrients. The levels apply to all feeding stuffs.

AGENDA ITEM 4 - Discussion

42. Members agreed that the Guidance Level is of relevance to those consumers with a habitual intake of between 1500 and 3000 µg/day, particularly in older consumers.

43. It was agreed that the advice from SACN should be presented as a report outlining the considerations of the Subgroup.

44. A number of points were noted:

- Retinol intake in the UK has fallen since 1986/7. Trends in retinol intake should be monitored along with new literature regarding the relationship between retinol intake and bone fracture.
- Literature on the relationship between retinol intake and bone fracture originates mainly from Scandinavia and the US. There are important differences in diet between these countries and the UK.
- Modelling should be carried out using 1500µg/day preformed retinol as the upper limit.
- Tables showing the contribution of foods to the intake of vitamin A by different population groups should be amalgamated. Carotenoids should be expressed in retinol equivalents.
- The strengths and weaknesses in the data need to be described.
- The relationship between vitamin D and A needs to be investigated further.
- The Guidance Level is a recommended habitual average intake and occasional excursions above this limit are not of concern.

- The potential for reducing retinol content of liver should be explored further and modelling be carried out assuming a 25% reduction in liver retinol content.

45. Although it was intended to be the last meeting, it became clear during the course of the meeting that more information was required and that the questions raised would be need to be addressed. It was agreed that the Secretariat would draft a report, which would include the suggestions and comments of members, and that a further meeting would be arranged to agree the report in 3-4 months. It was agreed that time would be allowed for comment by interested parties and that the final draft would be put to the main SACN meeting in February 2005.