



Scientific Advisory Committee on Nutrition

**1st MEETING OF THE SUBGROUP ON VITAMIN A
3 November 2003, 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 Feedingstuffs)
Dr Cliff Gay (Statistics Branch, FSA)
Dr Ray Smith (Animal Feed Unit, FSA)

Secretariat Dr Alison Tedstone (FSA)
Dr Sheela Reddy (DH)
Ms Lynn Burns (FSA)
Ms Rachel Elsom (FSA)

Chair's welcome and introductions

1. The Chair welcomed Members to the first meeting of the Subgroup on Vitamin A. Members were invited to introduce themselves. It was noted that four Members of the Subgroup (Peter Aggett, Alan Jackson, Anita Thomas and Antony Williams) had been members of the Expert Group on Vitamins and Minerals (EVM).

Background

2. Members were informed of current Government guidance on vitamin A (Department of Health, 1990) in which pregnant women or women thinking of becoming pregnant are advised not to take any supplement containing vitamin A 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. It is also recommended that infants and young children do not have liver or liver products more than once a week.

3. Members were informed that EVM set a Guidance Level¹ for total retinol intake of 1500µg retinol equivalents (RE) per day (EVM, 2003). This level was agreed due to emerging evidence that intakes above this level may increase the risk of bone fracture. Members were directed to the full EVM review of vitamin A available on the CD-ROM, that accompanied the report (EVM, 2003).
4. Members noted the findings from National Diet and Nutrition Surveys (NDNS) in adults showing that a significant proportion of the population exceed the EVM guidance level for vitamin A, with the risk of exceeding this level increasing with age. There are no guidance levels for children although EVM suggested that a proportional approach should be employed. Using this approach, a significant number of children have vitamin A intakes greater than the guidance level and younger children were most likely to exceed this level. In all age groups, both liver and supplements contributed to high vitamin A intakes.

Purpose of meeting

5. The Chair reminded Members of the purpose of the Group: “In light of the significant number of the population that are currently exceeding the EVM’s Guidance Level for total retinol intake 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.”
6. It was stressed that the Subgroup’s remit was not to review the EVM risk assessment. However, the recommendations made by EVM would inform the process. Members agreed that papers published since EVM reported should be considered.
7. Members were encouraged to consider all sources of vitamin A in the total diet, including the contribution made by butter and other fats (which are fortified by law), in addition to the key sources of liver and supplements.

Discussion

8. The Chair invited a general discussion of the current situation. The effects of vitamin A on bone were discussed, and included consideration of plausible mechanisms for the putative effect of retinol on bone.

¹ Guidance Levels were recommended by the EVM, where possible, for vitamins and minerals for which the available data were considered too limited to give clear advice on a Safe Upper Level (SUL). Guidance Levels are approximate indications of intakes that would not be expected to cause adverse effects when consumed daily over a lifetime. Because they are derived from limited data they are less secure than SULs and should not be confused with, or used as, SULs.

NDNS

9. Members discussed the limitations associated with the NDNS dietary intake data. The amount of vitamin A in food varies greatly and to obtain a reliable estimate of habitual intake, data have to be collected over an extended period of time, longer than the 4-7 days employed in NDNS. Members noted that it is likely that the proportion of people for whom habitual consumption exceeded the guidance level for vitamin A would be overestimated if dietary data were collected for shorter periods of time, as in the NDNS. Members recommended that other data sets should be considered, e.g. Health Survey for England (HSE) and the European Prospective Investigation of Cancer (EPIC) and that frequency of consumption data would be useful.
10. Members suggested that populations in which vitamin A intakes have been recorded for more than 7 days should be identified and data used for remodelling.
11. Members noted that remodelling NDNS data using day to day variation is not possible due to the highly skewed distribution of vitamin A intakes. Even if liver and supplements are removed from the model, the distribution may not be normal.
12. Members noted that the more recent papers relating vitamin A to bone health reported on populations in the USA and Scandinavia, and the distribution of vitamin A consumption in these populations needs to be compared with that in the UK. In Scandinavia, individuals with high vitamin A intakes have high intakes of other nutrients. Members suggested that nutrient clustering could be examined in NDNS data.
13. Members noted that EVM considered beta-carotene and retinol separately. Conversely, NDNS values for vitamin A include retinol precursors, including beta-carotene. The association between vitamin A and bone health is thought to be mediated through retinol. Therefore, it would be useful to remodel NDNS data separating retinol from retinol precursors.

Action: Secretariat

General population vs targeted advice

14. Members were asked to consider the extent to which advice on vitamin A should be directed to the total population or targeted to specific subgroups of the population, and the effect of either strategy on the overall profile of vitamin A status.
15. Members stated that it would be useful to determine the characteristics of individuals at different segments of the distribution of vitamin A intake (i.e. low, medium and high consumers). Age-related changes in the patterns of consumption can then be identified.
16. Members were cautious in identifying children as a group at special risk.

Exposure

17. Members were asked to consider the relative importance of ongoing moderate exposure compared with exposure in the short term to a single high intake of vitamin A. As vitamin A is stored in liver and circulating concentrations in blood are tightly regulated, there is the need to know whether any reported adverse pathophysiological effects in bone, show a dose response relationship with either liver retinol, or circulating levels of retinol. Members were not aware of any data which related hepatic vitamin A to adverse effects. The available data relate to dietary consumption and plasma concentrations of retinol.

Evidence

18. Members discussed two recent papers that had not been considered in the EVM risk assessment of vitamin A: 1) Kawahara *et al*, 2002, in which acute vitamin A exposure did not affect markers of bone turnover; and 2) Michaëlsson *et al*, 2003, reporting results from a longitudinal cohort study in which men with the highest serum retinol were at highest risk of fracture.
19. Members agreed that the new evidence added little to the risk assessment carried out by EVM. They noted that the study populations were heterogeneous and consideration of confounding factors was limited. Furthermore, individuals with the highest vitamin A intakes were also consuming the highest intakes of calcium, iron and vitamin D, suggesting that these may have different diet and lifestyle characteristics, including taking supplements. Members noted that associations between retinol intake and bone health could be due to reverse causality i.e. individuals concerned with their bone health may have adopted a diet rich in micronutrients, including taking more supplements.
20. Members agreed that the large differences in serum cholesterol seen between the high and low categories of serum retinol in the Michaëlsson *et al* study (2003) were of interest and highlighted the current limited understanding of the determinants of variability in serum retinol concentrations and the mechanisms of retinol homeostasis.
21. Members discussed the other known factors affecting retinol status including alcohol, zinc, vitamin D, inflammation and liver damage. They made the point of the need for a clearer understanding of the interactions between vitamins A and D since many supplements and fortified foods contain both vitamins and because they have actions at the metabolic and cellular level which influence each other.
22. Members recognised the increasing interest in the proposal that very high levels of retinol may cause bone health problems in older people. However, only three prospective studies have investigated bone fracture as an end point. In the USA it has been suggested that supplements aimed at older people (>50 years) should not contain vitamin A. There are no recent data on supplement usage in older people from NDNS since the 1994/5 NDNS of people aged 65 and over (Finch *et al*, 1998). Members requested that other possible sources of data (e.g. HSE & OPCS) on supplement usage should be investigated.

Action: Secretariat

23. There is some evidence that individuals taking supplements may have an increase in serum retinol in the form of retinyl ester levels. It was noted that no association has been found between the concentrations of retinyl esters in blood and markers of bone health. It is less clear whether there is any relationship between dietary intake and levels of retinol carried in the circulation with retinol binding protein.
24. Members stressed that the Subgroup's report should include a discussion on the quality of the evidence, where data is lacking, and other issues of concern.

Plausible mechanism

25. Members discussed the possible mechanisms that might explain the observed association between vitamin A intakes and bone fracture.
26. Members considered the extent to which vitamin A might have a direct effect on bone, or might affect bone indirectly through an effect on liver function (its storage site).
27. Members considered whether plasma retinol might be a marker of changed metabolic state (or process), in particular hepatic function. If this were the case, recommending a decrease in vitamin A intake may not rectify the problem. There is the need to be clear whether the evidence for a possible effect relates to pre-formed vitamin A rather than carotenoids.

Dietary sources of vitamin A

28. Members noted that in addition to liver and supplements, other dietary sources of vitamin A might also be important. The contribution of these sources, including fat spreads, other fortified foods (e.g. breakfast cereals), and dairy products, should be determined. It was noted that synthetic retinol palmitate is used to fortify margarine whilst cow's milk contains naturally occurring retinyl esters.
29. Members sought information on the relative contribution of vitamin A in the diet from fish and margarine, amongst different population sub-groups.
30. It was thought that the Consumers Association has reported that the vitamin A content in products varies. Members requested any available information on this and the extent of overages in fortified products and supplements.

Action: Secretariat to contact The Consumers Association and manufacturers

Vitamin A in animal feedingstuffs

31. Members considered whether animal feedingstuffs provided a potential area for management of vitamin A in the food chain.

32. Drs Bruce Cottrill and Ray Smith led the discussion on vitamin A in farm livestock nutrition. Members were informed that there are only limited data available for a number of animal feeds. This information has been obtained by local authorities across the UK and made available to the FSA. The data are unpublished and have not been collected according to FSA survey guidelines. Therefore certain information, such as label details and intended use, is not available and members were warned not to place too much faith in the claimed product descriptions and categorisations.
33. Members were informed that there are maximum permitted levels for vitamin A for complete feeding stuffs. Some products have been found to exceed these levels. This might be a result of manufacturers employing overage to account for deterioration of the vitamin while the feed is stored. Livestock have a relatively short lifetime exposure to these high levels and thus there is less time for toxicity to develop.
34. Members questioned whether similar practices were employed in the rest of the EU, which might have implications for food imports. Further information was requested.

Action: Bruce Cottrill

35. Members were directed to Vitamin Tolerance of Animals (NRC, 1987) which provides data on requirements for vitamin A by different classes of livestock, and presumed safe dietary levels which for many livestock are >10 times requirements. Data on typical specifications of livestock diets in the UK were also presented and discussed.
36. Members noted that animal studies with high exposures have been primarily conducted in rodents and monkeys. They were informed that the uptake of vitamin A in farm livestock is influenced by many factors, including the constituents of the diet and the level of vitamin A. Studies with ruminants indicate that the higher the concentration of retinol, the less is absorbed in relative terms. This is not the case for humans in whom vitamin A accumulates without reaching saturation.
37. Members noted that while farm livestock receive most of their nutrients from vegetable material, vitamin A (retinol) itself does not occur in plants. Rather, provitamin A carotenoids are the principle source of vitamin A for livestock. Since many of the feed materials contain insufficient β -carotene to meet requirements of high producing livestock, it is common practice to supplement diets with synthetic vitamin A. They queried whether there is any work showing the metabolism of retinyl palmitates in livestock.

Possible actions

38. Members discussed the relative risk:benefit of a number of options for future action.

39. 1) Do nothing. The relative risk:benefit of this course of action depends upon the confidence placed in the EVM Guidance Level. Approximately 10% of children are consuming less than the LRNI for vitamin A. Therefore, the effect of any advice to limit the consumption of vitamin A to help reduce the risk of bone fracture in older people has to be weighed against any possible negative effect in children who may be at risk of deficiency.
40. Members considered that there is no evidence to justify advice to decrease vitamin A intakes in children; that the situation in 18-50 year olds is unclear at this time; that in the over 50s there is some evidence that vitamin A may be a cause for concern.
41. Members recommended that the effects of advice to lower vitamin A consumption in one group of the population on other population groups should be considered. Notably, would it result in a shift in distribution resulting in an increase in the proportion of the population having an intake which was less than the LRNI, and therefore an increase in the risk of deficiency.

Action: Members and Statistics

42. 2) Amend dietary advice relating to the main dietary sources of retinol, in particular liver and supplements.
43. Members were informed that current animal feeding practices might provide more retinol than recommended by the guidelines due to overage. Members discussed the impact of more rigorous enforcement of these guidelines and possible effects this might have on animal husbandry. It was agreed that before considering any change in current recommendations to manufacturers, there would need to be reasonable evidence for benefit to older people and no detrimental impact on younger people.
44. Members requested information on the extent to which retinol and other forms of vitamin A transfer across to the liver in ruminants.

Action: Bruce Cottrill

45. Members requested that NDNS data be explored to assess the potential effects of decreasing liver intake and the effect of decreasing the retinol content of liver by changes in animal husbandry. As liver is an important source of other nutrients which might be limiting in the population, the wider nutritional implications of any possible advice to change patterns of consumption of liver would need to be considered.

Action: Statistics

46. Any exploration of the NDNS data should also include consideration of the relative contribution of liver-based products, breakfast cereals, and dairy products to vitamin A intakes. The effect of season on retinol status should be considered.

Action: Statistics

47. Given the wider implications of any advice which sought to change patterns of liver consumption, any exploration of the NDNS data should seek to assess the extent to which specific sub-groups of the population might be affected

differentially. Both high and low consumers should be included across all age groups.

Action: Statistics

48. Members noted that much of the literature which relates dietary intakes of vitamin A to bone health is derived from studies in populations in the USA and Scandinavia. There is the need to consider the extent to which these data are likely to reflect the situation in the UK. Therefore it is important to look at the diet profiles of the USA and Scandinavia, in relation to those in the UK.

Action: Statistics

49. Members discussed the contribution from supplements, particularly in groups with low vitamin A status, and the possible implications for advice (to whole population vs target groups) if this is found to be significant. Members considered that advice regarding supplements which contain vitamin A might be targeted at products for the over 50s to avoid adverse effects on other subgroups of the population, but appreciated that accumulation of vitamin A before the age of 50 was relevant to the risk above this age.

Action: Members

Any Other Business

50. The next Subgroup meeting will be held on 24 March 2004.