COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

VITAMIN E AND PREGNANCY – ADDITIONAL INFORMATION

Introduction

1. Vitamin E is a generic description for a group of eight lipid soluble chemicals. There are two classes, tocopherols and tocotrienols, which exhibit the biological anti-oxidant effect. Vitamin E is synthesised in plant products, the highest levels being found in plant oils, with lower levels being found in the leaves and other green parts. Vitamin E prevents lipid oxidation and maintains membrane integrity throughout the body.

2. In 2003, the Expert Group on Vitamins and Minerals (EVM) established a Safe Upper Level (SUL) of 540 mg (800 IU) for supplemental vitamin E, equivalent to 9 mg/kg bw/day in a 60 kg adult (EVM, 2003). This was based on data from two studies in human volunteers.

3. The FSA recommends that men and women need a daily intake of 4 and 3 mg vitamin E respectively. There is no specific UK RNI for vitamin E since it is related to intake of polyunsaturated fat. The EU labelling Recommended Daily Amount for vitamin E is 10 mg. Most food supplements contain the RDA for vitamin E, but supplements containing up to 400IU (540 mg) are available.

4. The FSA does not recommend the use of food supplements since most groups should be able to meet their nutritional needs by eating a healthy balanced diet. However, folic acid and vitamin D are recommended in pregnancy.

5. At the horizon scanning meeting in February, Members were informed of two papers which suggested that high doses of vitamin E taken during pregnancy could be associated with reduced birth weights. These were:

Boskovic et al (2005)

6. This was a small prospective observational study. This suggested that birth weights were significantly reduced (3173 ± 467 g) in the babies of women who had taken more than 400 IU vitamin E per day during pregnancy, compared to the babies of women in the control group (3417 ± 56 g). The authors noted that the finding could be due to chance. Members considered this was a small study with a strong potential for selection bias and that conclusions could not be drawn from it.

7. In this large randomised placebo-controlled trial, women were given 1000 mg vitamin C and 400 IU vitamin E or placebo. More low birth weight babies were born to women in the treatment group (28%) compared to the controls (24%). The mean birth weights of the babies in the treatment and placebo groups were 2901 and 2967g respectively. Members noted that although this was a large and randomised trial, the different characteristics of the two groups as described in the paper, indicated that the association could be due to chance. It was also noted that the dose of vitamin E used 400 IU (540 mg) which would not be achievable by dietary means.

8. Overall, Members considered that the two studies did not indicate any serious concern but requested additional information on a number of areas.

Further information

Intervention studies currently in progress

9. Members asked whether there were any trials of vitamin E in pregnancy currently in progress. No studies of vitamin E alone have been located but the following cohorts have been identified either from clinical trials registers or elsewhere (Fraser et al, 2005).

- INTAPP (International Trial of Antioxidants for the Prevention of Pre-eclampsia). Reported to be in progress as of 2005 (Fraser et al, 2005), but no publications have been identified (n=12,500) 1000 mg vitamin C, 400 IU vitamin E. This trial is not listed on the clinical trial registers searched, however, it is noted (Rumbold and Crowther, 2008) that the results were expected in 2007.

- CAPPS (Clinical Trial of Antioxidants to Prevent Pre-eclampsia). This began in 2003 and is listed as active but not recruiting (n=10,000) 1000 mg vitamin C, 400 IU vitamin E.

- DAPIT (The Diabetes and Pre-eclampsia Intervention Trial). Registered as completed but no publications identified to date (n= 945)1000 mg vitamin C, 400 IU vitamin E.

- TMT (Threatened Miscarriage Trial) 2004-2006. Registered as completed but no publications identified (n=580), 1000 mg vitamin C, 400 IU vitamin E.
Status of Cochrane reviews

10. Members asked whether the recent Cochrane systematic review of vitamin E had included the study by Poston et al (2006). There are three Cochrane systematic reviews related to this area. The review of vitamin E supplementation in pregnancy was conducted in 2004 and initially published in 2005 (Rumbold and Crowther, 2005a), with a revised version being published in 2008, though this was for re-editing rather than having any new data added to the analyses. The Poston et al (2006) study is noted as ongoing. This review concluded that there were insufficient data to assess benefits or harm from vitamin E supplementation. Of the primary outcomes assessed, there was no difference in the incidence of intra-uterine growth restriction or birth weights between the control and treatment groups. This was based on 2 and 1 studies respectively. There was little variation in the dosage used so that it was not possible to perform a sub-group analysis based on dosage. The only study which reported birth weights (Beazley et al, 2005) described a small, non-significant reduction in birth weight in the treatment group (1000 mg vitamin C, 400 IU vitamin E) compared to the controls. Birth weights were 3050 ± 1021g and 2911 ± 901g in the treatment and placebo groups respectively. This was a small study (n=100) which had to be terminated early due to withdrawal of funding.

11. However, a 2008 Cochrane review of anti-oxidants for preventing pre-eclampsia (largely vitamins C and E) concluded that there was no evidence to support the use of anti-oxidants in pregnancy and that there was no difference in birth weights between treated and placebo groups (Rumbold and Crowther, 2008). Birth weight was treated as a secondary outcome and the analysis was based on 5 studies of which three (Beazley et al, 2005; Poston et al, 2006; Rumbold et al, 2006) used vitamins C and E. In the study by Rumbold et al (2006) in which 1877 women were given 1000 mg vitamin C, 400 IU vitamin E or placebo, birth weights were very slightly (but not significantly) increased in the treatment group (3392 ± 599g) compared to the controls (3386 ± 584g).

12. A 2005 Cochrane systematic review of vitamin C in pregnancy (Rumbold and Crowther, 2005b) did not find any effects on birth weight. However, it was noted that only the study by Beazley et al (2005) provided data in a format suitable for inclusion in the review.

Animal data

13. Members asked whether there were any relevant animal data and asked to see the Expert Group on Vitamins and Minerals (EVM) review of vitamin E to assess the available animal data; this is attached at annex A and the related risk assessment is at annex B. The data on reproductive effects are described in paragraphs 92-96. From these data there does not appear to be anything that
indicates concern about the reproductive effects of vitamin E. No further data have been identified.

**Vitamin C**

14. Members asked whether any adverse effects on reproduction have been associated with vitamin C. Vitamin C was also assessed by the EVM (Annex C) and no relevant adverse effects were identified. No further data have been identified.

**Other information**

**Questions for Members**

15. Are Members content to keep the issue of vitamin E in pregnancy under review or is further work necessary?

**Secretariat**

**March 2009**
REFERENCES


Rumbold A, Crowther, C.A. (2005b) Vitamin C Supplementation in Pregnancy. Cochrane Database of Systematic Reviews, Issue 1, Article number CD004072. DOI:10.1002/14651858.CD004072.pub2


VITAMIN E AND PREGNANCY – ADDITIONAL INFORMATION

Expert Group on Vitamins and Minerals (EVM) review of Vitamin E will not be published on the website but is available at:

http://www.food.gov.uk/multimedia/pdfs/evm-00-13r.pdf

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March 2009
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This is a background paper for discussion. It does not represent the views of the Committee and should not be cited.

TOX/2009/12 Annex C

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