

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

**REPORT ON PHYTOESTROGENS AND HEALTH**

**Issue**

The Committee is asked to consider changes made to the Phytoestrogens & Health report following public consultation and to endorse the amended report.

**Introduction**

1. Phytoestrogens are chemicals of similar structure to the human hormone oestrogen and are present naturally in many foods of plant origin. A number of concerns have been raised over the last decade about the possible adverse effects of phytoestrogens. The COT has previously considered the issue in 1992, 1996 and 1999. A Working Group was set up in 1999 at the request of the COT to review the health implications of dietary phytoestrogens. The Working Group was chaired by Professor Frank Woods.
2. The Working Group completed its review and produced a draft report, which was considered in two parts by the COT at its meetings in February and July 2002. The report was modified in light of Member's comments.
3. The draft report was issued for public consultation (09/10/02 to 03/12/02) *via* the Food Standards Agency website. Respondents were asked to comment on the interpretation of the science and whether important studies had been missed. The Working Group received 47 submissions. In addition, the Scientific Advisory Committee on Nutrition (SACN) was asked to comment on the sections of the report relating to the use of soy-based infant formula.
4. The submissions and the opinion of SACN were considered by the Working Group and the report was modified. Many of the submissions asked the Working Group to consider studies published after the review cut-off date (30 April 2002). New data were included from such studies where the information altered the key points or conclusions.
5. The Phytoestrogens & Health report is appended (appendices 1-8 are not included). The background to the Working Group and its terms of reference are given in Chapter 2 of the report. The comments provided by SACN are appended at **Annex 1** to this paper.

**Changes made to the report**

6. The changes made to the report are underlined in the text and are summarised below, taking each chapter in turn.

## **Chapter 2 (Introduction)**

7. An explanation of the consultation process has been included in paragraphs 2.24-2.27.

## **Chapter 3 (Chemistry & Analysis)**

8. No substantive changes made.

## **Chapter 4 (Levels in food and intake)**

9. Paragraph 4.46 and key point 7 (page 53) have been amended to indicate that soy is not traditionally fed to infants in Asian cultures.

## **Chapter 5 (ADME)**

10. Paragraph 5.5 has been modified to indicate that the food matrix may influence the bioavailability of phytoestrogens in food.

11. Two human studies, which suggest that the bioavailability of phytoestrogens is independent of whether phytoestrogens are ingested as glucoside conjugates or aglucones have been added to paragraph 5.5. These data are in contrast to the findings of studies reviewed in paragraph 5.4. Therefore, key point 1 (page 81) has been amended to indicate that there is uncertainty on whether the bioavailability of isoflavone glucosides differs from that of the aglucones.

12. Paragraph 5.83 has been amended to include more detail on the efficiency of phytoestrogen absorption in infants fed soy-based infant formula. A comparison to the bioavailability of isoflavones in adults is provided. Key point 5 has been reworded accordingly.

## **Chapter 6 (Oestrogenic mechanisms)**

13. No substantive changes made.

## **Chapter 7 (Other mechanisms)**

14. A study which suggests that dietary genistein (a soy phytoestrogen) is not mutagenic in mice has been included at paragraph 7.37. Key point 7 (page 129) has been amended to indicate that a single study suggests that genistein, at levels found in the diet, is not mutagenic *in vivo*.

15. A number of studies, which suggest that soy may produce antioxidant effects, have been included at paragraphs 7.43-7.48. Key point 8 (page 129) has been amended to indicate that dietary soy may have antioxidant effects in humans, such as inhibition of LDL oxidation. However, these effects may not be attributable to the phytoestrogen content of soy.

## **Chapter 8 (Methods to measure oestrogenic potency)**

16.No substantive changes made.

## **Chapter 9 (Fertility and development)**

17.No substantive changes made. Paragraph 9.117 has been amended in line with SACN comments.

## **Chapter 10 (Effects on the thyroid gland)**

18.A human study, which suggests that dietary soy has minor effects on thyroid function, was included at paragraph 10.21. A key point (key point 3, page 216) was added to indicate that data from human studies suggest that dietary soy or isoflavones are unlikely to affect thyroid function in normal individuals with adequate iodine intake.

19.Key point 5 (page 216) has been altered to clarify the hypothesis that phytoestrogens may have an effect on thyroid function of hypothyroid individuals. The recommendation for monitoring hypothyroid individuals who ingest relatively large quantities of phytoestrogens included in the previous draft has been incorporated in the Conclusions chapter.

## **Chapter 11 (Effects on the CNS and immune system)**

20.A rodent study showing that *in utero* exposure to genistein induces minor changes in immune function has been added at paragraph 11.34. Key point 3 (page 232) has been amended to indicate that exposure to isoflavones in early life induced only minor changes in immune function in studies of intact rats.

21.A human study showing that dietary soy produced a small change in one parameter of immune function in female (but not male) human subjects has been added at paragraph 11.39. Key point 4 (page 232) has been amended to cover these findings.

## **Chapter 12 (Effects on osteoporosis)**

22.An intervention trial showing that the effects on bone from dietary genistein were comparable to HRT treatment in postmenopausal women has been added to paragraph 12.31. In this study, increases in the bone mineral density of the lumbar spine and femoral neck in the subjects were reported. Key point 3 (page 247) has been amended to refer to the latter finding.

## **Chapter 13 (Effects on CVD)**

23.A human study, which suggests that dietary phytoestrogens may have a protective effect on the risk of atherosclerosis, has been added to paragraph 13.73. Key point 5 (page 269) has been amended to reflect the findings of this study.

## **Chapter 14 (Hormonal effects)**

24. Two studies which suggest that isoflavones may have a beneficial impact on hot flushes in postmenopausal women have been added to paragraphs 14.18 and 14.19.

25. A section on the effect of dietary soy on aspects of diabetes has been added at paragraphs 14.41-14.45. A key point has been added on page 290 to cover this section suggesting that dietary soy rather than phytoestrogens *per se* may improve some aspects of diabetes.

## **Chapter 15 (Cancer)**

26. A footnote has been added to paragraph 15.2 to reflect the recent COC conclusions on metabolic polymorphisms and cancer risk. Key point 3 (page 311) reflects the conclusions of this paragraph.

27. Paragraphs 15.19 reviews the findings reported in a preliminary study suggesting that dietary soy induces markers of breast cell proliferation in women with breast cancer. However, no effects on these markers were evident in the full study (reviewed in 15.20). Paragraphs 15.19 and 15.20 have been amended to clarify this. Key point 5 (page 311) has been amended to reflect the data presented in these paragraphs.

28. Studies in animal models which suggest that dietary supplementation with the lignan, secoisolariciresinol may have a chemoprotective effect on breast cancer development have been added at paragraphs 15.39-15.44. Key point 6 (page 311) has been amended to refer to these studies.

29. Two rodent studies suggesting the lignan, secoisolariciresinol may inhibit experimentally induced metastasis of melanoma cells to the lung have been added at paragraphs 15.108 and 15.109. Key point 3 (page 234) has been amended to reflect these findings.

## **Chapter 16 (International policy on soy formula feeding)**

30. No substantive changes made.

## **Chapter 17 (Summary)**

31. This chapter has been amended to reflect the changes made to the key points elsewhere in the report.

## **Chapter 18 (Conclusions)**

32. The Working Group discussed the potential influence of selective genetic changes in populations that traditionally consume soy on the reported beneficial effects (and lack of adverse effects) of phytoestrogens in such populations. Paragraph 18.4 has been added to reflect these discussions.

33. The conclusions on soy formula feeding (paragraphs 18.9-18.15) have changed significantly. This was primarily due to the opinion expressed by SACN (**Annex 1**). After reviewing the data and conclusions in the report relating to soy-based infant formula, SACN considered that there is cause for concern about the use of soy-based infant formula. Additionally, there is neither substantive medical need for, nor health benefit arising from, the use of soy-based infant formulae.

34. In light of the SACN opinion, paragraphs 18.9-18.15 were modified. For comparison, the original text of the section on soy-based formula feeding is provided at **Annex 2**).

35. Paragraph 18.22 has been amended to reflect the changes outlined in paragraph 29 above.

36. Paragraph 18.28 has been amended to refer to the paucity of data on the effects of phytoestrogens on other factors important in the risk of cardiovascular disease i.e. blood pressure, thrombosis or atherosclerosis.

37. The Working Group prioritised the research recommendations (paragraph 18.38).

#### **Advice sought from the Committee**

38. The Committee is asked to consider the redrafted Phytoestrogens & Health report. As Members have already considered the report previously, they are directed to the areas where the key points or conclusions have been substantially altered. Members are invited to comment and endorse the report.

**Secretariat**  
**February 2003**

**Annex 1 TOX/2003/03**

**Scientific Advisory Committee on Nutrition view on soy formula feeding recommendation**

**Secretariat  
2003**

# Scientific Advisory Committee on Nutrition

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## **Response to The Committee on Toxicity on the draft report *Phytoestrogens and Health***

1. The Committee on Toxicity (COT) requested SACN's advice on an element of the draft report *Phytoestrogens and Health* that considers the public health implications of exposure to phytoestrogens in the diet. The report was drafted by a specially convened Working Group of the Committee with the following terms of reference:

“To advise on the health implications of dietary phytoestrogens through review of published scientific research and the Food Standards Agency's phytoestrogen research programme.”

SACN's opinion has been ascertained by correspondence with the members.

### ***Advice Sought***

2. COT has requested SACN's advice on the following recommendation in paragraphs 1.25 of the executive summary and 18.12 of the conclusions, which were drawn from the consideration of the evidence presented in Chapter 9 of the report:

“The Working Group *note* the advice by the Department of Health based on the 1996 COT advice. This stated that *breast and cows' milk formulae are the preferred sources of nutrition for infants. However, women who have been advised by their doctor or other health professionals to feed their baby soy-based infant formulae should continue to do so.* In the light of new data presented in this report, which

were unavailable in 1996, the Working Group recommend that the current advice be amended to state that soy-based infant formulae be fed to infants only when indicated clinically. The Working Group *note* that similar advice has been issued in other countries (e.g. New Zealand, Australia).”

## ***Background***

### *Usage*

3. Soy-based infant formula is the only choice available for feeding infants non-animal origin formula. Data providing a breakdown of which types of formulae are being given to infants at risk of developing cow’s milk allergy are not available. However, 1% of non-breast fed infants aged 4-10 weeks receive soy-based formula and this rises to 2% in infants aged 10-14 weeks (DH, Infant Feeding Survey 2000). More detailed data on the use of soy-based formula is not available. It is assumed that soy-based infant formula is chosen by mothers who are not breastfeeding but do not wish to feed their infants an animal derived milk. It is currently the only vegan option available.

### *Legislation on Infant Formulae*

4. Infant formulae and follow-on formulae intended for infants in good health are subject to the Infant Formula and Follow-on Formula Regulations 1995, as amended<sup>1</sup>, which implement European Union based legislation. The regulations control the composition, labelling and marketing of infant formulae and follow-on formulae manufactured from cow’s milk proteins, protein partial hydrolysates and soya protein isolates, including maximum and minimum protein levels and protein quality criteria.

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<sup>1</sup> As amended by the Infant Formula and Follow-on Formula (Amendment) Regulations 1997 and the Infant Formula and Follow-on Formula (Amendment) (England) Regulations 2000 – separate but similar regulations have been implemented in Northern Ireland, Scotland and Wales

Infant formulae that have been specially processed or formulated and are intended for the dietary management of infants with special medical conditions should comply with the requirements laid down in The Medical (England) Regulations 2000. Such formulae must be used under medical supervision only.

5. Both 'conventional' infant formulae and medical formulae are subject to the general provisions of the Food Safety Act 1990, the Trade Descriptions Act 1968 and the general requirements of the Food Labelling Regulations 1996, as amended.
6. Soy-based formula is marketed and sold alongside cow's milk infant formula, offering a choice to mothers who wish to avoid cow's milk.
7. In 1999, following the Food Advisory Committee's recommendation to reduce the levels of phytoestrogens in soy-based infant formulae as a precautionary measure, the COMA Panel on Child and Maternal Nutrition (PCMN) agreed that "*the use of soy-based infant formula should be discouraged through professional and parental education as more suitable alternatives, particularly those based on cow's milk protein hydrolysates, are available*"

### **SACN consideration**

#### ***Risk assessment***

8. SACN welcomed the report and commented that Chapter 9 gave a clear account of the possible effects of dietary phytoestrogens on fertility and sexual development. The summary of evidence in Chapter 9 and conclusions are persuasive.

#### ***Important new evidence since 1996***

9. Since the COT statement was made on soy-based infant formula in 1996, new data have emerged. On the basis of the literature review presented in Chapter 9, Strom et al (2001) and Sharpe et al (2002) appear to be the most important lines of evidence.

10. *Strom et al (2001)*. It appears that this paper was mis-cited in paragraph 9.117. It did not demonstrate any association with premature breast development (as stated in the report) but a statistically significant increase in the duration of menstruation (there may be confusion in this paragraph with the Freni-Titulaer et al, 1986 study but this should be corrected). Strom et al also state that significantly more women reported “extreme discomfort” during menstruation. Although multiple statistical comparisons were made inappropriately, this is a unique study and it is difficult to dismiss these findings. It should particularly be noted that the early feeding histories of these women were secure (despite description of the study as “retrospective”) because they had participated in controlled (non-randomised) formula trials as infants. Indeed the authors seem to have traced about 85% of the original subjects (which is good after 20-34 years) so there is minimal risk of selection bias. No comment can be made on biological plausibility (which seems a common problem with this literature) or on whether the menstrual abnormalities might have any implications for later health (e.g. risk of malignancy). However, it should be borne in mind, that the history of soy-formula feeding is still fairly brief (about 30-40 years) in terms of the human lifespan, so not all effects may yet be apparent. The participants’ symptoms could prove of more importance to the participants than the authors of the paper suggest. It was also noted that the study was partially funded by the Infant Formula Council.
  
11. *Sharpe et al (2002)*. This is an interesting primate study, in which 30 male baby marmosets (26 of whom were twins) were pair fed commercial formulae (*SMA* and *SMA-Wysoy*) by day but left with the mother at night. Total period of treatment was 6-weeks. The histological findings were “paradoxical” (i.e. more Leydig cells /testis despite lack of testosterone surge in the *Wysoy* group). It is a pity there were no naturally fed concurrent controls in this study, but the endocrine changes noted seem genuine and therefore of concern, particularly as the feeding was partial (daytime only) with natural suckling at night. Long term follow up is stated to be “in progress”.
  
12. In summary neither *Strom et al (2001)* or *Sharpe et al (2002)* definitively prove that soy- formula can cause long-term harm to human infants, but both studies raise significant concern.

### *Clinical place of soy-based infant formulae*

There appears to be no unique clinical indication for soy-based formula. In all cases an elemental formula or alternative based on hydrolysed cow's milk protein is available. Indeed these would be preferred in cow's milk protein allergy because there may be considerable overlap with soya protein allergy. These therapeutic alternatives are prescribable for such clinical indications. Also, there are galactose-free cow's milk protein based formulae available for the very small number of infants who have galactosaemia.

### *Need for soy-based formula purchased over the counter*

13. At present soy-formula is sold over the counter alongside other cow's milk based infant formulae meant for healthy infants. This recognises parental choice rather than clinical need. Only the very few vegan mothers who choose not to or cannot breastfeed might really need these, yet they are currently used by 1-2% of the population (*Infant Feeding* 2000). This suggests many use them for less clear reasons. No soy-based formula has ever been included on the approved list of Welfare Foods.

### *Other groups at risk?*

14. The data are too unclear to identify any critical window (an age at which soy-based formula might pose a particular risk), though young infants fed soy-based formula are presumably the main group at risk because they are wholly fed on these products for perhaps 4-6 months before weaning. In the case of older infants it should also be noted that the carbohydrate moiety of soy-based formula has greater cariogenic potential than standard infant formulae which contain lactose, the least cariogenic sugar.

### ***Risk management***

15. The COT draft recommendation falls within the boundary of risk management, and SACN are concerned about responding in this context as it is outside their remit.

16. SACN agree that on balance there is cause for concern about the use of soy-based infant formula. They are however apprehensive about the practicality of the recommendation of the COT working group “**that the current advice be amended to state that soy-based infant formulae be fed to infants only when indicated clinically**” as there appears to be no unique clinical indication for soy-based formula.

17. COT have recommended a change in wording from ‘*women who have been advised by their doctor or other health professionals.....*’ to ‘*.....soy-based infant formulae be fed to infants only when indicated clinically.*’ It was noted that the desired effect of this proposed change on current infant feeding practice and the use of soy-based infant formula is unclear. The new wording may represent a clarification rather than a change in the guidance, but in its current form is ambiguous.

18. The practical implications of the suggested change were also queried. The following points require clarification:

- will it mean that soy-based infant formulae should be provided only on prescription;
- how will it affect the infant feeding practice of mothers who do not wish to feed cow’s milk-based formula;
- what does it mean to doctors and health professionals in terms of their practice; and
- should the place of soy-based formulae on the Advisory Committee on Borderline Substances (ACBS) list of approved dietary products be reviewed?

19. In addition, greater emphasis of the importance of breastfeeding is also required. *Paragraph 1.25* should be amended to indicate that breast milk is the first choice for infant feeding, as agreed by COMA and endorsed by SACN. For example, the COMA report (45) *Weaning and Weaning Diet* states that breast milk provides the best source of nourishment for the early months of life and an infant who is not breastfed should receive infant formula. Thus it is clearly stated that breast milk is the preferred food for infants rather than cow’s milk or soy-based formula.

## **Conclusion**

20. Based on the evidence cited in the report, SACN is in agreement that the use of soy-based infant formulae is of concern. Whilst there is clear evidence of potential risk, there is no evidence that these products confer any health benefit or therapeutic advantage over products based on cow's milk protein isolates. Risk management steps are more difficult. The recommendation for use if *clinically indicated* is inappropriate, firstly on the grounds that there are no substantive medical or clinical indications for the use of soy-based formulae and, secondly on grounds of potentially important *sequelae*, principally amongst young infants. If the use of soy-based formula is to continue on "clinical" grounds, responsibility is placed upon health professionals rather than the industry and consumers. The issue appears to be one of consumer choice, but there must be an onus on industry to better inform firstly the general public and, secondly, through a health professional, parents actually using these products to feed their infants.

## **Summary**

21. SACN considers that:

- there is cause for concern about the use of soy-based infant formula;
- there is neither substantive medical need for soy-based infant formulae nor health benefit arising from their use;
- there is no information available on the likely effect of the proposed new advice on infant feeding practice, particularly for mothers who are not breastfeeding and do not wish to use an animal derived product; and that
- breast milk is the first choice for infant feeding. This must be indicated in any infant feeding recommendations.

## **References**

Sharpe RM, Martin B, Morris K, Greig I, McKinnell, McNeilly AS, Walker M. Infant feeding with soy formula milk: effects on the testis and on blood testosterone levels in marmoset monkeys during the period of neonatal testicular activity. *Human Reproduction*. 2002, 17:1692-1703.

Strom BL, Schinnar R, Ziegler EE, Barnhart KT, Sammel MD, Macones GA, Stallings VA, Drulis JM, Nelson SE, Hanson SA. Exposure to soy-based formula in infancy and endocrinological and reproductive outcomes in young adulthood. *JAMA*. 2001, 286:807-814.

**Conclusions on soy-based infant formula feeding from the previous version of the draft report**

## Does ingestion of soy-based infant formula pose any risk for human infants?

18.1 The concentration of phytoestrogens found in soy-based infant formula is several orders of magnitude higher than that found in human breast milk. It has been estimated that the infant isoflavone intake from soy-based formulae is approximately 4 mg/kg bw/day. The Working Group *concluded* that infants fed soy-based formula are the population subgroup exposed to the highest concentration of isoflavones and that exposure *via* breast milk is low by comparison. No data on the transfer of lignans from the maternal diet to breast milk have been published.

18.2 Only a single published study specifically examined the long-term health effects of soy infant formula. Although the study did not find any obvious adverse effects, it was based on recall and did not include any direct measurements of hormone levels or other parameters in the subjects. The Working Group *acknowledged* that it was difficult to draw general conclusions from the results of a single study.

18.3 Soy-based infant formula has been used since the 1960s. There is little published information to suggest that isoflavones affect thyroid function in infants fed soy-based formula. However, the Working Group *considered* that isoflavones could lower free thyroxine concentrations by inhibiting thyroid peroxidase. Although a normally functioning thyroid may compensate for this, by stimulating thyroxine production, it is possible that infants with congenital hypothyroidism may be unable to increase thyroxine production. This may represent a small but susceptible subgroup of the population, therefore the Working Group *recommend* that physicians and other health care workers are made aware of the potential interactions between isoflavones in soy-based infant formulae and thyroid function. The Working Group *advise* that it may be appropriate to monitor thyroxine levels in infants with congenital hypothyroidism who are fed soy-based infant formulae in order to establish the susceptibility of this sub-group.

18.4 Recent studies in rodents suggest that neonatal exposure to phytoestrogens may be associated with some potentially adverse changes to the immune system. However, investigations of human infants fed soy-based formula provide evidence that immune function is normal in this group.

18.5 A recent study conducted in male neonatal marmosets suggests that feeding them with soy-based infant formula can alter some parameters of reproductive health during the neonatal stage. The Working Group *acknowledged* that this work is still in progress, and therefore, no conclusions can be made about likely human health implications. The Working Group *advise* that future findings from this work be evaluated fully once it has been completed.

18.6 The Working Group *note* the advice issued in 1996 by the Department of Health. This stated that *breast and cows' milk formulae are the preferred sources of nutrition for infants. However, women who have been advised by their doctor or other health professional to feed their baby soy-based infant formulae should continue to do so.* In the light of new data presented in this report, which were unavailable in 1996, the Working Group *recommend* that the current advice be amended to state that soy-based infant formulae be fed to infants only when indicated

clinically. The Working Group *note* that similar advice has been issued in other countries (e.g. New Zealand, Australia).