

Scientific Advisory Committee on Nutrition

Paper for Information: The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) Statement on Phytoestrogens and Soy-Based Infant Formula.

Agenda Item 07

The COT working group on phytoestrogens has looked at phytoestrogen health implications with particular reference to soy-based infant formula. A draft report of its findings was issued for consultation which included seeking the views from SACN on the report's conclusions on soy formula feeding. SACN advice was duly sought (General 11 attached) and the results forwarded to COT (General 12 attached).

The phytoestrogens working group met to discuss the consultation responses and the SACN view and, as a result, has modified its conclusions on soy formula agreed by COT on 11 February¹.

¹ This is the final document rather than the draft seen by SACN, changes were made to the draft in response to the 11 February COT meeting.

COT *Phytoestrogens and Health* Report Section :Does ingestion of soy-based infant formula pose any risk for human infants?

In response to the consultation, which included comments received from SACN, the report was amended and agreed as follows;

1. In the UK, soy-based infant formulae have been used since the 1960s and are currently fed to approximately 1% of non-breast fed infants aged 4-10 weeks rising to approximately 2% of infants aged 10-14 weeks. However, detailed information on the prevalence of, and reasons for, soy-based infant formula feeding is unavailable.
2. The concentration of phytoestrogens found in soy-based infant formulae is several orders of magnitude higher than that found in human breast milk. It has been estimated that intake by infants of isoflavones from soy-based formulae is approximately 4 mg/kg body weight/day. The Working Group *concluded* that infants fed soy-based formulae are the population subgroup exposed to the highest concentrations 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.
3. There is little published information to suggest that isoflavones affect thyroid function in infants fed soy-based formulae. However, the Working Group *considered* that isoflavones may lower free thyroxine concentrations. 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. These individuals may represent a small susceptible sub-group of the population, therefore the Working Group *recommends* 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 is 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.
4. Few studies have examined the effect of isoflavones on the immune system. Studies in rodents have suggested that isoflavones may alter some parameters of immune function but the effects were inconsistent. However, the Working Group *considered* that investigations of human infants fed soy-based formulae provide reassurance that phytoestrogens in soy do not have a significant impact on the integrity of immune function in such children.
5. A recent study conducted in male neonatal marmosets suggests that feeding with soy-based infant formulae 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 definitive 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.
6. Only a single study specifically examining the long-term health effects of soy-based formula feeding on sexual development and fertility in humans has been

published. The Working Group *considered* that these data do not provide definite evidence for adverse clinical effects on sexual development or reproductive health, but *noted* the association between soy-based formula feeding and small increases in the duration and discomfort of menstruation. However, the study 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.

7. The Working Group *considered* that the findings from these studies do not provide definitive evidence that phytoestrogens present in soy-based infant formulae can adversely affect the health of infants. However, the findings, together with those from studies on the mechanism of action and biological activity of phytoestrogens reviewed in this Report, provide evidence of potential risks. For this reason, the Working Group *expressed* concern about the use of soy-based infant formulae. The Working Group *noted* that the Scientific Advisory Committee on Nutrition (SACN) *expressed* similar concern when considering evidence presented in this Report. SACN also *considered* there to be no substantive medical need for, nor health benefit arising from, the use of soy-based infant formulae. However, it was *noted* that soy-based infant formulae were the only vegan infant formula option available if babies were not exclusively breast fed². In light of the concerns expressed, the Working Group *recommends* that the Department of Health review current advice on the use of soy-based infant formulae.

² Scientific Advisory Committee on Nutrition response to the COT Working Group on Phytoestrogens draft report on phytoestrogens & health (2003).

Scientific Advisory Committee on Nutrition

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21 November 2002

Dear SACN member

Advice sought by Committee on Toxicity of Chemicals in Food Consumer Products and the Environment (COT) on soy-based infant formula

Background

COT has requested SACN's advice on an element of a report 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.”

The report is currently in consultation. The consultation period ends before the next SACN meeting, therefore I am requesting advice by correspondence.

Advice Sought

COT has requested SACN advice on the following paragraph that appears at point 1.25 of the executive summary (attached). Chapter 9 of the report provides some background (also attached).

1.25 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).

Notes

- COMA in 1999 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, were available
- Soy-based infant formula is the only choice available for feeding infants non-animal origin formula. Data providing a breakdown on which types of formulas parents give 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 soya milk and this rises to 2% in infants aged 10-14 weeks (DH, Infant Feeding Survey 2000)
- Full details on the consultation including the draft report are available on the COT web pages at;

<http://www.foodstandards.gov.uk/foodindustry/Consultations/ukwideconsults/cotphytohealth>

I would be grateful if all recipients of this document could be copied into your comments. In this way we hope to generate **an email discussion to be closed on 9 December**. The Secretariat will use the discussion as the basis for a response to COT. As the COT require comments by 15 December we will produce a draft response while the discussion is under way and this will be cleared by the Committee in the period between the 9 and the 15 December. Those members who do not have email will be kept informed by letter and phone.

A hard copy of the entire report is available from the Secretariat on request. Members are welcome to independently comment on the report, the COT Secretariat contact details are on the website address above.

Yours sincerely,

Dr Alison Tedstone
SECRETARIAT

Scientific Advisory Committee on Nutrition

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 amended¹, 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.
5. 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.
6. 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.
7. 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.

¹ 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

8. 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

9. 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

10. 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.
 11. *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
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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.

12. *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".
13. 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

14. 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

15. 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?

16. 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

17. 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.
18. 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.
19. 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.
20. 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?

21. 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

22. 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

23. 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.