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November 20 2006

Dr Michael Shelby,
CERHR Director, NIEHS, PO Box 12233,
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Comments on the NTP-CERHR Panel Reports on Reproductive and Developmental Toxicity of Genistein in Soy Infant Formulas

Dear Dr Shelby,

We note that your closing date for comments is now December 9, 2006.

It has puzzled us why a number of other national expert panels (eg the UK Committee on Toxicity in Food and the Environment ; C O T) and including France, Israel, New Zealnd/Australia (ANZFA), Switzerland and Italy, and the UK Chief Medical Officer have warned about the high levels of phytestrogens in the soy protein component of soy infant formulas, and of their risk to the reproductive health of infants. Words of these panels may vary, but the thrust of all is the same. Now look at your published summary of the panel's findings which says that the USA "Expert" Panel expresses negligible concern and it is "noteworthy that about !5 of total genistein in soy formula is present in its uncomplexed form, ie the aglycone."

Our comment is "So what? " There is a plethora of published science that shows that genistein/genistin is biologically active. Much of this scientific literature is referenced ** by your panel, and we have a suspicion that the panel members have not read the literature that they cite. The result of addressing only the aglycone is to under-value the reproductive toxicity of genistein by a factor of one-hundred. No wonder the USA thinks the concerns are "negligible" while other nations express concern at the risks of soy formulas

Yours Sincerely,
Soy Infor [Redacted]

Per Rich[illegible]
**

1: Irvine CH, Shand N, Fitzpatrick MG, Alexander SL.

Daily intake and urinary excretion of genistein and daidzein by infants fed soy- or dairy-based infant formulas.Am J Clin Nutr. 1998 Dec;68(6 Suppl):1462S-1465S.

2: Irvine CH, Fitzpatrick MG, Alexander SL. Phytoestrogens in soy-based infant foods: concentrations, daily intake, possible biological effects. Proc Soc Exp Biol Med. 1998 Proc Soc Exp Biol Med. 1998 Mar;217(3):247-53.

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CMO's Update 37

Department of Health

January 2004

Chief Medical Officer:
Sir Liam Donaldson
MSc, MD, FRCS(Ed), FRCP, FRCP(Ed), FRCGP, FFPHM, FMedSci

Health Policy Developments

The Department of Health recently published documents in three areas of interest to doctors: patient choice, healthcare associated infection and consent for the retention and use of human tissue and organs. All are accessible online:

Patients have been promised greater choice when accessing a range of medical products and services, including prescriptions, primary care and diagnostic tests.

Designs for a new patient-centred health service were detailed in the strategy paper *Building on the Best*, which was presented to Parliament by Secretary of State for Health John Reid in December 2003. The paper reflects a national consultation on choice, responsiveness and equity, which involved more than 110,000 people, including patients and professionals. It can be downloaded at **http://www.doh.gov.uk/choiceconsultation/.**

Detailed guidance on preventing healthcare associated infection (HCAI) has been released.

The guidance, much of which is already in the process of implementation, was presented in the CMO report *Winning Ways: Working Together to Reduce Healthcare Associated Infection in England.* Among other measures is a plan for every NHS organisation to have a designated, top-level director for infection control and prevention. This need not require the addition of a new staff member – more typically, a senior doctor or nurse on staff within the organisation will assume the role. The full report on HCAI may be accessed online at **http://www.doh.gov.uk/cmo/hai.**

The government's new Human Tissue Bill provides a clear framework on consent for the retention and use of human tissue and organs.

It is aimed at ensuring no human bodies, body parts, organs or tissue will be taken without the agreement of patients or relatives.

It also stresses the importance of medical research and teaching, as well as the vital work of NHS pathologists in the diagnosis of patients and in investigating deaths.

The Bill's release follows the Bristol, Alder Hey and Isaacs inquiries, which exposed major problems with lack of consent for the removal and storage of organs.

To access the document, Explanatory Memorandum and policy background, visit **http://www.doh.gov.uk/cmo/progress/organretention/developments.**

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Chief Medical Officer's website

www.doh.gov.uk/cmo

Smallpox preparedness update

The Department of Health has published a revised national contingency plan for smallpox preparedness.

The new document replaces the *Interim Guidelines for Smallpox Response and Management in the Post-eradication Era* (Smallpox Plan), which was released in December 2002 (www.doh.gov.uk/smallpox/smallpox.htm).

There still is no evidence of a specific threat of a smallpox attack on the UK. However, it is sensible and prudent to ensure that the NHS can deal effectively with any potential threat. The Department of Health recognises the need to ensure that the NHS is capable of responding to incidents in a way that delivers optimum care and assistance to exposed individuals, whilst controlling the spread of disease.

Guideline revisions incorporate input from a wide range of medical experts and groups within the NHS as well as other government departments. For example, advice from the Advisory Committee on Dangerous Pathogens (ACDP) led to a change in policy on decontamination. And among other changes, specifications for smallpox care and vaccination centres have been revised. Implementation of the plan is being co-ordinated by Health Protection Agency (HPA) regional leads and the Regional Directors of Pubic Health.

In releasing the original guidelines in December 2002, the CMO outlined the steps that were being taken to strengthen plans against any deliberate release of a range of biological agents, including smallpox. Smallpox preparedness measures included a plan of action, improved vaccine stock and the establishment of a cohort of immunised health staff.

Since then, vaccine stocks have been strengthened and regional smallpox teams have been established to deal with the operational aspects of the plan. These regional teams have been vaccinated to allow them to react quickly, work safely with suspected cases and manage the initial stages of a smallpox incident.

Vaccination will now be extended to a small number of ambulance staff to support the initial response to a smallpox emergency. Corresponding arrangements are being made for Scotland, Wales and Northern Ireland.

For more information on the revised contingency plan for smallpox preparedness, please contact Dr Charlie Easmon, Room 538B, Department of Health, Skipton House, London SE1 6LH. E-mail: charlie.easmon@doh.gsi.gov.uk.

Advice issued on soya-based infant formulas

The CMO is reiterating advice that soya-based infant formulas should not be used as the first choice for the management of infants with proven cow's milk sensitivity, lactose intolerance, galactokinase deficiency and galactosaemia.

Soya-based formulas have a high phytoestrogen content, which could pose a risk to the long-term reproductive health of infants, according to a 2003 report from the Committee on Toxicity (COT), an independent scientific committee that advises the Department of Health and other government agencies.

Furthermore, the Scientific Advisory Committee on Nutrition (SACN), another independent advisory body, has advised that there is no particular health benefit associated with the consumption of soya-based infant formula by infants who are healthy (no clinically diagnosed conditions). SACN also advised there is no unique clinical condition that particularly requires the use of soya-based infant formulas.

As an alternative to soya-based products, more appropriate hydrolysed protein formulas are available and can be prescribed. Soya-based formulas should only be used in exceptional circumstances to ensure adequate nutrition. For example, they may be given to infants of vegan parents who are not breast-feeding or infants who find alternatives unacceptable.

For more information contact Sheela Reddy, General Nutrition Policy, Department of Health, Wellington House, 133–155 Waterloo Road, SE1 8UG. Tel: 0207 972 2000. E-mail: sheela.reddy@doh.gsi.gov.uk.
Also see http://www.sacn.gov.uk and http://www.foodstandards.gov.uk/.

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1: Am J Clin Nutr. 1998 Dec;68(6 Suppl):1462S-1465S.

Full Text FREE Links
Am J Clin Nutr

Daily intake and urinary excretion of genistein and daidzein by infants fed soy- or dairy-based infant formulas.

Irvine CH, Shand N, Fitzpatrick MG, Alexander SL.

Animal and Veterinary Sciences Group, Lincoln University, Canterbury, New Zealand.

Our aims were to measure isoflavone intake from soy- and dairy-based infant formulas and breast milk and to assess the ability of infants to digest and absorb soy isoflavones by measuring daily urinary excretion rates. We recruited 29 infants: 4 received soy-based formula and 25 received dairy-based formula. We collected pooled urine samples from 3-5 disposable diapers worn during a 24-h period and developed and validated methods for extracting isoflavones from the diapers. Infants were studied every 1 or 2 wk, starting at 2-6 wk of age and continuing until 16 wk. Only soy-based formulas contained isoflavones in concentrations detectable by HPLC (limits: 0.05 mg/L for liquids and 0.1 mg/kg for solids). Soy-based formulas provided a mean (+/-SEM) daily dose of isoflavones (genistein plus daidzein) of 3.2 +/- 0.2 mg/kg body wt, which remained fairly constant (CV: 12%) regardless of age < or = 16 wk. Isoflavones were measurable in all samples from soy-fed infants, but not in urine from dairy-fed infants. Daily isoflavone excretion rates varied little among infants [range of mean individual values (mg x kg(-1) d(-1)): daidzein, 0.37 +/- 0.03 to 0.58 +/- 0.06; genistein, 0.15 +/- 0.03 to 0.32 +/- 0.04] and did not change with age < or = 16 wk. The mean percentage of the daily intake recovered in the urine of soy-fed infants was 38 +/- 4% for daidzein and 13 +/- 3% for genistein, and remained constant with age. These values are similar to those for adults and indicate that young infants are able to digest, absorb, and excrete genistein and daidzein from soy-based formulas as efficiently as do adults consuming soy products.

PMID: 9848517 [PubMed - indexed for MEDLINE]

Related Links

Isoflavone content of infant formulas and the metabolic fate of these phytoestrogens in early life. [Am J Clin Nutr. 1998]

Exposure of infants to phyto-oestrogens from soy-based infant formula. [Lancet. 1997]

Phytoestrogens in soy-based infant foods: concentrations, daily intake, and possible biological effects. [Proc Soc Exp Biol Med. 1998]

Plasma and urinary kinetics of the isoflavones daidzein and genistein after a single soy meal in humans. [Am J Clin Nutr. 1998]

Dietary fructooligosaccharides modify intestinal bioavailability of a single dose of genistein and daidzein and affect their urinary excretion and kinetics in blood of rats. [J Nutr. 2001]

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1: Proc Soc Exp Biol Med. 1998 Mar;217(3):247-53.

Links

Phytoestrogens in soy-based infant foods: concentrations, daily intake, and possible biological effects.

Irvine CH, Fitzpatrick MG, Alexander SL.

Animal and Veterinary Sciences Group, Lincoln University, Canterbury, New Zealand. irvinech@whio.lincoln.ac.nz

Exposure to estrogenic compounds may pose a developmental hazard to infants. Soy products, which contain the phytoestrogens, genistein and daidzein, are becoming increasingly popular as infant foods. To begin to evaluate the potential of the phytoestrogens in these products to affect infants, we measured total genistein and daidzein contents of commercially available soy-based infant formulas, infant cereals, dinners, and rusks. We also assayed phytoestrogens in dairy-based formulas and in breast milk from omnivorous or vegetarian mothers. In most cases, the glucoside forms of the phytoestrogens were hydrolyzed before separation by HPLC. Mean (+/-SEM) total genistein and daidzein contents in four soy infant formulas were 87+/-3 and 49+/-2 microg/g, respectively. The phytoestrogen content of cereals varied with brand, with genistein ranging from 3-287 microg/g and daidzein from 2-276 microg/g. By contrast, no phytoestrogens were detected in dairy-based infant formulas or in human breast milk, irrespective of the mother's diet (detection limit = 0.05 microg/ml). When fed according to the manufacturer's instruction, soy formulas provide the infant with a daily dose rate of total isoflavones (i.e., genistein + daidzein) of approximately 3 mg/kg body weight, which is maintained at a fairly constant level between 0-4 months of age. Supplementing the diet of 4-month-old infants with a single daily serving of cereal can increase their isoflavone intake by over 25%, depending on the brand chosen. This rate of isoflavone intake is much greater than that shown in adult humans to alter reproductive hormones. Since the available evidence suggests that infants can digest and absorb dietary phytoestrogens in active forms and since neonates are generally more susceptible than adults to perturbations of the sex steroid milieu, we suggest that it would be highly desirable to study the effects of soy isoflavones on steroid-dependent developmental processes in human babies.

Related Links

Daily intake and urinary excretion of genistein and daidzein by infants fed soy- or dairy-based infant formulas [Am J Clin Nutr. 1998]

Exposure of infants to phyto-oestrogens from soy-based infant formula. [Lancet. 1997]

Isoflavone content of infant formulas and the metabolic fate of these phytoestrogens in early life. [Am J Clin Nutr. 1998]

Isoflavone content of infant foods and formulas. [J Paediatr Child Health. 1998]

Estrogenic isoflavones in rodent diets. [Toxicol Lett. 2002]

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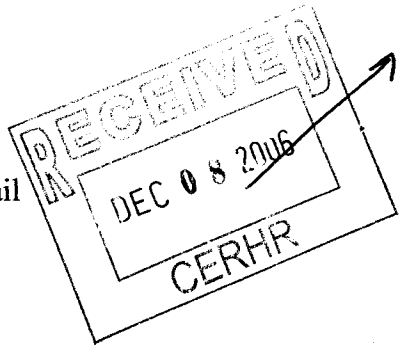

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November 30 2006

Dr Michael Shelby,
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Comments on the NTP-CERHR Panel Reports on Reproductive and Developmental Toxicity of Genistein in Soy Infant Formulas

Dear Dr Shelby,
There is a legal and moral imperative that advice provided to parents and to health professionals is accurate and broadly based on both national and international expert opinions.
I enclose copies of relevant conclusions. I quote:

(1) The USA National Research Council 1999 "The concentrations of soy phytoestrogens that inhibited thyroid hormone biosynthesis are in the range of exposure of infants maintained on soy formula....."
(2) The UK Scientific Advisory Committee on Nutrition 2002...SACN considers "that there is cause for concern about the use of soy-based infant formula. There is neither substantive need for soy-based infant formulae nor health benefit arising from their use."
(3) The French food Safety Agency 2005..."The consumption of phytoestrogens cannot a priori be considered safe because they interfere with the hormonal system, and as such merit examination. On the basis of safety studies it is considered that.....some consumers need to take special precautions. For infants and young children taking soy-protein based formulas, it is recommended that phytoestrogen intake be limited to 1mg/l of formula. In the same way in utero and neonatal exposure needs to be limited."
(4) The European Committee on Nutrition (ESPGHAN) published in the Jour Pediatrics 2006...."Cows' milk-based formula should be preferred as the first choice for feeding healthy infants that are not fully breast-fed. Soy protein-based formulae should only be used in specified circumstances because they may have nutritional disadvantages and contain high concentrations of phytate, aluminium, and phytoestrogens, the long-term effects of which are unknown."

Yours Sincerely,
Valerie A James [Redacted]

(1)

HORMONALLY ACTIVE AGENTS *IN THE* ENVIRONMENT

NATIONAL RESEARCH COUNCIL

HORMONALLY ACTIVE AGENTS *IN THE* ENVIRONMENT

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population. Furthermore, PCB concentrations in breast milk of women who ate Great Lakes fish were almost twice those of a control group (Fitzgerald et al. 1998, as cited in ATSDR 1999). PCB concentrations in blood were correlated with the number of years an individual had consumed Great Lakes fish. Individuals who consumed less than 6 pounds of fish per year had a geometric mean for PCB blood concentrations of 6.8 ppb, whereas those who consumed more than 24 pounds of Great Lake fish had mean blood PCB concentrations of 19 ppb (Hovinga 1993).

Phytoestrogens

Human and animal exposures to the phytoestrogens, particularly isoflavones, can be very high, because these compounds are found in many foods. Genistein, daidzein, formononetin, and equol are all present in clover. Infertility in sheep, "clover disease," has been traced to isoflavone concentrations as high as 5% of the dried weight of clover (Verdeal and Ryan 1979).

The recent practice of feeding infants soy-based formula has raised concerns with regard to the long-term health effects of exposure during development (Setchell et al. 1997; Irvine et al. 1998). For example, it has been recognized for some time that feeding infants soy-based formula was associated with goiter (thyroid enlargement associated with thyroid hormone deficiency) in animals and human infants (Shepard et al. 1960). One mechanism by which isoflavonoids, such as genistein, reduce thyroid hormone concentrations and result in goiter is by inhibiting thyroid peroxidase activity; this enzyme catalyzes thyroid hormone biosynthesis (Divi and Doerge 1996). The concentration of soy phytoestrogens that inhibited thyroid hormone biosynthesis are within the range of exposure of infants maintained on soy formula. Soy-based formulas contained isoflavones at 32-47 µg/mL, which corresponded to a daily exposure to total isolfavones of 4.5-8.0 mg/kg of body weight per day for a 4-month-old infant. That concentration is 6- to 11-fold higher than concentrations known to cause hormonal effects in adults. (Divi et al. 1997; Setchell et al. 1997). In a study by Irvine et al. (1998), the phytoestrogen content of soy-based formulas and cereals were compared with dairy-based formulas and human breast milk. Again, infants received approximately 3 mg/kg of body weight per day from the soy-based formula, but a single daily serving of infant cereal could increase the isoflavone intake by more than 25%. Dairy-based formula and human breast milk contained isoflavones below the limit of detection. Human breast milk had undetectable concentrations of phytoestrogens regardless of the diet of the mother, including women who were vegetarians and consumed greater than 50 g of soy products in a 48-hr period before sampling.

Potential exposure to plant estrogens found in wood has been assessed by various in vitro and in vivo bioassays. Wood-derived estrogens, such as beta-sitosterol, could represent environmental hormone exposures, particularly from pulp and paper mill effluents, downstream of wood-processing facilities. Mellanen et al. (1996) used two breast-cancer cell lines in vitro (MCF7 and T-47D) and expression of the vitellogenin gene in rainbow-trout livers to estimate estrogenic activity of wood-derived compounds. Some compounds, such as beta-sitosterol, were estrogenic in human and fish bioassays, but some phytoestrogens, such as betulin and pinosylvin, were estrogenic only in humans.

(2)

PEG/2002/01

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

WORKING GROUP ON PHYTOESTROGENS

Scientific Advisory Committee on Nutrition view on soy formula feeding recommendation

Issue

Members are asked to consider the comments made by the Scientific Advisory Committee on Nutrition on the Phytoestrogens & Health report advice on the use of soy-based infant formula.

Background

1. The Scientific Advisory Committee on Nutrition (SACN) have been asked to comment on the sections of the Phytoestrogens & Health report which relate to the use of soy-based infant formula (the Conclusions and Fertility & Development chapters). The comments provided by SACN are appended.

2. Members will note that the SACN view is restricted to the use of soy-based infant formula rather than phytoestrogens *per se*. Members will wish to consider the SACN comments along with the other comments relating to the use of soy-based infant formula summarised in PEG/2002/02.

Secretariat 2002

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

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.

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 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.

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(3)

ACTUALITES

Présentation du rapport sur "Sécurité et bénéfices des phyto-estrogènes apportés par l'alimentation - Recommandations (9 mars 2005)

L'Afssa a organisé une réunion d'échanges et d'information le 9 mars 2005 à 14 heures.

A cette occasion, le rapport sur "Sécurité et bénéfices des phyto-estrogènes apportés par l'alimentation - Recommandations" a été présenté.

Les conclusions de ce rapport ont été développées lors de cette réunion en présence des membres du groupe de

- Communiqué de presse

-Rapport

- Annexes du rapport

- Composition du groupe de travail

- Synthèse du rapport "Sécurité et bénéfices des phyto-estrogènes apportés par l'alimentation"

- L'essentiel du rapport

- Ensemble des points clés et recommandations pour les phyto-estrogènes de l'alimentation

afssa
AGENCE FRANÇAISE
DE SECURITE SANITAIRE
DES ALIMENTS

afssaps
Agence française de sécurité sanitaire
des produits de santé

Maisons-Alfort, le 9 mars 2005

Communiqué de presse

Sécurité et bénéfices des phyto-estrogènes apportés par l'alimentation

L'Afssa, en relation étroite avec l'Afssaps, a évalué la sécurité et les bénéfices pour la santé des phyto-estrogènes. Le terme de « phyto-estrogènes » regroupe plusieurs molécules issues du monde végétal, de structures différentes mais présentant une similarité avec la structure de l'estradiol (l'une des hormones sexuelles majeures). *A priori*, cette similarité structurale leur donne la possibilité d'exercer un effet estrogénique sur les tissus cibles. De fait, les phyto-estrogènes sont associés à une image ambiguë, liée tant à l'étude de leurs effets délétères (notamment par leur appartenance au grand groupe des « perturbateurs endocriniens »), que de leurs effets bénéfiques (notamment par les observations d'épidémiologie analytique menées en Asie). Le travail d'expertise a été réalisé sur la base de la littérature scientifique et l'audition d'experts et d'industriels des secteurs concernés. Plus de 1500 études scientifiques publiées et validées ont ainsi été analysées.

L'identification de ces molécules repose sur leur capacité à présenter chez l'animal des effets de type estrogénique à travers la liaison aux récepteurs de l'estradiol. Cependant les caractéristiques de cette fixation et les effets qu'elle entraîne présentent certaines différences avec l'estradiol.

Les phyto-estrogènes sont présents dans des denrées alimentaires variées : ils sont naturellement présents dans certains aliments destinés aux nourrissons et aux jeunes enfants préparés à base de protéines de soja, et dans les aliments à base de soja (tofu, tonyu ou « jus » de soja, desserts à base de soja). Ils sont volontairement concentrés par les industriels dans les compléments alimentaires visant les femmes ménopausées. Au delà de la présence commune de phyto-estrogènes, chacune de ces catégories d'aliments possède sa problématique propre : le soja constitue un aliment intéressant sur le plan nutritionnel en dehors de la problématique des phyto-estrogènes, tandis que les compléments alimentaires doivent être considérés au regard de leur usage frontière entre aliment et médicament.

Six familles de molécules pouvant prétendre à l'appellation « phyto-estrogènes » en alimentaire ont été identifiées. Cette identification ne préjuge pas des effets de chacun des phyto-estrogènes sur des états physiopathologiques spécifiques. En fait, les données de la littérature concernent essentiellement une seule de ces familles, celle des isoflavones, molécules présentes en grande quantité dans le soja. Dans un régime occidental traditionnel, n'incluant donc pas le soja, l'apport journalier moyen en isoflavones dites « aglycones » est très faible, inférieur à 1 mg/j. L'introduction mesurée d'aliments à base de soja dans un régime occidental augmente cet apport de 1000 à

10 000 fois, tout en restant inférieur à celui des asiatiques. Dans le cas de prise de compléments alimentaires, l'apport peut être aussi important qu'en Asie, il pourrait tendre à le dépasser.

La consommation de phyto-estrogènes ne peut-être considérée anodine *a priori*, puisqu'ils interfèrent avec le système hormonal, et mérite donc examen. Sur la base des études de sécurité, il a pu être estimé que :

- l'apport de 1 mg/kg de poids corporel/j d'isoflavones aglycones (soit 60 mg pour un individu pesant 60 kg) ne présente pas de risque pour la population générale,
- des précautions particulières doivent être prises chez certains consommateurs :
    - pour les nourrissons et les jeunes enfants consommant des préparations à base de protéines de soja, il est recommandé de limiter l'apport en phyto-estrogènes à 1 mg/L de préparation reconstituée. De même, il faut veiller à limiter l'exposition *in utero* et néo-natale
    - les personnes présentant un cancer du sein ou des antécédents personnels ou dans leur famille devraient limiter leur apport en phyto-estrogènes.

Par ailleurs, comme cela a été montré chez l'enfant, la consommation de phyto-estrogènes peut augmenter les besoins en hormones thyroïdiennes chez les patients hypotyroïdiens traités.

En comparaison aux effets associés au traitement hormonal substitutif de la ménopause (THS) :

- **Les études concernant les phyto-estrogènes ne permettent pas à ce jour d'établir un effet des phyto-estrogènes sur les bouffées de chaleur.**
- **Les isoflavones pourraient avoir un effet limité sur l'ostéoporose et la perte des fonctions cognitives. Cependant, ces effets nécessitent d'être confirmés par des études cliniques bien menées.**
- **Les données disponibles à ce jour montrent que les phyto-estrogènes ne sont pas associés à une augmentation du risque de cancer du sein chez la femme. Chez les Asiatiques, ce risque est diminué. Mais les différences importantes qui existent entre Asiatiques et Occidentales, excluent la possibilité d'une transposition des effets.**

Au vu de ces données, d'autres études réalisées avec une méthodologie adéquate doivent venir compléter l'ensemble des données disponibles, et les phyto-estrogènes doivent encore rigoureusement prouver leur place dans la prévention ou la prise en charge des troubles liés à la ménopause.

Enfin sur le plan cardio-vasculaire, les isoflavones aglycones de soja ont un effet bénéfique sur le tonus des vaisseaux sanguins (vasotonicité) à partir de 45 mg/j mais des effets délétères pourraient se produire à partir de 73mg/j.

Des recommandations de recherche, de santé publique et d'information du consommateur sont émises.

Le rapport « *Sécurité et bénéfices des phyto-estrogènes apportés par l'alimentation – Recommandations* » est rendu public ce 9 mars 2005. A cette occasion, ses conclusions, élaborées en lien avec l'Afssaps, seront présentées et discutées à 14h00, à l'Afssa lors d'une réunion d'échanges et d'information, en présence du Dr. Mariette Gerber, présidente du groupe de travail et des experts membres de ce groupe.

Le rapport intégral et sa synthèse sont téléchargeables sur le site internet www.afssa.fr

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Translation from French
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SECURITE SANITAIRE
DES ALIMENTS
[French Food Safety
Agency]

Afssaps
Agence française de
sécurité sanitaire des
produits de santé
[French Health Product
Safety Agency]
Maisons-Alfort, 9 March 2005

Press Release

Safety and Benefits of Phytoestrogens in Food

The Afssa, in collaboration with the Afssaps, has assessed the safety and health benefits of phytoestrogens. The term "phytoestrogens" includes several molecules from the plant world with different structures, but all of which show similarities to the structure of oestradiol (one of the major sex hormones). As far as is known, this structural similarity gives them the ability to carry out an oestrogenic effect on target tissues. At the moment, phytoestrogens suffer from a mixed reputation, linked as much to research on their harmful effects (particularly in that they belong to the large group of "endocrine disruptors") as their beneficial effects (particularly from analytical epidemiological research carried out in Asia). This expert report has been carried out based on scientific literature and in response to requests from experts and businesses from the areas concerned. As such, more than 1,500 published and recognised scientific studies have been analysed.

Idenfication of these molecules depends on their capacity to show oestrogen-type effects in animals by means of binding to oestradiol receptors. However, the characteristics of this bond and its effects show some differences to oestradiol.

Phytoestrogens are present in a range of foods: they are naturally present in some soy protein based foods designed for infants and young children, and in soy-based food products (tofu, "Tonyu" or soy "juice", soy-based desserts). Manufacturers also add them in concentrate to dietary supplements aimed at post-menopausal women. In addition to the common presence of phytoestrogens, each of these food categories has its own set of problems: soy is an interesting food from a nutritional point of view even without the problems of phytoestrogens, while dietary supplements must be considered in the light of their borderline status between food and medicine.

Six families of molecules that fit the description of "phytoestrogens" have been identified in food. This identification does not prejudge the effects of any of these phytoestrogens on particular physiopathological states. In fact, most of the information in the literature relates to only one of these families, the isoflavones, molecules that are present in large quantities in soy. In a traditional Western diet, which does not include soy, the average daily intake of isoflavones known as "aglycones" is very low; less then 1mg/day. Measured introduction of soy-based foods into a Western diet increases the intake by 1,000 to 10,000 times, which is still lower than that of Asians. If dietary supplements are being taken, the intake can be as high as it is in Asia, and could tend towards being higher.

The consumption of phytoestrogens cannot *a priori* be considered safe, because they interfere with the hormonal system, and as such merit examination. On the basis of safety studies, it is considered that:

- an intake of 1mg/kg of body weight per day of aglycone isoflavones (that is, 60 mg for a person weighing 60 kg) presents no risk for the general population,
- some consumers need to take special precautions:
    - for infants and young children taking soy protein-based formula, it is recommended that phytoestrogen intake be limited to 1mg/l of formula. In the same way, *in utero* and neo-natal exposure needs to be limited
    - people with breast cancer or a personal or family history of breast cancer should limit their intake of phytoestrogens.

In addition, as has been shown in children, phytoestrogen consumption can increase thyroid hormone requirements in patients being treated for hypothyroidism.

As compared with effects associated with hormone replacement therapy for menopause (HRT):

- **Studies on phytoestrogens have not yet established the effect of phytoestrogens on hot flushes.**
- **Isoflavones may have a limited effect on osteoporosis and the loss of cognitive function. However, these effects need to be confirmed by well-managed clinical studies.**
- **The data available at present show that phytoestrogens are not associated with an increased risk of breast cancer in women. In Asian people, there is a decreased risk. However, the significant differences between Asian and Western people exclude the possibility of transposing the effects.**

In the light of this information, other studies with adequate methodology need to be performed in order to complete the available information, and the place of phytoestrogens in prevention or management of problems linked to menopause requires rigorous proof.

Finally, in the cardiovascular area, soy aglycone isoflavones have a beneficial effect on blood vessel tone (vasotonia) at levels from 45mg/day, but negative effects may be produced from 73mg/day.

Recommendations for research, public health and consumer information are being issued.

The *"Sécurité et bénéfices des phyto-estrogènes apportés par l'alimentation – Recommandations"* [Safety and Benefits of Phytoestrogens in Food – Recommendations] report is being made public on 9 March 2005. The conclusions, as developed in conjunction with the Afssaps, will be presented at that time, and discussed at the Afssa at 2pm, during a discussion and information meeting which will be attended by Dr. Mariette Gerber, president of the working group and an expert member of the group.

The complete report and a summary of it can be downloaded from www.afssa.fr

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(4)

Medical Position Paper

Soy Protein Infant Formulae and Follow-On Formulae: A Commentary by the ESPGHAN Committee on Nutrition

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ABSTRACT: This comment by the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) Committee on Nutrition summarizes available information on the composition and use of soy protein formulae as substitutes for breastfeeding and cows' milk protein formulae as well as on their suitability and safety for supporting adequate growth and development in infants. Soy is a source of protein that is inferior to cows' milk, with a lower digestibility and bioavailability as well as a lower methionine content. For soy protein infant formulae, only protein isolates can be used, and minimum protein content required in the current European Union legislation is higher than that of cows' milk protein infant formulae (2.25 g/100 kcal vs. 1.8 g/100 kcal). Soy protein formulae can be used for feeding term infants, but they have no nutritional advantage over cows' milk protein formulae and contain high concentrations of phytate, aluminum, and phytoestrogens (isoflavones), which might have untoward effects. There are no data to support the use of soy protein formulae in preterm infants. Indications for soy protein formulae include severe persistent lactose intolerance, galactosemia, and ethical considerations (e.g., vegan concepts). Soy protein formulae have no role in the prevention of allergic diseases and should not be used in infants with food allergy during the first 6 months of life. If soy protein formulae are considered for therapeutic use in food allergy after the age of 6 months because of their lower cost and better acceptance, tolerance to soy protein should first be established by clinical challenge. There is no evidence supporting the use of soy protein formulae for the prevention or management of infantile colic, regurgitation, or prolonged crying. *JPGN 42:352–361, 2006.* **Key Words:** soy—infant formula—follow-on formula—food allergy—phytoestrogens. © 2006 Lippincott Williams & Wilkins

INTRODUCTION

Soy formula was first introduced in the United States for feeding young infants in the early 1900s (1). In 1929, soy formula was proposed as a cows' milk substitute for babies with cows' milk intolerance (2). Soy protein formulae are given at some time during the first year of life to approximately 25% of infants in the United States, 13% in New Zealand, 7% in the United Kingdom, 5% in Italy, and 2% in France (3–6).

During the past few years, concerns have been raised over potential risks of soy protein formulae, in particular with regard to high phytoestrogen contents. Authorities or pediatric societies from Australia, Canada, France, Ireland, New Zealand, Switzerland, and the United Kingdom have recently advised health professionals and caregivers that because of concerns raised and limited availability of data, the use of soy protein formulae in infants should be restricted to specific cases (7–9).

The purpose of this comment by the Committee is to review available information on the composition and use of soy protein formulae as substitutes for breastfeeding and cows' milk protein formulae as well as on their suitability and safety for supporting adequate growth and

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Berthold Koletzko is Committee Chair, Hania Szajewska is Committee Secretary, and Daniel Rieu is a guest of the ESPGHAN Committee on Nutrition.
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elopment of infants. In preparing this comment, the Committee reviewed expert consensus documents on the use of soy protein formulae in dietetic products for infants (5,7–13). Products that do not meet the standards of infant and follow-on formulae or foods for medical purposes designed for infants, such as soy "milks" or juices and fermented soy products, that do not fulfill nutritional requirements of infants are beyond the scope of this review.

FROM SOYBEANS TO SOY PROTEIN ISOLATE FORMULAE

Soybeans comprise approximately 40% proteins, 35% carbohydrates, 20% fat, and 5% minerals (percent dry weight). Soybean products include oil and soy flour obtained from roasted soybeans ground into a fine powder. Soy protein isolates are derived from delipidated soy flour (90–95%) by elimination of soluble carbohydrates and mineral salts (5). Soy protein has a lower biologic value than cows' milk protein. The nitrogen conversion factor, which allows us to calculate the protein content from the total nitrogen content, is lower for soy protein isolate than for cows' milk protein. Soy and cows' milk proteins have a different amino acid pattern (i.e., soy protein contains lower amounts of methionine, branched chain amino acids lysine, and proline and higher quantities of aspartate, glycine, arginine, and cystine than cows' milk protein) (14). To ensure adequate growth, nitrogen balance, and plasma albumin concentrations, methionine supplements have been recommended (15,16). Because soy based products have a very low content of L-carnitine that may induce low plasma carnitine concentrations in infants (17), the addition of carnitine to soy formulae has also been recommended (7,18).

COMPOSITION OF SOY PROTEIN INFANT AND FOLLOW-ON FORMULAE

Recommendations and Regulations

The ESPGHAN Committee on Nutrition published recommendations on the composition of soy protein infant and follow-on formulae in 1990 (16). Soy protein infant and follow-on formulae marketed in the European Union must meet the compositional criteria defined by EU directives (19,20). For soy protein infant formulae, only protein isolates should be used, and the minimum protein content required by European legislation is higher than that of cows' milk protein infant formulae (2.25 g/100 kcal vs. 1.8 g/100 kcal) to account for potentially lower digestibility and therefore lower bioavailablility of soy protein compared with intact cows' milk protein. The main differences in compositional criteria between soy protein and cows' milk protein infant formulae, and between soy protein and cows' milk protein follow-on formulae, are listed in Table 1.

Nutritional Adequacy of Soy Protein Formulae

In the 1970s, Fomon et al. (21) studied infants fed, as desired, an infant formula based on methionine supplemented soy protein isolate with a protein content of 1.64 g/100 kcal and an energy content of 67 kcal/100 mL. Infants were fed the formula exclusively for 28 days and thereafter combined with complementary feeding until the age of 112 days. The infants had a similar growth pattern and similar normal markers of plasma protein metabolism as breast-fed infants. However, energy intakes were slightly higher than in infants fed a cows' milk formula with a protein content of 1.77 g/100 kcal. In a study designed to estimate the requirement of sulfur amino acids of infants up to the age of 112 days, a beneficial effect of L-methionine supplementation (7.5 mg/100 kcal) on nitrogen balance was only seen with a concomitant soy protein content of 1.8 g/100 kcal. A beneficial effect of methionine supplementation on weight gain or serum concentrations of urea nitrogen and albumin was only demonstrated at soy protein concentrations of 2.2 and 2.6 g/100 kcal, respectively (22).

Fomon et al. and other investigators demonstrated that infants exclusively fed methionine-supplemented soy protein formulae during the first 4 to 12 months of life showed weight gain and linear growth similar to that of infants fed conventional cows' milk protein formulae

TABLE 1. *Compositional criteria of soy protein isolate infant and follow-on formulae, alone or mixed with cows' milk protein, according to the Commission Directive 91/321/EEC of May 14, 1991 on infant formulae and follow-on formulae (19)*

	Soy protein infant formulae		Soy protein follow-on formulae	
	Minimum (/100 kcal)	Maximum (/100 kcal)	Minimum (/100kcal)	Maximum (/100 kcal)
Protein (g)*	2.25	3.0	2.25	4.5
Methionine (mg)	29	–	29	–
L-carnitine (μmoles)	7.5	–	–	–
Lactose (g)†	3.5	–	1.8	–
Iron (mg)	1	2	1	2
Zinc (mg)	0.75	2.4	0.75	–

*Soy protein isolate has to have a minimal chemical index of at least 80% in comparison with human milk protein for infant formulae and in comparison with human milk or casein for follow-on formulae.

†There is no minimal content for lactose when soy protein represents more than 50% of total protein.

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(23,24). Studies were generally less than 1 year in duration, with exclusive soy protein formula feeding from birth to 4 months. Blood markers of protein metabolism in children fed soy protein formulae were not significantly different from those of infants fed cows' milk formulae. Healthy term infants fed a soy protein formula during their first year of life achieved a bone density similar to breast-fed or cows' milk formula fed infants (25,26). Outcome parameters included serum calcium, magnesium, phosphorus, alkaline phosphatase, parathyroid and 1,25-dihydroxyvitamin D concentrations, and bone mineral content measured with absorptiometry. These data indicate that soy protein formulae can be used for feeding term infants but have no nutritional advantage over cows' milk protein formulae.

In a randomized, controlled study performed in very low birthweight infants from 3 to 8 weeks of age, Hall et al. (27) compared a soy protein infant formula supplemented with calcium, phosphorus, and vitamin D (n = 17) with a whey-predominant premature infant formula (n = 15). Birth weight (1,206 ± 178 g) and gestational age (30 ± 1.9 weeks) of the soy formula-fed group were not significantly different from the whey formula-fed group (1,143 ± 158 g and 30 ± 1.8 weeks, respectively). The energy content of the whey formula was higher than that of the soy formula (81 kcal/100 mL vs. 67 kcal/100 mL), whereas the protein/energy ratio was identical in both formulae (3 g/100 kcal). The caloric (kcal/kg/day) and protein (g/kg/day) intake was not significantly different between each group because a greater volume of feed was consumed in the soy formula-fed infants. Those fed soy formula had lower weight gain (11.3 ± 2.3 g/kg/day) than infants fed whey-predominant formula (15.3 ± 2.5 g/kg/day) as well as lower protein and albumin blood concentrations. Bone mineralization pattern was the same in both groups. Although no more information is available in this population, the Committee concludes that soy protein formulae should not be used in preterm infants.

Phytate

Soy protein isolate contains some 1% to 2% phytate, which may impair the absorption of minerals and trace elements. In experimental animals and in human adults, phytate has a negative effect on intestinal zinc and iron absorption (28). A reduction in phytate contents of soy protein formulae can be achieved by precipitation methods or treatment with phytase. Reduction of the phytate content of soy formula increased the absorption and availability of zinc and copper in infant rhesus monkeys and rat pups and of iron in infants (29,30). Using stable isotope techniques in infants fed a soy protein isolate formula with low contents of phytate (<6 mg/kg liquid formula) or a conventional content (300 mg/kg liquid formula), Davidsson et al. (31) showed that zinc absorption was significantly greater with dephytinized formula (22.6% vs. 16.7%, $P = 0.03$), whereas no significant difference was observed for calcium, iron, copper, and manganese absorption.

Phytate may also interfere with iodine metabolism. Before the supplementation of soy formulae with iodine and the use of isolated soy protein instead of high-fiber soy flour in the mid-1960s, cases of goiter and hypothyroidism were described in infants fed soy formulae (32,33). The persistence of thyroid insufficiency despite the use of a high dose of levothyroxine has also been observed more recently in infants with congenital hypothyroidism fed soy protein formulae (34,35). A recent study showed that infants with congenital hypothyroidism fed soy protein formulae had a prolonged increase of thyroid stimulating hormone (TSH) when compared with infants fed nonsoy formulae. These infants need close monitoring of free thyroxine and TSH measurements and may need increased levothyroxine doses to achieve normal thyroid function (36). The mechanism of the prolonged increase in TSH blood concentrations is not clear. Malabsorption and increased fecal loss of the supplemented levothyroxine have been shown in animal studies performed before the use of isolated soy protein. Soy protein may also act as a goitrogen. A glycopeptide isolated from soy that blocks iodine uptake and decreases its organification has been described.

Information on the phytate contents of soy protein formulae used in Europe is not publically available. Such information should be disclosed by manufacturers. In view of the considerations discussed above, the Committee strongly recommends that phytate contents in soy protein infant formulae should be effectively reduced, for example, by precipitation methods or phytase treatment.

Nucleotides

The nucleotide content of soy protein formulae is much higher (approximately 310 mg/L) than that of human milk (68–72 mg/L) or cows' milk infant formulae (8–72 mg/L) (37). The Commission Directive 1991/321/EEC has approved the addition of nucleotides to infant and follow-on formulae with a total concentration of up to 5 mg/100 kcal, which is similar to reported data for free ribonucleotides in human milk (approximately 4–6 mg/100 kcal) (19). Because there is no adequate scientific basis at present to conclude that the addition of nucleotides in higher concentrations would provide additional benefits, the Committee discourages the further addition of nucleotides to formulae based on soy protein isolates given their high natural contents.

Aluminum

In 1996, the Committee on Nutrition of the American Academy of Pediatrics (AAP) highlighted the potential risk of aluminum toxicity in infants and children related to the use of soy protein formula contaminated with

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aluminum (38). The source of the aluminum is thought to be the aluminum equipment used during the production of soy protein isolates and the nature of mineral salts used in formula production (3). Much higher concentrations of aluminum were found in soy protein formulae (500–2,400 μg/L) than in cow's milk protein formulae (15–400 μg/L) and breast milk (4–65 μg/L). However, daily aluminum intake remained less than 1 mg/kg, which the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives in 1989 considered as the tolerable intake of aluminum (39). Infants fed formulae with the highest contents of aluminum (2.35 mg/L) at the time of the publication would receive an aluminum dose less than 0.5 mg/kg per day at feed intakes up to 200 mL/kg per day. There is inadequate information on the aluminum content of soy protein formulae. Such information should be made available by manufacturers. Although long-term consequences of higher levels of aluminum observed in soy formulae are unknown, continued efforts should be made by manufacturers to reduce the aluminum content of soy protein formula.

Phytoestrogens

Phytoestrogens represent a broad group of plant-derived compounds of nonsteroidal structure that are ubiquitous within the plant kingdom and have weak estrogen activity (9,40). They are present in beans in general and soybeans in particular. Lignanes and isoflavones are the major classes of phytoestrogens of interest from a nutritional and health perspective. The main compounds contained in soy protein-based foods are the isoflavones genistein and daidzein (41). Isoflavones can bind to estrogen receptors, interact with enzyme systems influencing estrogenic activity, and exert weak estrogenic activity (42). It has been suggested that isoflavones may have anticancer properties in animals (43,44) and in human adults (45,46). Isoflavones may contribute to the prevention of cardiovascular disease, breast cancer, osteoporosis, and menopausal disorders (47), and they have been proposed to slow progression of renal disease in adults (48).

Infant formulae based on soy protein isolates contain relatively high concentrations of isoflavones (49). Isoflavone content found in soy formulae commercially available in the United States, United Kingdom, New Zealand, and France ranges from 17.5 to 47 μg/mL and from 123 to 281 μg/g of milk powder, with a higher proportion of genistein than of daidzein (8,50–53). Concentrations of isoflavones were much lower in cows' milk and breast milk samples, ranging from 0.1 to 5 μg/L in cows' milk (54) and from 1.6 to 13.6 μg/L (U.S.) and from 0 to 32 μg/kg (U.K.) in breast milk, respectively (8,41). Isoflavone content of breast milk varies with mother's diet. Setchell et al. (41) estimated that infants aged 1 to 4 months would receive 6 to 12 mg/kg body-weight per day of total isoflavones, whereas an adult consuming 57 to 85 g of soy-based products may receive 50 to 100 mg of total isoflavones (i.e., 0.7 to 1.4 mg/kg/d).

Glycosidic conjugates of isoflavones present in soy protein formulae are hydrolyzed by intestinal glucosidases to their aglucon form, then are absorbed, metabolized in the liver to glucuronide and sulphate conjugates, and subsequently excreted in urine. Short-term studies have shown that no more than 30% of the ingested dose of isoflavones are recovered in urine and feces (41). Knowledge on the bioavailability of isoflavones is still incomplete in young infants (41,52). In 4-month-old infants exclusively fed soy protein isolate formula, Setchell et al. found plasma total isoflavone concentrations ranging from 552 to 1,775 μg/L, with a mean concentration of 980 μg/L. Mean (SD) plasma concentration was 684 (443) μg/L for genistein and 295 (60) μg/L for daidzein. These values were significantly higher ($P < 0.001$) than the mean values for plasma total isoflavone concentrations in infants fed either cows' milk formula (9.4 ± 1.2 μg/L) or breast milk (4.7 ± 1.3 μg/L) (41,50). On a molar basis, isoflavones demonstrated weak estrogenic activity relative to physiologic estrogens, possessing between 1×10^{-4} and 1×10^{-3} of the activity of 17 β-estradiol (55).

Phytoestrogens given at the high dosage contained in soy-based formulae adversely affected development and neuroendocrine function in different animal species (7,41,56). Isoflavones were found to cause infertility in sheep, known as "clover disease" (57). In utero exposure of rats to high doses of genistein impairs the pituitary secretion of luteinizing hormone (58).

It has been hypothesized that phytoestrogens have the potential to increase thyroid binding globulin (8). Any such increase could transiently increase the binding capacity for thyroxine, thus lowering free thyroxine concentrations. However, there are no data to suggest that phytoestrogens acting by this mechanism produce clinical effects. A retrospective telephone recall epidemiologic study found that children with autoimmune thyroid disease were significantly more likely to have been fed soy formula in infancy (31% vs. 13% in infants without autoimmune thyroid disease) (59). There was no group difference in the frequency and duration of breast feeding. The aglucons of genistein and daidzein were demonstrated to inhibit the activity of thyroid peroxidase purified from porcine thyroid glands when present at concentrations of 1 to 10 μM, resulting in iodinated isoflavone compounds. The presence of at least 150 μM of iodine per liter in the incubation mixture completely protected against the isoflavone-mediated thyroid peroxidase inactivation (60).

Few data are available on the potential consequences of exposure to high doses of phytoestrogens in human infants on the later sexual and reproductive development. A three-fold increase in the number of patients with premature thelarche seen between 1978 and 1981 in Puerto

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Rico led to further investigation in a case-control study (61). Onset of thelarche before 2 years of age was significantly associated with consumption of soy protein isolate based infant formula and of various meats. However, less than 20% of cases were soy formula fed, which points to the importance of additional causative factors.

Strom et al. (62) conducted telephone interviews in 811 adults aged 20 to 34 years who had participated as infants during the years 1965 to 1978 in comparative but not randomized feeding trials with soy protein based infant formula (n = 248; 120 males) or cows' milk protein formula (n = 563; 295 males). Outcome measures were self-reported: pubertal maturation, menstrual and reproductive history, height, weight, and education levels. The study did not include any direct measurements of hormone levels. Females previously fed on soy formulae had a lower prevalence of sedentary activities (8.9 ± 3.4 hours/wk vs. 9.6 ± 3.5 hours/wk, $P = 0.05$), whereas there was no difference for males. No statistically significant differences were observed between groups in either men or women for adult height, weight, pubertal development, and incidence of thyroid disease. Women fed soy formula in infancy experienced a slightly but significantly longer duration of menstrual bleeding (by 0.37 days; 95% confidence interval [CI]: 0.06–0.68), with no difference in self-assessed intensity of menstrual flow. They also reported greater discomfort with menstruation (unadjusted relative risk for extreme discomfort vs no or mild pain, 1.77; 95% CI, 1.04–3.00). Pregnancies were reported by 42% of women fed soy-formulae and 48% of women fed cows' milk formulae (NS). Outcomes of pregnancies were not different, and neither were there differences between the groups in the prevalence of cancer, hormonal disorders, sexual orientation, or birth defects in the offspring. No conclusions can be drawn on possible effects on fertility in men previously exposed to soy-based formulae, considering their relatively young age at the time of the follow-up study. Although exposure to soy formulae in this study did not appear to be responsible for major health or reproductive problems, more information is needed on potential long-term effects of phytoestrogens.

Yellayi et al. (56) showed that subcutaneous genistein injections in ovariectomized adult mice produced dose responsive decreases in thymic weight of up to 80%. Genistein injection caused decreases in relative percentages of thymic CD4+CD8− and double positive CD4+CD8+ thymocytes, providing evidence that genistein may affect early thymocyte maturation and the maturation of CD4+CD8− helper T-cell lineage. Dietary genistein at concentrations that produced serum genistein levels substantially less than those found in soy protein formula-fed infants produced marked thymic atrophy.

In infants fed soy protein formula from birth to 4 months, Ostrom et al. and Cordle et al. (63,64) did not find differences compared with a control group that was breastfed for 2 months or more at 6 and 12 months of age for the level of immunoglobulins (Ig)G and A, the titre of antibodies against diphtheria, tetanus, poliovirus, and *Hemophilus influenzae* b, as well as the count of lymphocytes B, T, and NK. The only significant difference was the higher percentage of $CD57^+$ NK cells in the control group at 12 months.

Information on the phytoestrogen content of soy protein formulae should be made available by manufacturers. Although studies in humans are lacking, on the basis of available data in animal models, the Committee recommends that the content of phytoestrogens in soy protein formulae be reduced because of uncertainties regarding safety in infants and young children.

COMMENTS ON POSSIBLE INDICATIONS FOR SOY FORMULAE

Severe persistent lactose intolerance and galactosemia

Severe persistent lactose intolerance, including severe mucosal damage and the rare cases of hereditary lactase deficiency (McKusick 223000) and classic galactosemia (galactose-1-phosphate uridyltransferase deficiency) (McKusick 230400), are indications for the use of lactose free soy formulae (65). It should be noted that some soy protein formulae contain raffinose and stachyose that are cleaved in the digestive tract under the action of bacterial galactosidases, leading to the liberation of 1,4 galactose that may contribute to elevated galactose-1-P values in erythrocytes of galactosemic patients (66).

Acute gastroenteritis

A meta-analysis of clinical trials on the use of formulae in the management of acute gastroenteritis concluded that lactose-containing diets do not need to be withdrawn in the vast majority of cases, whereas lactose free diets were beneficial in a limited number of cases with severe dehydration (67). An ESPGHAN multicentric study has shown that the early use of lactose containing cows' milk formula after oral rehydration does not aggravate or prolong diarrhea in well-nourished infants presenting with acute gastroenteritis and mild to moderate dehydration and has the advantage of preventing malnutrition (68). Therefore, switching from lactose-containing formula to lactose free formula such as soy formulae is not routinely recommended in acute gastroenteritis (10). Moreover, there are theoretical concerns regarding the introduction of a new protein source in the presence of increased mucosal permeability, with a potential increased risk of allergic sensitization (69,70).

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Cows' milk allergy

Before the availability of therapeutic formulae based on cows' milk protein hydrolysates, soy formula was the only dietetic product available for feeding infants with cows' milk protein allergy. However, soy protein is also a common allergen. The identification and characterization of soybean allergens have identified fractions containing conglycinin (molecular weight 180,000 d) and glycinin (molecular weight 320,000 d) as probably the major allergens and trypsin inhibitor as the minor allergen responsible for soy protein allergy (71). Patients with soy protein allergy present with either acute symptoms within a few hours after soy ingestion (i.e., urticaria, angioedema, vomiting, diarrhea, or anaphylactic shock) or with chronic symptoms (i.e. chronic diarrhea and failure to thrive, malabsorption, and villous atrophy) (72,73). Symptoms usually resolve after elimination of soy from the diet.

Among infants with cows' milk allergy fed soy protein based formulae, some 30% to 50% were reported to present with concomitant soy protein allergy, with a higher frequency reported in nonIgE-mediated enterocolitis-enteropathy syndrome (71,74–76). A review of 2,108 infants with cows' milk protein allergy followed at 33 Italian pediatric gastroenterology units reported that 50% of these infants had received soy protein-based formulae as the substitute for milk containing formulae. Soy protein formulae were discontinued in 47% of cases overall, ranging from 53% of infants younger than 3 months of age to 35% of children older than 1 year of age (4). The reasons for this discontinuation were not given in the publication.

In 1983, the AAP Committee on Nutrition discouraged the use of soy formulae in the dietary management of infants with documented allergy to cows' milk protein (77). The AAP Nutrition Committee concluded in 1998 that infants with documented cows' milk protein-induced enteropathy or enterocolitis are frequently sensitive to soy protein and should not be given soy protein formula routinely, whereas it emphasized that most infants with documented IgE-mediated cows' milk protein allergy will do well when fed soy formula (3). In 1990, the ESPGHAN Committee on Nutrition considered that available data did not support the view that soy formula should be the preferred choice in case of suspected or proven adverse effects to cows' milk protein (16). A joint statement of the ESPGHAN Committee on Nutrition and the European Society for Pediatric Allergology and Clinical Immunology stipulated that, in general, formulae based on intact soy protein isolates are not recommended for the initial treatment of food allergy in infants, although a proportion of infants with cows' milk protein allergy tolerate soy formula (11). The AAP Nutrition Committee stated in 2000 that infants with IgE-associated symptoms of allergy may benefit from a soy formula, either as the initial treatment or instituted after 6 months of age after use of a therapeutic hydrolysate formula (12).

The exclusion of soy protein from the diet of infants with IgE-mediated cows' milk protein allergy has been a controversial issue for a long time. In 93 children aged 3 to 41 months with IgE-mediated cows' milk protein allergy, Zeiger et al. (78) found a prevalence of concomitant soy allergy of only 14% (Table 2); 3% of the cohort were under 6 months of age at the time of evaluation and challenge. Diagnosis of soy protein allergy in this study was assessed by double-blind, placebo-controlled food challenge response to soy, open challenge response under the direction of a physician, or history of more than one immediate anaphylactic reaction to an isolated ingestion of soy. These investigators regard soy formula as a safe alternative to cows' milk formula for the vast majority of children with IgE-mediated cows' milk allergy, particularly those shown to have negative responses to soy challenge at the time of introduction of soy formula (78).

Klemola et al. (79) recently reported that the presence of concomitant soy allergy in infants with cows' milk allergy is less frequent than previously thought (Table 2). They conducted a prospective, randomized study to evaluate the cumulative incidence of allergy or other adverse reactions to soy formula compared with extensively hydrolyzed formula up to the age of 2 years in infants with

TABLE 2. *Studies on prevalence of soy allergy in immunoglobulin (Ig)E-associated cows' milk allergy (CMA) (78) and incidence of allergy to soy formula (SF) and extensively hydrolyzed formula (EHF) in cow's milk allergy (79)*

Reference	Study design	Allocation concealment	Blinding	Intention-to-treat analysis	Completeness to follow-up	Participants
Klemola et al., 2002 (79)	RCT	No	Single-blinded	Yes	Yes	n = 170 (with CMA confirmed by DBPCFC or history of an anaphylactic reaction)
Zeiger et al., 1999 (78)	Cohort study	NA	NA	NA	NA	n = 93, with IgE-mediated CMA

DBPCFC, double-blind, placebo-controlled food challenge; NA, not applicable RCT, randomized clinical trial; RR, relative risk; CI, confidence interval.

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confirmed cows' milk allergy. The parents suspected adverse reactions significantly more often in infants randomly assigned to the soy formula than in infants randomly assigned to the extensively hydrolyzed formula (28%; 95% CI 18–39% vs. 11%; 95% CI 5–19%, respectively; relative risk [RR], 2.48; $P = 0.006$). Physicians diagnosed adverse reactions more often with soy than with the extensively hydrolyzed formula (10%; 95% CI 4.4%–18.8% vs. 2.2%; 95% CI 0.3%–7.8%, respectively; RR, 4.50; $P = 0.031$). Adverse reactions to soy were similar in IgE-associated and nonIgE-associated cow's milk allergy (11% and 9%, respectively). Adverse reactions were more common in younger (<6 months) than in older (6 to 12 months) infants (5 of 20 vs. 3 of 60, respectively, $P = 0.01$).

The use of soy formulae may play a role in the etiology of peanut allergy. Evaluating data from the Avon longitudinal study, a geographic-defined cohort study of 13,971 preschool children, Lack et al. (80) showed that peanut allergy was independently associated with intake of soy milk or soy infant formula during the first 2 years of life (odds ratio 2.6; 95% CI 1.4–5.0), suggesting the possibility of cross-sensitization through common epitopes. Soy protein fractions have been shown to be homologous to major peanut proteins (81). It is likely that children with allergy to cows' milk are at increased risk for food allergies, and soy consumption in infancy is increased in response to these atopic disorders. Indeed, a history of allergy to cows' milk (reported prospectively at 6 months) was significantly associated with peanut allergy ($P = 0.03$). In their study assessing the long-term effects of soy protein formulae, Strom et al. (62) showed that, as adults, females who had received soy formula in infancy more frequently used antiallergic and antiasthmatic drugs (18.8% vs. 10.1%, $P = 0.047$), whereas males showed a similar but nonsignificant trend (15.8% vs. 10.2%, $P = 0.08$).

The Committee concludes that for treatment of cows' milk protein allergy, the use of therapeutic formulae based on extensively hydrolyzed proteins (or amino acid preparations if hydrolysates are not tolerated) should be preferred to that of soy protein formulae. Given the limited number of infants studied (78,79) and the higher reported rate of adverse reactions to soy protein in infants under 6 months of age (79), the Committee recommends that soy protein formulae should not be used in infants with food allergy during the first 6 months of life. If soy protein formulae are used for therapeutic use after the age of 6 months because of their lower cost and better acceptance, tolerance to soy protein should first be established by clinical challenge.

Prevention of Atopic Disease

The role of soy protein formulae for the prevention of allergic disease in healthy and at-risk infants has been controversial (76,82) and is not supported by evidence from controlled trials (83–87). A recent meta-analysis of five randomized and quasi-randomized clinical trials with appropriate methodology concluded that soy formulae do not prevent food allergy in high-risk infants (13). The joint statement of the European Society for Paediatric Allergology and Clinical Immunology Committee on Hypoallergenic Formulas and the ESPGHAN Committee on Nutrition did not support the use of soy protein formulae for the prevention of allergy in at-risk infants (11).

Infantile Colic and Regurgitation

Soy protein formulae have been widely used in the industrialized countries for symptoms such as infantile colic, regurgitation, or prolonged crying without any convincing evidence for efficacy (23). Controversial data on the use of soy formulae have been obtained in infants with severe infantile colic attributed to cows' milk protein allergy (88,89). One randomized clinical trial showed a mean weekly duration of colic symptoms of 8.7 hours during treatment with soy formula, as compared with 18.8 hours during the control periods (mean difference = 10.1; 95% CI 3.8–16.5) (90). If persisting colic is defined as weeks in which there were 9 or more hours of colic symptoms, then colic persisted in only 31.6% of infants during the soy formula periods as opposed to 94.7% during the control periods (RR 0.33; 95% CI 0.017–0.65). The other randomized clinical trial of soy protein formulae did not allow firm conclusions to be drawn because of methodologic drawbacks (91). The meta-analysis of Lucassen et al. (92) collected 27

TABLE 2. *(continued).*

Age (mo)	Intervention group	Control group	Outcomes	Results	RR (95% CI)
2–11	SF (n = 80)	EHF (n = 90)	Parents suspected adverse reaction to the study formula	SF vs. EHF: 28% (95% CI 18–39) vs. 11% (95% CI 5–19)	2.5 (CI not given)
			DBPCFC confirmed adverse reaction to the study formula	SF vs. EHF: 10%; (95% CI 4.4–18.8) vs. 2.2%; (95% 0.3–7.8)	4.5 (1.1–18.4)
3–41	NA	NA	Soy allergy	14% (95% CI 7.7–22.7)	

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ntrolled trials on the effectiveness of diets, drug treatment, and behavioral interventions on infantile colic. Soy protein formulae were not effective when only trials of good methodologic quality were considered.

Ethical and Religious Considerations

Some parents (e.g., vegans) seek to avoid cows' milk based formulae for their infants for religious, philosophical, or ethical reasons. Soy protein infant formulae is an acceptable alternative for these families.

CONCLUSIONS

1. Cows' milk-based formulae should be preferred as the first choice for feeding healthy infants that are not fully breast fed.
2. Soy protein based formulae should only be used in specified circumstances because they may have nutritional disadvantages and contain high concentrations of phytate, aluminum, and phytooestrogens, the long-term effects of which are unknown.
3. Indications for soy formulae include severe persistent lactose intolerance, galactosemia, religious, ethical, or other considerations that stipulate the avoidance of cows' milk based formulae and treatment of some cases of cows' milk protein allergy.
4. The Committee recommends that the use of therapeutic formulae based on extensively hydrolyzed proteins (or amino acid preparations if hydrolysates are not tolerated) should be preferred to that of soy protein formula in the treatment of cows' milk protein allergy. Soy protein formula should not be used in infants with food allergy during the first 6 months of life. If soy protein formulae are considered for therapeutic use after the age of 6 months because of their lower cost and better acceptance, tolerance to soy protein should first be established by clinical challenge.
5. Soy protein formulae have no role in the prevention of allergic diseases.
6. There is no evidence supporting the use of soy protein formulae for the prevention or management of infantile colic, regurgitation, or prolonged crying.
7. Manufacturers should aim to reduce the concentrations of trypsin inhibitors, lectins, goitrogenic substances, phytate, aluminum, and phytoestrogens in soy protein formulae.

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