

Consensus Statement

Dietary fat intakes for pregnant and lactating women

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Consensus recommendations on behalf of the European Commission research projects Perinatal Lipid Metabolism (PeriLip; www.perilip.org) and Early Nutrition Programming (EARNEST; www.metabolic-programming.org), developed jointly with representatives of the Child Health Foundation (Stiftung Kindergesundheit; www.kindergesundheit.de), the Diabetic Pregnancy Study Group (DPSG; www.medfak.uu.se/dpsg), the European Association of Perinatal Medicine (EAPM; www.europerinatal.com), the European Society for Clinical Nutrition and Metabolism (ESPEN; www.espen.org), the European Society for Paediatric Gastroenterology, Hepatology and Nutrition, Committee on Nutrition (ESPGHAN; www.espghan.org), the International Federation of Placenta Associations (IFPA; <http://aculeate.hopto.org/IFPA>) and the International Society for the Study of Fatty Acids and Lipids (ISSFAL; email www.issfal.org.uk).

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Dietary fat intake in pregnancy and lactation affects pregnancy outcomes and child growth, development and health. The European Commission charged the research project PERILIP, jointly with the Early Nutrition Programming Project, to develop recommendations on dietary fat intake in pregnancy and lactation. Literature reviews were performed and a consensus conference held with international experts in the field, including representatives of international scientific associations. The adopted conclusions include: dietary fat intake in pregnancy and lactation (energy%) should be as recommended for the general population; pregnant and lactating women should aim to achieve an average dietary intake of at least 200 mg DHA/d; intakes of up to 1 g/d DHA or 2.7 g/d *n*-3 long-chain PUFA have been used in randomized clinical trials without significant adverse effects; women of childbearing age should aim to consume one to two portions of sea fish per week, including oily fish; intake of the DHA precursor, α -linolenic acid, is far less effective with regard to DHA deposition in fetal brain than preformed DHA; intake of fish or other sources of long-chain *n*-3 fatty acids results in a slightly longer pregnancy duration; dietary inadequacies should be screened for during pregnancy and individual counselling be offered if needed.

PUFA: DHA: Arachidonic acid: Lipid soluble antioxidants: Vitamin E: Vitamin C

The dietary fat intake of pregnant women affects pregnancy outcomes, and fat intake during pregnancy and lactation modulates the growth, development and health of their children. In view of the relevance of this issue for public health, the European Commission charged the European research project PeriLip (Influence of Dietary Fatty Acids on the Pathophysiology of Intrauterine Foetal Growth and Neonatal Development; <http://www.imperial.ac.uk/agriculturalsciences/PeriLip/>) in their project contract to develop recommendations

on dietary fat intake in pregnancy and lactation, based on current scientific evidence and any new findings from the PeriLip project. The PeriLip Steering Committee and the Project Coordinating Committee of the Early Nutrition Programming project (EARNEST, www.metabolic-programming.org) agreed to jointly perform this task, to approach it by a review of the available scientific evidence and by a consensus workshop with leading international experts in the area. Issues to be addressed included advisable intakes of dietary fat, fatty

Abbreviations: LC-PUFA, long-chain PUFA.

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acids and antioxidants during normal pregnancies and lactation. This report describes the conclusions drawn and recommendations made.

Methods

Berthold Koletzko and Irene Cetin were asked to coordinate the project and asked J. Thomas Brenna to join the coordination committee. Based on an initial search and review of the available scientific literature, critical topics were chosen and collaborators identified to perform the detailed literature reviews. The effects of *n*-3 PUFA intakes for women with low-risk pregnancies and with high-risk pregnancies were reviewed by Andrea Horvath, Berthold Koletzko and Hania Szajewska. Maternal PUFA intake during lactation and its effects on human milk composition and infantile outcome were reviewed by Hans Demmelmair and Berthold Koletzko. The effects of antioxidant intakes in pregnant and lactating women were reviewed by Hans Konrad Biesalski. Recent reviews of toxicological evaluations on sea fish consumption in women of childbearing age by the European Food Safety Authority as well as a Cochrane review on the effects of *n*-3 PUFA intakes and of antioxidants for pregnant women were also evaluated.

These reviews, further background information and pertinent publications were shared through a dedicated website with the participants of an expert workshop held from 11–14 September 2005 at Wildbad Kreuth, Bavaria, Germany. The invited participants were project partners of the PeriLip and EARNEST research projects with expertise in the field, experts nominated by scientific societies related to the area and experts in science, nutrition, clinical medicine and public health nominated by project partners. The workshop participants reviewed and discussed the systematic literature reviews mentioned earlier and other data presented at the workshop and they unanimously agreed on the conclusions presented herein.

Results of the evaluation

Total dietary fat intake

Pregnancy leads to a modest increase of energy needs in the order of 375, 1200, 1950 kJ per d for the first, second and third trimesters of pregnancy, respectively^{1,2}. Well-nourished lactating women have a net increase of energy needs of the order of 1900 kJ per d above the energy requirements of non-pregnant, non-lactating women. These added energy needs can normally be met by a modest increase in consumption of a balanced diet. There is no indication that recommendations for dietary total fat intake, expressed as a percentage of energy intake, need to differ in pregnancy and lactation from those for non-pregnant, non-lactating women.

Dietary fatty acid intake

No evidence was identified to demonstrate a need for changing the dietary fatty acid composition of pregnant or lactating women, with regard to the intake of saturated, trans-isomeric, MUFA and PUFA relative to recommended intakes for the

general population, except for the intake of *n*-3 long-chain PUFA (LC-PUFA).

The *n*-3 LC-PUFA, DHA, must be deposited in appreciable amounts in the central nervous system during the perinatal brain growth spurt, as well as in other membrane-rich tissues. Fetal DHA accretion amounts to about 30–45 mg per d in the last trimester of gestation, while arachidonic acid accretion mainly occurs postnatally^{3,4}. The pathways to form DHA from the precursor essential fatty acid, α -linolenic acid, exist in man. The fractional conversion of α -linolenic acid to *n*-3 LC-PUFA may be greater in women than in men, which may contribute to meeting the demands of the fetus and the breast-fed neonate for DHA, but most evidence indicates that the overall contribution of α -linolenic acid to DHA is limited; therefore, adequate intakes of preformed *n*-3 LC-PUFA, and in particular DHA, appear important for maintaining optimal tissue function^{5–7}. In intrauterine growth-restricted pregnancies, indications for reduced placental and/or fetal conversion of precursor essential fatty acids to LC-PUFA have been reported⁸. Moreover, recent data indicate a considerable inter-individual variation in the ability to convert the precursor α -linolenic acid to *n*-3 LC-PUFA, related to common polymorphisms in the human Δ -5 and Δ -6 desaturase genes FADS1 and FADS2⁹. Preformed DHA is preferentially transferred across the human placenta to the fetus mediated by specific transfer proteins^{10,11}. In non-human primates, preformed dietary DHA is about an order of magnitude more efficient as a source for the neonatal brain accretion of DHA than is α -linolenic acid¹².

The effects of supplementing pregnant women with *n*-3 LC-PUFA from fish oil or single cell oils on pregnancy outcomes have been evaluated in a number of randomized controlled clinical trials, which provided daily DHA intakes ranging from 150–200 mg up to about 1200 mg/d, or up to 2.7 g total *n*-3 LC-PUFA/d. Systematic evaluation of these studies in recent meta analyses revealed that *n*-3 LC-PUFA prolonged gestation by a mean of 1.6 or 2.6 d in two independent analyses, respectively^{13,14}, accompanied by a slight increase of birth weight by a mean 47 or 54 g, respectively^{13,14} and reduced the risk of preterm birth before 34 weeks of gestation by 31 % in all pregnancies¹⁴ or by 61 % in high-risk pregnancies¹⁵. Except for some reported discomfort associated with the intake of *n*-3 oil capsules, such as belching and unpleasant taste, no adverse effects were detected up to the highest intake of 2.7 g total *n*-3 LC-PUFA/d tested in a randomized controlled trial in pregnancy.

Enhanced maternal dietary intakes of DHA increase fetal supply and lead to higher DHA concentrations in cord blood¹⁶. A higher DHA supply to the fetus during pregnancy and to the infant after birth was associated with beneficial effects on the development of visual acuity, cognitive functions and attention, maturity of sleep patterns, spontaneous motor activity, immune phenotypes in cohort studies and in a limited number of randomized clinical trials^{17–28}. Further randomized trials with large sample sizes of pregnant women are currently in progress, which should provide more information on the extent of benefits. Based on the information available at this time, it is advisable that pregnant women aim at achieving an average intake of at least 200 mg DHA/d. Supplementation of lactating women with 200 mg DHA/d increased human milk DHA content by

about 0.2% fatty acids to a level considered desirable for infant outcomes^{29,30}. Therefore, an average dietary intake of at least 200 mg DHA/d appears to be also adequate during lactation.

The desired average intake of at least 200 mg DHA/d can be reached with the consumption of one to two portions of sea fish per week, including oily fish such as herring, mackerel and salmon. Since fish can contribute significantly to the dietary exposure of contaminants such as methylmercury, dioxins and polychlorinated biphenyls, brominated flame retardants, camphechlor and organotin, the safety of fish consumption with particular regard to the vulnerable groups of pregnant and lactating women and their children has been reviewed^{31,32}. Levels of bioaccumulative contaminants tend to be greater in large fish that are higher in the food chain. Individuals consuming high levels of particular fish may exceed the provisional tolerable weekly intake, even without taking into account other sources of dietary exposure. The greatest susceptibility to the critical contaminants methylmercury and the dioxin-like compounds occurs during early development. Methylmercury is particularly toxic to the developing brain and may also adversely affect child growth^{20,33,34}. A woman can decrease the amounts of methylmercury in her body by reducing the intake of contaminated foods in the months prior to and during pregnancy. The fish with the highest methylmercury contents are predator fish such as marlin, pike, swordfish and shark; hence, women of childbearing age should not give undue preference to consumption of these fish species. In contrast, food choice during pregnancy has little effect on fetal exposure of dioxin-like compounds and polychlorinated biphenyls, because avoidance of contaminated foods would take many years to markedly decrease the amounts stored in the body. The fish with the highest levels of dioxin-like compounds and polychlorinated biphenyls are herring, which are caught from the wild, and salmon, which are mostly farmed. The European Food Safety Authority concluded that pregnant women eating up to two portions per week of fish are unlikely to exceed the provisional tolerable weekly intake for dioxin and dioxin-like compounds. However, particularly high levels of contamination are found in herring or wild salmon from the Baltic Sea and women of childbearing age should limit the consumption of Baltic Sea herring or wild salmon to no more than one portion per week.

Since cohort studies both in Europe and in the USA reported positive associations of higher fish intake by pregnant women with higher infant cognition, verbal intelligence quotient, pro-social behaviour, fine motor, communication and social development scores^{20,35}, the beneficial effects of regular fish consumption providing *n*-3 LC-PUFA during pregnancy appear to outweigh potential disadvantages from increased intakes of contaminants.

Plasma and tissue contents of the *n*-6 LC-PUFA arachidonic acid are relatively stable, even if pregnant women are supplemented with DHA-rich oils^{16,36}. Tissue arachidonic acid does not appear to be influenced by the dietary intake of preformed arachidonic acid as much as DHA. There are no indications that women of childbearing age with an adequate dietary intake of the precursor fatty acid linoleic acid would need an additional dietary supply of arachidonic acid.

Antioxidants

Oxidative stress has been implicated in many pathological processes during pregnancy, child birth and the postnatal period, but the possible preventive or therapeutic effects of antioxidants remain controversial^{37,38}. Recent systematic reviews on the effects from supplementation of antioxidant vitamins in pregnancy did not reveal conclusive evidence of benefits of intakes above reference nutrient intakes^{39,40–43}. A review of all randomized and quasi-randomized trials performed prior to 2005 on the effects of one or more antioxidants during pregnancy for the prevention of pre-eclampsia, which included seven trials involving 6082 women, found that supplementing women with any antioxidants during pregnancy, compared with control or placebo, was associated with a 39% reduction in the risk of pre-eclampsia and a 35% risk reduction of having a small-for-gestational-age infant⁴⁴. Infants of women receiving antioxidants also had a greater mean birth weight (weighted mean difference 92 g), but they were more likely to be born preterm (relative risk 1.38). However, the authors of the review point out that these data should be interpreted with caution because most of the data come from poor quality studies. Two further, large randomized controlled trials, with supplementation of high dosages of both vitamins C and E, did not show any reduction in the incidence of pre-eclampsia, but in one of the two trials vitamin C and E supplementation was associated with a significantly higher rate of low birth weight infants^{45,46}. Overall, the currently available data do not provide a basis for recommending antioxidant intakes for pregnant and lactating women in excess of reference nutrient intakes.

Conclusions and recommendations

1. Dietary fat intake during pregnancy and lactation, as a proportion of energy intake, should be the same as that recommended for the general population.
2. The *n*-3 LC-PUFA, DHA, must be deposited in adequate amounts in brain and other tissues during fetal and early postnatal life. Several studies have shown an association between maternal dietary intake of oily fish or oils providing *n*-3 LC-PUFA during pregnancy and/or lactation and visual and cognitive development as well as other functional outcomes of the infants. Pregnant and lactating women should aim to achieve a dietary intake of *n*-3 LC-PUFA that supplies a DHA intake of at least 200 mg/d. Intakes of up to 1 g/d DHA or 2.7 g/d *n*-3 LC-PUFA have been used in randomized trials without occurrence of significant adverse effects.
3. Women of childbearing age can meet the recommended intake of DHA by consuming one to two portions of sea fish per week, including oily fish, which is a good source of *n*-3 LC-PUFA. This intake of oily fish rarely exceeds the tolerable intake of environmental contaminants. Dietary fish should be selected from a wide range of species without undue preference for large predatory fish, which are more likely to be contaminated with methylmercury.

4. Intake of the precursor, α -linolenic acid, is far less effective with regard to DHA deposition in fetal brain than the intake of preformed DHA.
5. There is no evidence that women of childbearing age whose dietary intake of linoleic acid is adequate need an additional dietary intake of arachidonic acid.
6. Some studies have shown that maternal intake of fish, fish oils or *n*-3 LC-PUFA results in a slightly longer duration of gestation, a somewhat higher birth weight and a reduced risk of early preterm delivery. The clinical importance of such effects with regard to infant health has not been fully elucidated.
7. Screening for dietary inadequacies should be performed during pregnancy, preferably during the first trimester. If less than desirable dietary habits are detected, individual counselling should be offered during pregnancy as well as during lactation.

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References

1. Prentice AM & Goldberg GR (2000) Energy adaptations in human pregnancy: limits and long-term consequences. *Am J Clin Nutr* **71**, Suppl. 5, 1226S–1232S.
2. Butte NF & King JC (2005) Energy requirements during pregnancy and lactation. *Public Health Nutr* **8** (7A), 1010–1027.
3. Fleith M & Clandinin MT (2005) Dietary PUFA for preterm and term infants: review of clinical studies. *Crit Rev Food Sci Nutr* **45**, 205–229.
4. Martinez M & Mougan I (1998) Fatty acid composition of human brain phospholipids during normal development. *J Neurochem* **71**, 2528–2533.
5. Brenna JT (2002) Efficiency of conversion of alpha-linolenic acid to long chain *n*-3 fatty acids in man. *Curr Opin Clin Nutr Metab Care* **5**, 127–132.
6. Burdge GC & Calder PC (2005) Conversion of alpha-linolenic acid to longer-chain polyunsaturated fatty acids in human adults. *Reprod Nutr Dev* **45**, 581–597.
7. Innis SM (2005) Essential fatty acid transfer and fetal development. *Placenta* **26**, S70–S75.
8. Cetin I, Giovannini N, Alvino G, *et al.* (2002) Intrauterine growth restriction is associated with changes in polyunsaturated fatty acid fetal-maternal relationships. *Pediatr Res* **52**, 750–755.
9. Schaeffer L, Gohlke H, Muller M, *et al.* (2006) Common genetic variants of the FADS1 FADS2 gene cluster and their reconstructed haplotypes are associated with the fatty acid composition in phospholipids. *Hum Mol Genet* **15**, 1745–1756.
10. Larque E, Demmelmair H, Berger B, Hasbargen U & Koletzko B (2003) *In vivo* investigation of the placental transfer of (13)C-labeled fatty acids in humans. *J Lipid Res* **44**, 49–55.
11. Larque E, Krauss-Etschmann S, Campoy C, *et al.* (2006) Docosahexaenoic acid supply in pregnancy affects placental expression of fatty acid transport proteins. *Am J Clin Nutr* **84**, 853–861.
12. Greiner RC, Winter J, Nathanielsz PW & Brenna JT (1997) Brain docosahexaenoate accretion in fetal baboons: bioequivalence of dietary alpha-linolenic and docosahexaenoic acids. *Pediatr Res* **42**, 826–834.
13. Szajewska H, Horvath A & Koletzko B (2006) Effect of *n*-3 long-chain polyunsaturated fatty acid supplementation of women with low-risk pregnancies on pregnancy outcomes and growth measures at birth: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* **83**, 1337–1344.
14. Makrides M, Duley L & Olsen SF (2006) Marine oil, and other prostaglandin precursor, supplementation for pregnancy uncomplicated by pre-eclampsia or intrauterine growth restriction. *Cochrane Database Syst Rev* **3**, CD003402.
15. Horvath A, Koletzko B & Szajewska H (In Press) Effect of supplementation of women in high-risk pregnancies with long-chain polyunsaturated fatty acids on pregnancy outcomes and growth measures at birth: a meta-analysis of randomized controlled trials. *Br J Nutr*. Published online 10 April 2007. doi: 10.1017/S0007114507709078.
16. Krauss-Etschmann S, Shadid R, Campoy C, *et al.* (In Press) Fish oil and folate supplementation of pregnant women and maternal and fetal DHA and EPA plasma levels - a randomized European multicenter trial. *Am J Clin Nutr*.
17. Cheruku SR, Montgomery-Downs HE, Farkas SL, Thoman EB & Lammi-Keefe CJ (2002) Higher maternal plasma docosahexaenoic acid during pregnancy is associated with more mature neonatal sleep-state patterning. *Am J Clin Nutr* **76**, 608–613.
18. Helland IB, Smith L, Saarem K, Saugstad OD & Drevon CA (2003) Maternal supplementation with very-long-chain *n*-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. *Pediatrics* **111**, e39–e44.
19. Lauritzen L, Jorgensen MH, Mikkelsen TB, *et al.* (2004) Maternal fish oil supplementation in lactation: effect on visual acuity and *n*-3 fatty acid content of infant erythrocytes. *Lipids* **39**, 195–206.
20. Oken E, Wright RO, Kleinman KP, *et al.* (2005) Maternal fish consumption, hair mercury, and infant cognition in a U.S. Cohort. *Environ Health Perspect* **113**, 1376–1380.
21. Dunstan JA & Prescott SL (2005) Does fish oil supplementation in pregnancy reduce the risk of allergic disease in infants? *Curr Opin Allergy Clin Immunol* **5**, 215–221.
22. Jensen CL, Voigt RG, Prager TC, *et al.* (2005) Effects of maternal docosahexaenoic acid intake on visual function and neurodevelopment in breastfed term infants. *Am J Clin Nutr* **82**, 125–132.
23. Lauritzen L, Jorgensen MH, Olsen SF, Straarup EM & Michaelsen KF (2005) Maternal fish oil supplementation in lactation: effect on developmental outcome in breast-fed infants. *Reprod Nutr Dev* **45**, 535–547.
24. Dunstan JA, Simmer K, Dixon G & Prescott SL (2006) Cognitive assessment at 2 1/2 years following fish oil supplementation in pregnancy: a randomized controlled trial. *Arch Dis Child Fetal Neonatal Ed* 21 Dec.
25. Uauy R & Dangour AD (2006) Nutrition in brain development and aging: role of essential fatty acids. *Nutr Rev* **64** (5 Pt 2), S24–S33.
26. Jensen CL (2006) Effects of *n*-3 fatty acids during pregnancy and lactation. *Am J Clin Nutr* **83**, Suppl. 6, 1452S–1457S.
27. Hadders-Algra M, Bouwstra H, van Goor SA, Dijk-Brouwer DA & Muskiet FA (2007) Prenatal and early postnatal fatty acid status and neurodevelopmental outcome. *J Perinat Med* **35**, Suppl. 1, S28–S34.

28. Birch EE, Garfield S, Castaneda Y, Hughbanks-Wheaton D, Uauy R & Hoffman D (2007) Visual acuity and cognitive outcomes at 4 years of age in a double-blind, randomized trial of long-chain polyunsaturated fatty acid-supplemented infant formula. *Early Hum Dev* 18 Jan.
29. Fidler N, Sauerwald T, Pohl A, Demmelmair H & Koletzko B (2000) Docosahexaenoic acid transfer into human milk after dietary supplementation: a randomized clinical trial. *J Lipid Res* 41, 1376–1383.
30. Koletzko B, Agostoni C, Carlson SE, *et al.* (2001) Long chain polyunsaturated fatty acids (LC-PUFA) and perinatal development. *Acta Paediatr* 90, 460–464.
31. European Food Safety Authority (2007) Opinion of the Scientific Panel on Contaminants in the Food Chain on a request from the Commission related to mercury and methylmercury in food (Request N° EFSA-Q-2003-030, adopted on 24 February 2004). *The EFSA Journal* 34, 1–14.
32. European Food Safety Authority (2007) Opinion of the Scientific Panel on contaminants in the food chain on a request from the European Parliament related to the safety assessment of wild and farmed fish (Question N° EFSA-Q-2004-22, Adopted on 22 June 2005). *The EFSA Journal* 236, 1–118.
33. Grandjean P, White RF, Nielsen A, Cleary D & Oliveira Santos EC (1999) Methylmercury neurotoxicity in Amazonian children downstream from gold mining. *Environ Health Perspect* 107, 587–591.
34. Grandjean P, Budtz-Jorgensen E, Steuerwald U, *et al.* (2003) Attenuated growth of breast-fed children exposed to increased concentrations of methylmercury and polychlorinated biphenyls. *FASEB J* 17, 699–701.
35. Hibbeln JR, Davis JM, Steer C, *et al.* (2007) Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. *Lancet* 369, 578–585.
36. Klingler M, Demmelmair H, Larque E & Koletzko B (2003) Analysis of FA contents in individual lipid fractions from human placental tissue. *Lipids* 38, 561–566.
37. Shoji H & Koletzko B (2007) Oxidative stress and antioxidant protection in the perinatal period. *Curr Opin Clin Nutr Metab Care* 10, 324–328.
38. Herrera E, Ortega H, Alvino G, Giovannini N, Amusquivar E & Cetin I (2004) Relationship between plasma fatty acid profile and antioxidant vitamins during normal pregnancy. *Eur J Clin Nutr* 58, 1231–1238.
39. Van DE, Kulier R, Gulmezoglu AM & Villar J (2002) Vitamin A supplementation during pregnancy. *Cochrane Database Syst Rev* 4, CD001996.
40. Rumbold A, Middleton P & Crowther CA (2005) Vitamin supplementation for preventing miscarriage. *Cochrane Database Syst Rev* 2, CD004073.
41. Rumbold A & Crowther CA (2005) Vitamin C supplementation in pregnancy. *Cochrane Database Syst Rev* 2, CD004072.
42. Rumbold A & Crowther CA (2005) Vitamin E supplementation in pregnancy. *Cochrane Database Syst Rev* 2, CD004069.
43. Polyzos NP, Mauri D, Tsappi M, *et al.* (2007) Combined vitamin C and E supplementation during pregnancy for preeclampsia prevention: a systematic review. *Obstet Gynecol Surv* 62, 202–206.
44. Rumbold A, Duley L, Crowther C & Haslam R (2005) Antioxidants for preventing pre-eclampsia. *Cochrane Database Syst Rev* 4, CD004227.
45. Rumbold AR, Crowther CA, Haslam RR, Dekker GA & Robinson JS (2006) Vitamins C and E and the risks of preeclampsia and perinatal complications. *N Engl J Med* 354, 1796–1806.
46. Poston L, Briley AL, Seed PT, Kelly FJ & Shennan AH (2006) Vitamin C and vitamin E in pregnant women at risk for preeclampsia (VIP trial): randomised placebo-controlled trial. *Lancet* 367, 1145–1154.