



Conversion of Linolenic Acid to n-3 LCPUFA Metabolites: Estimates and Regulation

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Evidence for Linolenic and Linoleic Acid Conversion to n-3 and n-6 LCPUFA Metabolites

- *In vitro* studies:
 - enzyme, homogenized tissue, cultured cells
- Animal studies:
 - whole body balance, diet, tissue analysis, isotope
- Human studies:
 - controlled and habitual diet studies
 - ^{18}O - ^{18}O infusion (^{18}O - ^{18}O deficient patients)
 - stable isotope

**Bio-equivalence of Preformed 22:6n-3 vs. 18:3n-3
Derived 22:6n-3 in Baboons ^a**

Model	Tissue					Reference
	Brain	Retina	Liver	Plasma	RBC	
Fetus	20X*	23X	33X	no data	no data	Pediatric Res 1997
Fetus	8.1X**	13X	no data	no data	no data	J Lipid Res 2001
Neonate	7X***	12X	27X	29X	51X	Pediatric Res 1999

a) uptake of 13C-18:3n-3 derived 13C-22:6n-3 compared to preformed 13C-22:6n-3

* Bio-equivalence of preformed 22:6n-3 = 20 times 18:3n-3 derived 22:6n-3
Estimated maternal dietary 18:3n-3 intake of 0.45% en meets fetus needs

** 0.6% of 13c-18:3n-3 dose found in brain as 13c-22:6n-3

*** 0.23% (0.418 mg/d) of dietary 18:3n-3 converted to brain 22:6n-3

**Linolenic Acid Conversion: Human Adult Isotope Studies
Plasma Lipid Metabolites, % Label**

Diet	20:5n-3	22:5n-3	22:6n-3	Total n-3	Reference
Habitual ♀	21.1	5.9	9.2	36.2	Br J Nutr 2002
Habitual †	7.9	8.1	0.0	16.0	Br J Nutr 2002
Low n-3 †	12.8	6.6	3.9	23.3	J Lipid Res 2001
Low n-3 †*	9.3	4.8	1.6	15.7	J Lipid Res 2001
18:1n-9 †	2.6	0.9	0.3	3.8	Lipids 2000
18:3n-3 †	1.4	0.7	0.2	2.3	Lipids 2000
HI-DHA †	6.4	1.4	1.8	9.6	Lipids 1999
LO-DHA †	20.0	9.5	11.2	40.7	Lipids 1999
HI-18:2 †	3.4	2.6	3.6	9.6	BBA 1994
LO-18:2 †	8.0	4.2	4.0	16.2	BBA 1994
Beef ?	0.2	0.0015	0.0005	0.20	J Lipid Res 2001

♀ females † males †* males-blind † female & male ? unknown

Linoleic Acid Conversion: Human Adult Isotope Studies

Plasma Lipid Metabolites, % Label

Diet	18:3n-6	20:3n-6	20:4n-6	Total n-6	Reference
HI-22:6n-3 †	0.6	0.8	1.0	2.4	Lipids 1999
LO-22:6n-3 †	1.3	2.5	3.0	6.9	Lipids 1999
HI-20:4n-6 †	1.4	1.8	2.9	6.1	Lipids 1998
LO-20:4n-6 †	1.3	0.9	1.5	3.8	Lipids 1998
HI-18:2n-6 †	0.0	0.7	0.3	1.0	Lipids 1994
LO-18:2n-6 †	0.3	1.2	0.7	2.2	Lipids 1994
Habitual ☐	no data	1.6	0.20	1.7	J Lipid Res 1998
Low Fat ☐	no data	0.44	0.06	0.5	AJCN 2001

† male subjects ☐ mother's milk data

Linolenic Acid Conversion: Human Infant Isotope Studies

Infants	Diet	% 22:6n-3 Total Label	Reference
term	milk/formula	3.7 ☐	Pediatric Res 2000
pre-term	milk/formula	18.4 ☐	Pediatric Res 2000
low growth	milk/formula	11.1 ☐	Pediatric Res 2000
pre-term	3.2% 18:3n-3	1.8 †	Pediatric Res 1997
term	3.2% 18:3n-3	2.0 †	Pediatric Res 1997
term	0.4% 18:3n-3	6.9 †	Lipids 1996
term	1.0% 18:3n-3	12.1 †	Lipids 1996
term	3.2% 18:3n-3	9.7 †	Lipids 1996
pre-term	10:1 n-6/n-3	14.1 †	Pediatric Res 1996

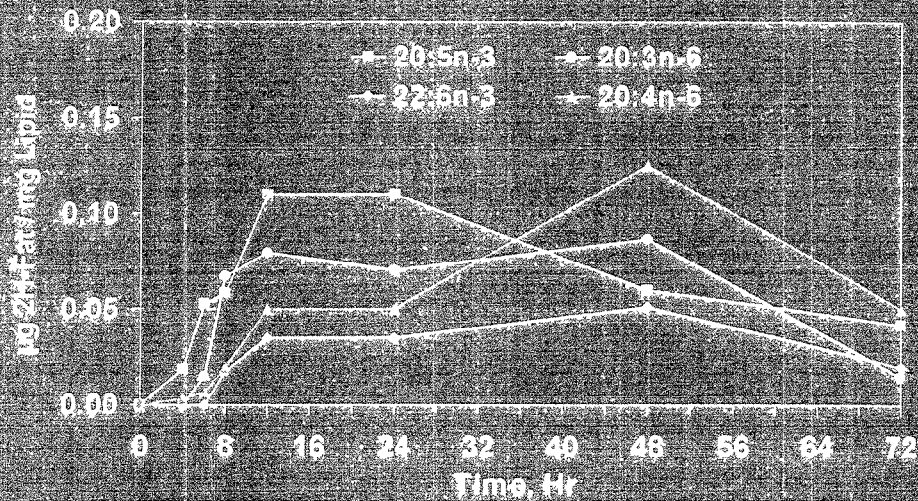
☐ max. enrich. data † kinetic model data † AUC data

Linoleic Acid Conversion: Human Infant Isotope Studies

<u>Infants</u>	<u>Diet</u>	<u>% 20:4n-6</u> <u>Total Label</u>	<u>Reference</u>
term	milk/formula	0.6 □	Pediatric Res 2000
pre-term	milk/formula	4.3 □	Pediatric Res 2000
low growth	milk/formula	14.6 □	Pediatric Res 2000
new born	not fed	1.2 †	Pediatric Res 1999
pre-term	3.2% 18:3n-3	2.6 †	Pediatric Res 1997
term	0.4% 18:3n-3	5.9 †	Lipids 1996
term	1.0% 18:3n-3	4.4 †	Lipids 1996
term	3.2% 18:3n-3	2.7 †	Lipids 1996
pre-term	10:1 n-6/n-3	6.1 †	Pediatric Res 1996

□ max. enrich. data † kinetic model data † AUC data

LCPUFA Metabolites in Total Plasma of Adult Male Fed 2H-18:2n-6 and 2H-18:3n-3

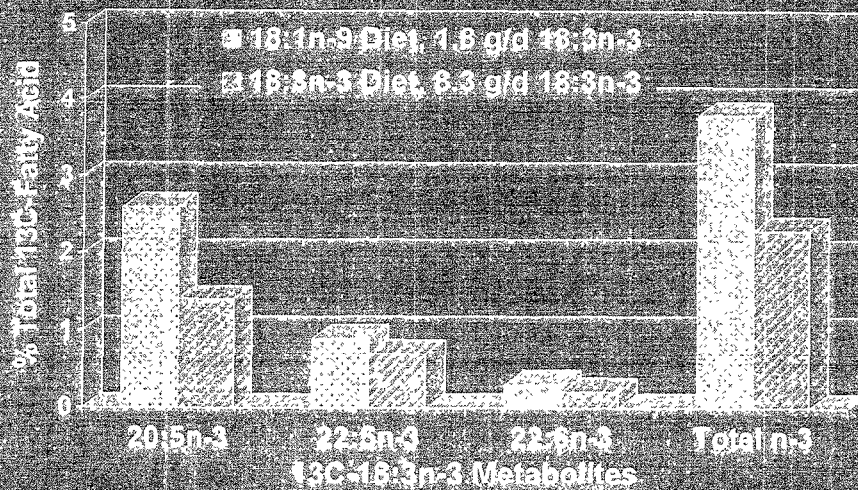


Factors that Influence 18:3n-3 and 18:2n-6 Conversion and Metabolite Accretion

- Substrate inhibition
- Product inhibition
- Competitive inhibition
- Gender (men vs. women)
- Age (infant vs. adult)
- Age (infants vs adult)
- Diseases and disorders
- Genetics
- Physiological (stress, pregnancy)
- Unknown / other

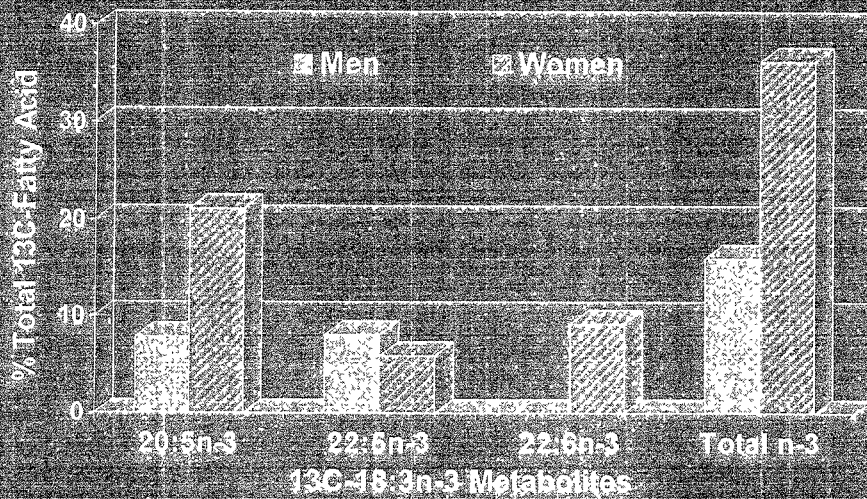
Substrate Inhibition: Human Plasma Total Lipid

Calculated from maximum enrichment data. *Lipids* 35:137, 2000

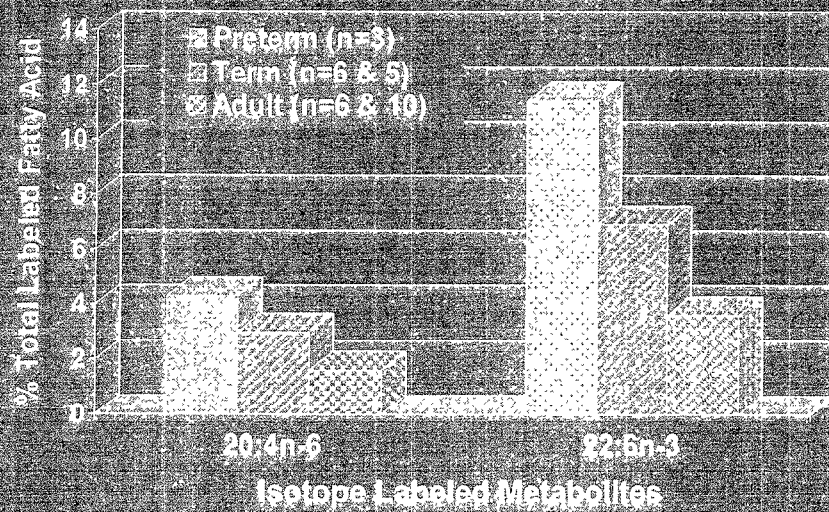


Gender Factor: Men vs. Women

Br. J. Nutr. 88:355, 2002 and Br. J. Nutr. 88:411, 2002



Age Factor: Infants vs. Adults



**Summary of Stable Isotope Results:
Percent Conversions for Linolenic and Linoleic Acid**

18:3n-3	# Subject	# of	20:5n-3 ± SD	22:6n-3 ± SD
	Groups	Subjects	%	%
Males, adult	10	47	9.2 ± 6.8	3.6 ± 3.8
Term Infants	6	59	—	7.6 ± 4.2
Preterm Infants	3	30	—	11.4 ± 8.6

18:2n-6	# Subject	# of	20:3n-6 ± SD	20:4n-6 ± SD
	Groups	Subjects	%	%
Males, adult	7	25	1.3 ± 0.7	14 ± 1.3
Term Infants	7	69	—	4.3 ± 5.0
Preterm Infants	3	30	—	4.3 ± 1.7

**Controlled Diet and Vegetarian Studies
Fatty Acid, %**

Subjects	Diet	18:3n-3 (g/d)	Tissue	Fatty Acid, %			Ref.
				18:3n-3	20:5n-3	22:6n-3	
Men	Flax oil	20.5	Serum	3.2	0.6	1.1	Kelly
Men	Control	0.8	Serum	0.5	0.5	1.1	Lipids, 93
Men	Mix Veg	13.0	Platelet PC	0.4	0.2	0.5	Chan
Men	Mix Veg	4.0	Platelet PC	0.2	0.1	0.6	Lipids, 95
Nuns	Canola	3.6	Serum PL	0.3	0.8	6.1	Lasserre
Nuns	Sun oil	0.3	Serum PL	<0.01	0.8	4.0	Lipids, 85
Infant	n6/n3=44	—	Plasma PL	0.90	0.11	1.13	Jensen
Infants	n6/n3=5	—	Plasma PL	0.48	0.29	1.72	Lipids, 96
Vegan	Habitual	no data	RBC	0.1	0.5	3.3	Agren
Omnivore	Habitual	no data	RBC	0.1	1.4	6.7	Lipids, 95

Estimated Synthesis of n-6 and n-3 Metabolites

Life Stage	Fatty Acid	AI †	AI † g/d	% ‡	Calc. Synthesis, mg/d		
					20:4n-6	22:6n-3	Total n-3
Males, 19-50 yr	18:2n-6	17	1.6	n=6	272	—	—
	18:3n-3	1.6	3.6	n=9	—	58	277
Female, 19-50 yr	18:2n-6	17	no data		—	—	—
	18:3n-3	1.1	9.2	n=1	—	101	398
Infants, 0-6 mo.	18:2n-6	4.4	3.0	n=5	132	—	—
	18:3n-3	0.5	6.9	n=5	—	35	65

† AI = adequate intake reference value listed in DRI 2002 report

‡ % = avg. % conversion based on human isotope data; n = # of studies

