

The Mean of Milk: A Review of Human Milk Oligosaccharide Concentrations throughout Lactation

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To understand the calculation of data into a pooled scenario, it is important to know that humans can be categorized into 4 distinct milk groups observed in various frequencies across populations. The milk groups are categorized according to the presence (or absence) of the specific oligosaccharide products of 2 distinct fucosyltransferase enzymes, namely α 1,2- and α 1,4 fucosyltransferase, encoded by the genes FUT2 and FUT3, respectively.

Milk group 1 is known as Lewis-positive secretor mothers with Lewis blood group (Lea- b+) expressing both FUT2 and FUT3 thus can synthesize both α 1,2- and α 1,4-fucosylated HMOs. Milk group 2 is Lewis-positive non-secretor mothers with Lewis blood group (Lea+ b-) expressing FUT3 but not FUT2 and thus produce α 1,4-fucosylated HMOs but not α 1,2-fucosylated HMOs. Milk group 3 is Lewis-negative secretor mothers with Lewis blood group (Le a- b-) expressing FUT2 but not FUT3 and therefore can synthesize α 1,2-fucosylated but not α 1,4-fucosylated HMOs.

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Finally, milk group 4 is Lewis-negative non-secretor mothers with Lewis blood group (Lea- b-) expressing neither FUT2 nor FUT 3 therefore cannot produce neither α 1,2- not α 1,4-fucosylated HMOs.

Table below illustrates the typically observed proportions of the four milk groups in humans. Some studies expressed concentration data simply as secretor (group 1+3) or non-secretor (2+4) while some studies distinctively categorized subjects by one of the four milk groups.

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Table S1. Genetic background in population was used as the basis of the pooling calculations, where unpooled levels were converted into a pooled level using the below stated percentage ratios.

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Secretor Status	Secretor	Non-secretor	Secretor	Non-secretor
Milk Group	1	2	3	4

Milk Phenotype	Se+ / Le (a-b+)	Se- / Le (a+b-)	Se+ / Le (a-b-)	Se- / Le (a-b-)
α1,2-fucosylated HMOs (FUT2 enzyme)	+	-	+	-
α1,3-fucosylated HMOs (FUT3, FUT5, FUT6 enzymes)	+	+	+	+
α1,4-fucosylated HMOs (FUT3 enzyme)	+	+	-	-
Typically observed frequency	~ %70	~ %20	~ %9	~ %1
HMOs contained	2FL, LNFP I, LNDFH I, LNT, 3FL, DSLNT, LDFT, 6SL, LNFP III, DF-LNH I, LNFP II, LSTc, F-LNH II, LNnT, LNFP V, LNDFH II, 3SL, LSTa, F-LNH I, LNnH, LNH, LSTb, FSL	LNT, 3FL, DSLNT, 6SL, LNFP III, LNFP II, LSTc, F-LNH II, LNnT, LNFP V, LNDFH II, 3SL, LSTa, LNnH, LNH, LSTb, FSL	2FL, LNFP I, LNT, 3FL, DSLNT, LDFT, 6SL, LNFP III, LNFP II, DF-LNH I, LSTc, F-LNH II, LNnT, LNFP V, LNDFH II, 3SL, LSTa, F-LNH I, LNnH, LNH, LSTb, FSL	LNT, 3FL, DSLNT, 6SL, LNFP III, LSTc, F-LNH II, LNnT, LNFP V, 3SL, , LSTa, LNnH, LNH, LSTb, FSL

1. When Lewis milk group was not given, secretor (Lewis group 1+3) values were multiplied by 0.8 (80% of the population), and non-secretor (Lewis group 2+4) values were multiplied by 0.2 (20% of the population). This calculation was followed only for the FUT2 dependent HMOs: 2'-FL, LNFP I, LNDFH I, LDFT, DF-LNH I (a), F-LNH I, FS-LNH, S-LNFP I, TF-LNH, DF-LNH III (c).

Paper	Sample	Country	Lactation phase	Milk group	Milk type	2'-FL
<i>Sprenger et al. PlosOne 2017</i>	34	Singapore	10 - 60 days	1+3	Secretor	2.170
<i>Sprenger et al. PlosOne 2017</i>	34	Singapore	10 - 60 days	2+4	Non-secretor	0.026

Equation 1)

$$2'-\text{FL}_{1+3} = 2.180 \text{ g/L}$$

$$2'-\text{FL}_{2+4} = 0.026 \text{ g/L}$$

$$2'-\text{FL}_{\text{pooled}} = (2.170 \cdot 0.8) \text{ g/L} + (0.026 \cdot 0.2) \text{ g/L}$$

$$2'-\text{FL}_{\text{pooled}} = 1.7412 \text{ g/L}$$

2. When Lewis milk group was specifically given, values were multiplied by 0.7 for milk group 1 (70% of the population), 0.2 for milk group 2 (20% of the population), 0.09 for milk group 3 (9% of the population), 0.01 for milk group 4 (1% of the population). This calculation was followed for all analyzed HMOs.

Paper	Sample	Country	Lactation phase	Milk group	Milk type	3 FL
<i>Austin et al. Nutrients 2019</i>	28	Switzerland	0-5 days	1	Secretor	0,212
<i>Austin et al. Nutrients 2019</i>	28	Switzerland	0-5 days	2	Non-secretor	0,995
<i>Austin et al. Nutrients 2019</i>	28	Switzerland	0-5 days	3	Secretor	0,039
<i>Austin et al. Nutrients 2019</i>	28	Switzerland	0-5 days	4	Non-secretor	0,224

Equation 2)

$$3\text{FL}_1 = 0.212 \text{ g/L}$$

$$3\text{FL}_2 = 0.995 \text{ g/L}$$

$$3FL_3 = 0.039 \text{ g/L}$$

$$3FL_4 = 0.224 \text{ g/L}$$

$$3FL_{pooled} = (0.212 \cdot 0.7) \text{ g/L} + (0.995 \cdot 0.19) \text{ g/L} + (0.039 \cdot 0.1) \text{ g/L} + (0.224 \cdot 0.01) \text{ g/L}$$

$$3FL_{pooled} = 0.344 \text{ g/L} \quad (2)$$

Numbers in red are the result of pooling calculations. This method of pooling was followed for the 15 papers where trial subjects were divided according to their milk groups.