At the request of FSANZ, Abbott Nutrition addresses below the safety and suitability of the use of short-chain fructooligosaccharides (scFOS) in infant and follow-on formulas to meet clauses (d), (e) and (j) of the 2011 Ministerial Policy Guideline on the regulation of infant formula products.

*d) The composition of infant formula must be safe, suitable for the intended use and must strive to achieve as closely as possible the normal growth and development (as measured by appropriate physiological, biochemical and/or functional outcomes) for healthy full term exclusively breastfed infants when infant formula used as the sole source of nutrition up to six months of age.*

*e) The composition of follow-on formula must be safe, suitable for the intended use and must strive to achieve as closely as possible the normal growth and development (as measured by appropriate physiological, biochemical and/or functional outcomes) for healthy full term exclusively breastfed infants when follow-on formula used as the principal source of liquid nourishment in a progressively diversified diet.*

Exclusively breastfed infants consume total oligosaccharides roughly in the range of 5 to 10g per day, assuming typical concentrations in human milk and an approximate human milk intake of 750 mL per day (Raiten, Talbot, & Waters, 1998). These human milk oligosaccharides are not currently available to provide in infant formula. However, a recognized source of oligosaccharides with demonstrated safe use are the β-2,1 fructans. In Japan, scFOS has been, used extensively in infant formula and foods for young children for many years, with the acceptable intake level of 4.2 g scFOS/day determined for infants less than one year of age based primarily on published safety and tolerance information from a large nationwide survey of infants in Japan (Yamamoto & Yonekubo, 1993). In that survey of 20,742 infants (up to 4.5 months of age), physical growth, nutritional intake, faecal properties and general health parameters for both breast milk- and infant formula‐fed infants were reported. No adverse effects were reported for any of the health parameters surveyed. Based on the concentration of scFOS in infant formula in Japan at the time of the survey (3.2 g scFOS/L), infants were estimated to consume a mean and 90th percentile intake of 3.0 and 4.2 g/day of scFOS, respectively.

A systematic review of randomized controlled trials evaluating the efficacy and safety of prebiotic supplementation in full‐term infants (Rao et al., 2009), made no differentiation of the oligofructan types in the selection criteria, including the 2006 study of Bettler and Euler (oligofructose supplemented) alongside other prebiotics. The conclusion of Rao et al (2009) was that prebiotic-supplemented formula is well tolerated by term neonates, and that it results in beneficial changes to bacterial microflora, and stool consistency that is similar to those of breastfed infants, without compromising weight gain. Several recent reviews of the roles of oligosaccharides in infant formula recognize scFOS as one of the range of prebiotics substances suitable for this purpose (Braegger et al., 2011; Sherman et al., 2009). Additionally, a study cited in the dossier that evaluated the effects of infant consumption and tolerance to oligofructose/inulin containing formulas was recently published by the Journal of Pediatric Gastroenterology and Nutrition (Veereman-Wauters et al., 2011). This work demonstrates the safety and suitability over a period of 28 days of a combination of short and long-chain inulin-derived fructooligosaccharides. It also confirmed that infants fed formulas with a combination of scFOS and lcFOS had softer stools, with no effects on hydration status, when compared to those fed the control formula. Moreover the total number of fecal bacteria was observed to increase, and more closely resembled the pattern from human milk-fed infants.

Abbott Nutrition has conducted multiple prospective, randomized, controlled clinical trials demonstrating that infant and toddler growth, tolerance and formula intake were not different when infants consuming scFOS-containing formula were compared to those consuming either a control formula without scFOS or human milk. A review of the infant and toddler trials is shown in the Table 1, which displays growth results for over 300 infant and toddlers fed various levels of scFOS. There were no significant differences in infant body weight gain over the duration of the studies when compared within study formula groups, and the values were in line with reported expected infant weight gains per age (Guo et al., 1991). These studies are further elaborated in Application A1055 and demonstrate substantively that formulas containing scFOS are safe, well tolerated, suitable for the intended use and meet the standards set by recognized international experts for healthy term breastfed infants.

*(j) Substances subject to pre-market assessment for use in infant formula and follow-on formula should have a substantiated beneficial role in the normal growth and development of infants or children, or a technological role, taking into account, where relevant, the levels of comparable substances in breastmilk. A substance’s role in normal growth and development is substantiated where there is appropriate evidence to link the physiological, biochemical and/or functional effects of the substance to specific health outcomes for infants, in infancy or childhood. Particular caution should be applied by the authority where such links are less clear.*

A wide variety of oligosaccharides have been detected in human milk, some of which may contribute to the anti‐infective and allergy-preventive properties of human milk. The carbohydrates in greatest abundance in human milk comprise lactose (~7% of the milk) and oligosaccharides (1‐2%). Oligosaccharides with a degree of polymerization (DP) of 3‐10 are found in human milk. These human milk oligosaccharides account for the third largest component of human milk, with the peak concentration of around 25 g/L in the colostrum during the first few weeks following birth and decline thereafter in normal human milk.

Because of the presence of oligosaccharides in human milk, the non-digestible substances scFOS and oligofructose have been developed for addition to infant formula and foods to mimic the effects of oligosaccharides that occur naturally in breast milk. These substances are not absorbed in the small intestine and reach the large intestine essentially intact. Breastfed infants generally have a specific pattern of intestinal bacteria which can impart defensive benefits in the gastrointestinal tract. They also have softer stools compared with formula fed infants and these differences may be due in part to the presence of oligosaccharides in breast milk. In currently marketed infant formulas, the inulin-derived fructooligosaccharides (both short- and long-chain) and the short-chain galactooligosaccharides (scGOS) provide that functionality for infants fed formulas containing those oligosaccharides. The scFOS described in Application A1055 may be added to infant formula to similarly provide this functionality that breastfed infants routinely obtain from human milk, and to soften stool consistency. The safety and suitability for the appropriateness of addition level have been evaluated in clinical studies to ensure safe use in the intended population (see above (d), (e)).

It is of interest to note, recent publications now refer more correctly to galacto-oligosaccharides (GOS) as short-chain GOS (scGOS), whereas earlier literature simply used the term GOS. This reflects the true nature of the lactose derived scGOS which are manufactured using similar technology to scFOS, that is, cleavage of the disaccharide followed by elongation. Furthermore, scFOS is enzymatically synthesized from sucrose, and has the technological advantage over the inulin-derived fructooligosaccharides in that it will not undergo Maillard browning to the same extent during manufacture of infant formula because the end sugar is a sucrose moiety, a non-reducing sugar which does not interact with amino groups.

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# **Table 1: Abbott Studies Demonstrating Normal Growth of Infants Consuming Short-chain Fructooligosaccharides in Infant and Toddler Formulas**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Abbott, 2011d (2 wk)**  **Milk-based** | | | **Abbott, 2011d (16 wk)**  **Milk-based** | | | **Abbott, 2011 (4 wk; Confidential submittal)**  **Milk-based** | | | | **Abbott, 2011a (5 wk)**  **Soy-based** | | | **Abbott, 2011c (16 wk)**  **Milk-based** | |
| **scFOS Level (g/L)** | **0** | **1.5** | **3.0** | **0** | **1.5** | **Human Milk** | **0** | **2.0** | **3.0** | **Human**  **Milk** | **0** | **2.5** | **2.5\*** | **0** | **3.4** |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Enrolled (M/F) [completed]** | 23 (18/5)  [20] | 22 (13/9)  [17] | 21 (11/10)  [16] | 52 (25/27) [34] | 50 (23/27) [36] | 25 (13/12) [23] | 24 (11/13)  [19] | 25 (14/11)  [18] | 26 (15/11)  [23] | 22 (13/9)  [19] | 62(31/31)  [50] | 64 (32/32)  [55] | 62 (30/32)  [54] | 144 (81/63)  [124] | 139 (79/60)  [118] |
| **Age at study entry (day)** | 39 ± 2 a | 41 ± 3 a | 49 ± 3 b | 7 (1-18) a | | 0 (0 – 9) b | 2.5 ± 0.2 | 2.2 ± 0.3 | 2.3 ± 0.3 | 1.6 ± 0.2 | 5.3 ± 0.02 | 4.8 ± 0.03 | 5.3 ± 0.02 | 19.7 (median) 18.5 (median)  10 – 24 months | |
| **Weight at study entry (g)** | 4737 ± 206 (23) | 4692 ± 157 (22) | 4957 ±156 (21) | 3334 ± 66 (47) | 3474 ± 66 (49) | 3545 ± 98 (25) | 3204 ± 76  (24) | 3387 ± 99  (25) | 3367 ± 79  (26) | 3361 ± 82  (22) | 3297  58 (62) | 3311  50 (64) | 3150  48 (62) | 10,914 ± 120  (144) | 10,936 ± 134  (139) |
| **Weight gain (g/d)** | 28.2 ± 4.0  (21) | 29.2 ± 2.3 (18) | 25.4 ± 2.0 (18) | 24.6 ± 1.0 (33) | 23.1 ± 1.0 (36) | 20.8 ± 2.0 (23) | 39.5 ± 2.3  (20) | 36.2 ± 2.5  (21) | 39.0 ± 1.8  (23) | 36.3 ± 3.0  (20) | 35.1  1.6 (50) | 34.7  1.4 (54) | 35.6  1.4 (54) | 5.7 ± 0.6  (124) | 6.4 ± 0.6  (118) |

All values are mean ± SEM (n). Within studies, values with different superscripts are significantly different (p<0.05). \* Product was sucrose-free.