Annex A - Statement on vitamin D Exposure Levels in Formula Fed Infants and Children

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A summary of EFSA’s Vitamin D Tolerable Upper Level (TUL) For 6-12 month-olds

1. In 2018, on the basis of the information that was available, EFSA's NDA Panel were unable to define a NOAEL for vitamin D intake (EFSA, 2018). However, the Panel identified a serum 25(OH)D concentration of ≤200 nmol/L which they considered unlikely to pose a risk of adverse health outcomes in healthy infants. This concentration was based on published studies in which no clinical symptoms suggestive of hypercalcaemia or abnormal growth were observed in infants who, following varying levels of daily vitamin D supplementation, had serum 25(OH)D concentrations >125 nmol/L (Valkama *et al*., 2017), >150 nmol/L (Czech-Kowalska *et al.,* 2012; Holmlund-Suila *et al*., 2012), >200 nmol/L (Gallo *et al*., 2013), or >250 nmol/L (Grant *et al.,* 2014).

2. In reaching the concentration value of ≤200 nmol/L, the Panel had also considered previous assessments of EFSA and other bodies that discussed 'high' serum 25(OH)D concentrations (though not specifically for infants), where the values ranged from 125 to 250 nmol/L. For example, the NDA Panel (2016) previously considered that a concentration >220 nmol/L may lead to hypercalcaemia (EFSA, 2016).

3. The Panel recognised that a 'high' serum 25(OH)D concentration is not an adverse health outcome per se, but can be considered as a surrogate endpoint. Thus, regarding the serum 25(OH)D concentration of ≤200 nmol/L, the NDA Panel noted that this level "should not be regarded as a cut-off for toxicity but as a conservative value from which a UL could be derived".

4. The NDA Panel used the serum concentration of 200 nmol 25(OH)D/L as the basis for establishing new TULs for infants: 25 µg/person/day for 0 - <6 month-olds, and 35 µg/day for 6 - <12 month-olds. Further details on the derivation of these TULs are provided in EFSA (2018, Annex A).

5. Briefly, the NDA Panel assessed the dose-response relationship between 'high' intake levels of vitamin D in a healthy population of infants (ages 0 - <12 months) and their corresponding mean serum concentrations of 25(OH)D. 'High' vitamin D intake levels are those that lead to 'high' serum concentrations of 25(OH)D.

6. These dose-response data were collected from EFSA's systematic review of literature studies (EFSA, 2018). In these studies, however, vitamin D intakes from the background diet of 0 - <12 month-olds (i.e. from infant formulae and other fortified and unfortified foods for infants) were rarely measured or reported.

7. Therefore, the NDA Panel established their intake-response relationship for vitamin D only on the basis of the additional dose of vitamin D provided in the study, which was always through a supplement (not a fortified food).

8. The Panel therefore assumed that there is no difference in vitamin D bioavailability when supplemented, naturally present, or added to food. The same assumption was applied to the form of supplementation, e.g. as drops or pills. Indeed, the NDA Panel had previously noted in 2016 that "limited data are available on the effect of the food or supplement matrix on absorption of vitamin D (vitamin D2 or D3), and that age *per se* has no effect on vitamin D absorption efficiency" (EFSA, 2016).

9. The NDA Panel therefore considered that their assessment of vitamin D intakes (from supplements only) is an underestimation of infants' actual (total) vitamin D intake. Subsequently, the Panel considered that by not including the background intake, this leads to an "underestimation of the vitamin D dose corresponding to the UL and assessed the approach as conservative".

10. Using a dose-response dataset derived from the literature studies that EFSA reviewed in 2018, the NDA Panel created a "mixed-effect meta-regressive model" to compute percentages of infants expected to exceed a serum concentration of 200 nmol/L of 25(OH)D following different intakes of vitamin D (between 5 and 50 µg/person/day with a step size of 5 µg). The NDA Panel concluded that this model (which uses the assumption of linearity) "seems to fit the data relatively well, except at high vitamin D intake (i.e. ≥40 µg/person/day), where most of the points systematically lie above or below the regression line". The serum concentrations were plotted on the original (non-logarithmic) scale and also on a natural logarithmic-transformed scale.

11. As noted above, the NDA Panel considered 200 nmol/L to be a serum concentration of 25(OH)D below which adverse effects (hypercalciuria, hypercalcaemia, nephrocalcinosis, abnormal growth) would be unlikely to occur in infants.

12. These percentages are shown in Table 15 (0 - <6 month-olds) and Table 16 (6 - <12 month-olds) of EFSA's Annex A (EFSA, 2018). These Tables indicate that at any given intake of vitamin D, 6 - <12 month-olds achieve lower serum 25(OH)D concentrations than 0 - <6 month-olds (who also have the same baseline serum 25(OH)D concentrations). This information is also shown in Tables 1-2 below.

13. For example, for 0 - <6 month-olds, based on the results of the model (original scale), at a vitamin D intake of up to 25 µg/person/day, depending on the baseline serum 25(OH)D concentration, 0 - 4 % of these individuals would achieve serum 25(OH)D concentrations >200 nmol/L (Table 1). Meanwhile, for 6 - <12 month-olds, the percentage of individuals exceeding serum 25(OH)D concentrations of 200 nmol/L would be 0 - 1 % at supplemental vitamin D intakes of up to 25 µg/person/day, and 1 - 4 % for intakes of up to 35 µg/person/day (Table 2). This information is shown below in Table 1 (0 - <6 month-olds) & Table 2 (6 - <12 month-olds), which are adapted from EFSA's annex.

Table 1: Percentage of 0 - <6 month-olds exceeding serum 25(OH)D concentrations of 200 nmol/L (using model in original scale).

Vitamin D intake (µg/person/day)	**% infants with serum 25(OH)D concentration >200 nmol/L (using baseline concentration of 10 - 30 nmol/L)**	**% infants with serum 25(OH)D concentration >200 nmol/L (using baseline concentration of 30 - 60 nmol/L)**	**% infants with serum 25(OH)D concentration >200 nmol/L (using baseline concentration of 60 - 100 nmol/L)**
5-10	0	0	0
10-15	0	0	1
15-20	0	1	2
20-25	0	2	4
25-30	1	3	7
30-35	3	6	11

Table 2: Percentage of 6 - <12 month-olds exceeding serum 25(OH)D concentrations of 200 nmol/L (using model in original scale).

Vitamin D intake (µg/person/day)	% infants with serum 25(OH)D concentration >200 nmol/L (using baseline concentration of 10 - 30 nmol/L)	% infants with serum 25(OH)D concentration >200 nmol/L (using baseline concentration of 30 - 60 nmol/L)	% infants with serum 25(OH)D concentration >200 nmol/L (using baseline concentration of 60 - 100 nmol/L)
5-10	0	0	0
10-15	0	0	0
15-20	0	0	0
20-25	0	0	1
25-30	0	1	2
30-35	1	2	4

14. The NDA Panel emphasised that these exceedance percentages should not be interpreted as “precise estimates”, but rather “informed quantitative judgements”.

15. In summary, results of the NDA Panel’s analysis indicated that a larger dose of vitamin D (35 µg/person/day) is needed for 6 - <12 month-olds to have the same serum 25(OH)D concentrations as 0 - <6 month-olds (25 µg/person/day). The NDA Panel noted that this may be explained by 6 - <12 month-olds having a larger body mass than 0 - <6 month-olds (EFSA, 2018).

16. The NDA Panel had discussed whether, in their model, mean body weight or mean age was more relevant to explain serum 25(OH)D concentrations. Age was selected because age was always reported for the study participants in the literature studies reviewed, whereas body weight was sometimes missing.