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March 27, 2018

Name of Petitioner: Organic & Natural Health Association

Post office address: P.O. Box 42385  
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Subject of the petition: Petition for a health claim for the relationship between vitamin D<sub>3</sub> and a decreased risk of preterm birth

Food and Drug Administration  
Office of Nutritional Products  
Labeling and Dietary Supplements (HFS-800)  
5001 Campus Drive  
College Park, MD 29740

The undersigned, Organic & Natural Health Association (O&N), submits this petition pursuant to section 403(r)(4) or 403(r)(5)(D) of the Federal Food, Drug, and Cosmetic Act with respect to a health claim concerning the relationship between vitamin D<sub>3</sub> supplementation and a decreased risk of preterm birth (“Pregnant women who have higher serum vitamin D levels have a decreased risk of preterm birth. Adding a vitamin D<sub>3</sub> supplement to your healthy diet can help increase your serum vitamin D levels. Your healthcare practitioner can measure your serum vitamin D levels and determine the appropriate dosage of vitamin D<sub>3</sub> for you.”).

Attached hereto, and constituting a part of this petition, are the following:

A. Preliminary requirements. A complete explanation of how the substance conforms to the requirements of §101.14(b) (21 CFR 101.14(b)). For petitions where the subject substance is a food ingredient or a component of a food ingredient, the petitioner should compile a comprehensive list of the specific ingredients that will be added to the food to supply the substance in the food bearing the health claim. For each such ingredient listed, the petitioner should state how the ingredient complies with the requirements of §101.14(b)(3)(ii), e.g., that its use is generally recognized as safe (GRAS), listed as a food additive, or authorized by a prior sanction issued by the agency, and what the basis is for the GRAS claim, the food additive status, or prior sanctioned status.

B. Summary of scientific data. The summary of scientific data provides the basis upon which authorizing a health claim can be justified as providing the health benefit. The summary

must establish that, based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), there is significant scientific agreement among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence.

The summary shall state what public health benefit will derive from use of the claim as proposed. If the claim is intended for a specific group within the population, the summary shall specifically address nutritional needs of such group and shall include scientific data showing how the claim is likely to assist in meeting such needs.

The summary shall concentrate on the findings of appropriate review articles, National Institutes of Health consensus development conferences, and other appropriate resource materials. Issues addressed in the summary shall include answers to such questions as:

1. Is there an optimum level of the particular substance to be consumed beyond which no benefit would be expected?
2. Is there any level at which an adverse effect from the substance or from foods containing the substance occurs for any segment of the population?
3. Are there certain populations that must receive special consideration?
4. What other nutritional or health factors (both positive and negative) are important to consider when consuming the substance?

In addition, the summary of scientific data shall include a detailed analysis of the potential effect of the use of the proposed claim on food consumption, specifically any change due to significant alterations in eating habits and corresponding changes in nutrient intake resulting from such changes in food consumption. The latter item shall specifically address the effect on the intake of nutrients that have beneficial and negative consequences in the total diet.

If the claim is intended for a significant subpopulation within the general U.S. population, the analysis shall specifically address the dietary practices of such group, and shall include data sufficient to demonstrate that the dietary analysis is representative of such group (e.g., adolescents or the elderly).

If appropriate, the petition shall explain the prevalence of the disease or health-related condition in the U.S. population and the relevance of the claim in the context of the total daily diet.

Also, the summary shall demonstrate that the substance that is the subject of the proposed claim conforms to the definition of the term “substance” in §101.14(a)(2).

C. Analytical data that show the amount of the substance that is present in representative foods that would be candidates to bear the claim should be obtained from representative samples using methods from the AOAC INTERNATIONAL (AOAC), where available. If no AOAC method is available, the petitioner shall submit the assay method used and data establishing the validity of the method for assaying the substance in food. The validation data should include a statistical analysis of the analytical and product variability.

D. Model health claim. One or more model health claims that represent label statements that may be used on a food label or in labeling for a food to characterize the relationship between

the substance in a food to a disease or health-related condition that is justified by the summary of scientific data provided in section C of the petition. The model health claim shall include:

1. A brief capsulized statement of the relevant conclusions of the summary, and
2. A statement of how this substance helps the consumer to attain a total dietary pattern or goal associated with the health benefit that is provided.

E. The petition shall include the following attachments:

1. Copies of any computer literature searches done by the petitioner (e.g., Medline).
2. Copies of articles cited in the literature searches and other information as follows:
  - a. All information relied upon for the support of the health claim, including copies of publications or other information cited in review articles and used to perform meta-analyses.
  - b. All information concerning adverse consequences to any segment of the population (e.g., sensitivity to the substance).
  - c. All information pertaining to the U.S. population.

F. The petitioner is required to submit either a claim for categorical exclusion under §25.30 or §25.32 of this chapter or an environmental assessment under §25.40 of this chapter.

Yours very truly,

Petitioner Organic & Natural Health Association



By Karen E. Howard  
CEO and Executive Director

I, Karen E. Howard, certify that, to the best of my knowledge, this petition is a representative and balanced submission that includes unfavorable information as well as favorable information, known to me to be pertinent to the evaluation of the proposed health claim.



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Signature

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## A. PRELIMINARY REQUIREMENTS

Vitamin D<sub>3</sub> conforms to the requirements in 21 C.F.R. § 101.14(b). As described in detail below, vitamin D deficiency is associated with a health-related condition (preterm birth) for which an identified U.S. population subgroup (pregnant women) is at risk. As required by 21 C.F.R. § 101.14(b)(3), vitamin D<sub>3</sub> contributes to the nutritive value of foods, including dietary supplements, and it retains that attribute when it is consumed at the levels necessary to justify the health claim. As described below, vitamin D<sub>3</sub> is contained in foods (it is both a food ingredient and is also a naturally-occurring component of many foods), and its use at the levels necessary to justify the proposed health claim has been demonstrated to be safe and lawful under the applicable food safety provisions of the Federal Food, Drug, and Cosmetic Act (“FDCA”).

### **1. Vitamin D<sub>3</sub> contributes to the nutritive value of foods, including dietary supplements, and it retains that attribute when it is consumed at the levels necessary to justify the health claim.**

Vitamin D<sub>3</sub> (cholecalciferol) is a well-known and long-studied nutrient. The nutrient is a naturally-occurring component of many foods, such as fatty fish, egg yolks, beef liver, and fortified dairy and cereals.<sup>1</sup> In addition, cholecalciferol is a permitted food additive under FDA’s regulations.<sup>2</sup> In that regard, vitamin D<sub>3</sub> has undergone FDA safety review as part of the agency’s review and approval of several food additive petitions.<sup>3</sup> FDA has also affirmed that vitamin D<sub>3</sub> is generally recognized as safe (GRAS) for use in breakfast cereals, grain products and pastas, milk, and milk products.<sup>4</sup> In addition to its use as a food ingredient in multiple conventional foods, it is also frequently a component of dietary supplements. The health claim proposed in this petition would be used on or in conjunction with dietary supplements containing solely vitamin D<sub>3</sub> or vitamin D<sub>3</sub> in combination with other dietary ingredients, such as vitamins, minerals, or herbs. Cholecalciferol meets the definition of a “dietary ingredient” under 21 U.S.C. § 321(ff). In particular, as a form of vitamin D, vitamin D<sub>3</sub> is a “vitamin” pursuant to 21 U.S.C. § 321(ff)(1)(A), and it was marketed as a dietary supplement or food prior to being investigated as a new drug, antibiotic, or biologic.

Vitamin D is recognized as an important nutrient for a complete, healthy diet. It has nutritive value as defined in 21 C.F.R. § 101.14(3); specifically, it has value in sustaining human existence and promoting health. Indeed, the FDA has very recently recognized its significant

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<sup>1</sup> U.S. Department of Health and Human Services and U.S. Department of Agriculture, *2015-2020 Dietary Guidelines for Americans* (8th ed. Dec. 2015), Appendix 12 at 111, 113 (hereinafter “USDA 2015-2020 Dietary Guidelines”); De-Regil, L.M., *et al.*, *Vitamin D supplementation for women during pregnancy (Review)*, 1 COCHRANE DATABASE OF SYSTEMATIC REVIEWS CD008873, 1-121, 7 (2016) (hereinafter “De-Regil *et al.* (2016)”); Johnson, D.D., *et al.*, *Vitamin D Deficiency and Insufficiency is Common During Pregnancy*, 28(1) AM J PERINATOL 7-12 (2011), 8 (hereinafter “Johnson *et al.* (2011)”); National Institutes of Health, Office of Dietary Supplements, *Vitamin D – Fact Sheet for Health Professionals (last updated Mar. 2, 2018)*, <https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/> (hereinafter “NIH Vitamin D Factsheet”).

<sup>2</sup> 21 C.F.R. § 172.380 (Vitamin D<sub>3</sub> or cholecalciferol).

<sup>3</sup> *Food Additives Permitted for Direct Addition to Food for Human Consumption; Vitamin D<sub>3</sub>*, 68 Fed. Reg. 9000 (Feb. 27, 2003) (as an additive in calcium-fortified fruit juices); *Food Additives Permitted for Direct Addition to Food for Human Consumption; Vitamin D<sub>3</sub>*, 79 Fed. Reg. 46993 (Aug. 12, 2014) (as an additive in meal replacement beverages); *Food Additives Permitted for Direct Addition to Food for Human Consumption; Vitamin D<sub>2</sub> and Vitamin D<sub>3</sub>*, 81 Fed. Reg. 46578 (July 18, 2016) (as an additive in plant-based beverages and plant-based yogurts).

<sup>4</sup> 21 C.F.R. § 184.1950.

importance in promoting the health of the U.S. population, going so far as to identify it as a nutrient of public health concern because a large portion of the U.S. population is vitamin D deficient. Data examined by FDA as it reevaluated nutrition labeling requirements showed “inadequate intakes, poor vitamin D status, and high prevalence of osteoporosis and osteopenia among the general U.S. population.”<sup>5</sup>

Vitamin D’s role (with calcium and phosphorus) in maintaining skeletal health is well-known and understood, both for the general U.S. population and for the subpopulation of pregnant women. The FDA has set a Recommended Daily Intake (“RDI”) for the nutrient – at 20 mcg or 800 IU for adults and children age 4 and over.<sup>6</sup> For pregnant women, the recommendation is 15 mcg or 600 IU per day.<sup>7</sup> The FDA largely based these RDIs on the Institute of Medicine (IOM) recommendations in its publication, *Dietary Reference Intakes for Calcium and Vitamin D* publication. However, we note that IOM has acknowledged that there were methodological (mathematical) errors in its analysis of one study used to determine the Recommended Dietary Allowances (RDAs) for vitamin D as set forth in its *Dietary Reference Intakes for Calcium and Vitamin D* publication.<sup>8</sup>

Much of the research on which this RDI is based focused on the nutrient’s role in bone health and addressing osteoporosis and rickets. In fact, based on the strength of this research, FDA has authorized a health claim about vitamin D and calcium (whose absorption vitamin D aids) on lowering the risk of osteoporosis.<sup>9</sup> Recent research into how vitamin D works in the body has, however, revealed that the nutrient likely has more than skeletal benefits, and that it may have immunomodulatory and anti-inflammatory roles, making it crucial for pregnant women and their developing fetuses.<sup>10</sup>

Vitamin D<sub>3</sub>, therefore, contributes to the nutritive value of food and dietary supplements to which it is added, both for the general U.S. population and, more particularly, for the subpopulation of pregnant women who do not include sufficient vitamin D<sub>3</sub> in their daily diets and who are most likely to benefit from the health claim.

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<sup>5</sup> *Food Labeling: Revision of the Nutrition and Supplement Facts Labels*, 81 Fed. Reg. 33,742, 33,890 (May 27, 2016) (codified at 21 C.F.R. Part 101).

<sup>6</sup> 21 C.F.R. § 101.9(c)(8)(iv).

<sup>7</sup> *Id.*

<sup>8</sup> See <http://www.nationalacademies.org/hmd/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx> (“Note: In response to claims of methodological errors in this report after its release, the National Academies undertook a two-phased review process to identify whether errors had been made and if so what effect those errors had on the findings. Here are the reports of the two review panels: Phase I and Phase II.”); May 15, 2017 memorandum to Marcia K. McNutt concerning Purported mathematical errors in the 2011 IOM report, *Dietary Reference Intakes: Calcium and Vitamin D*, available at <https://www.nap.edu/resource/13050/Vit%20D%20panel%20report%20final.pdf>; November 15, 2017 memorandum to Marcia McNutt concerning Impact on the RDA for vitamin D of mathematical errors in the 2011 IOM report, *Dietary Reference Intakes: Calcium and Vitamin D*, available at [https://www.nap.edu/resource/13050/FINAL%20Vitamin%20D%20Phase%20II%20Panel%20Report\\_11-17-17.pdf](https://www.nap.edu/resource/13050/FINAL%20Vitamin%20D%20Phase%20II%20Panel%20Report_11-17-17.pdf).

<sup>9</sup> 21 C.F.R. § 101.72.

<sup>10</sup> Liu, N.Q. & Hewison, M., *Vitamin D, the placenta and pregnancy*, 523 ARCH BIOCHEM. BIOPHYS. 37-47 (2012) (describing the mechanisms by which vitamin D exhibits immunomodulatory effects at various stages of a woman’s reproductive cycle, including conception and fertility and placental metabolism, implantation, and anti-inflammatory action) (hereinafter “Liu & Hewison (2012)”); see also Heyden, E.L. & Wimalawansa, S.J., *Vitamin D: Effects of human reproduction, pregnancy, and fetal well-being*, 2017 J STEROID BIOCHEM MOL BIOL pii (2017).

## **2. Use of vitamin D<sub>3</sub> at the levels necessary to justify the proposed claim is safe and lawful under the FDCA.**

Importantly, vitamin D<sub>3</sub> retains its contributions to the nutritive value of food and dietary supplements when consumed at the levels necessary to justify the proposed health claim.

With regard to the levels of vitamin D<sub>3</sub> necessary to justify the proposed health claim, we note that maternal circulating vitamin D levels are best indicated by measuring serum levels of 25-hydroxyvitamin D (25(OH)D),<sup>11</sup> and that serum 25(OH)D levels are measured in terms of ng/mL or nmol/L. Conversion between the two units is possible; for example, 20 ng/mL is equivalent to 50 nmol/L, and 30 ng/mL is equivalent to 75 nmol/L. While IOM determined that “persons are at risk of deficiency *relative to bone health* at serum [25(OH)D] levels below 30 nmol/L (12 ng/mL)” and that “persons are potentially at risk for inadequacy at serum [25(OH)D] levels between 30 and 50 nmol/L (12 and 20 ng/mL),”<sup>12</sup> these IOM deficiency/inadequacy/sufficiency designations are all related to the role of vitamin D in bone health; they do not contemplate the levels that are adequate to support maternal and fetal health during pregnancy, and in particular, the levels needed to help reduce the risk of preterm birth.

The U.S.-based Endocrine Society has adopted different cut-off levels for 25(OH)D to assess and classify an individual as vitamin D deficient, inadequate, or sufficient. Specifically, according to the Endocrine Society, vitamin D “deficiency is defined as a 25(OH)D below 20 ng/ml (50 nmol/liter), and vitamin D insufficiency as a 25(OH)D of 21–29 ng/ml (52.5–72.5 nmol/liter).”<sup>13</sup> The Society’s reasoning for different, higher cut-off levels for assessment and classification are largely due to its consideration of vitamin D’s skeletal and *extra*-skeletal benefits. Again, however, these guidelines were not developed specifically for maternal and fetal health.

In that regard, there is general consensus in the literature that for pregnant women with serum 25(OH)D levels of less than 40 ng/mL (100 nmol/L), there is a benefit to raising serum vitamin D levels; specifically, there is a decreased risk of preterm birth. Because pregnant women have different starting serum 25(OH)D levels, the level of vitamin D<sub>3</sub> needed to increase their serum levels (and thereby reduce the risk of preterm birth) is patient specific.

For example, one placebo-controlled study tested the effect of vitamin D<sub>3</sub> supplementation on the serum 25(OH)D concentrations in pregnant women and their babies.<sup>14</sup> Researchers found that supplementation with 1,000 IU and 2,000 IU between 27 and 36 weeks’ gestation led to a statistically-significant increase in the percentage of women with serum levels that were not deficient ( $\geq 20$  ng/mL or  $\geq 50$  nmol/L) and that were vitamin D sufficient ( $\geq 30$  ng/mL or  $\geq 75$

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<sup>11</sup> Holick, M. F., *High Prevalence of Vitamin D Inadequacy and Implications for Health*, 81(3) MAYO CLIN PROC 353-373, 355 (2006) (explaining that serum 25(OH)D is “the major circulating metabolite of vitamin D and reflects vitamin D inputs from cutaneous synthesis and dietary intake.” It is the “Standard clinical measure of vitamin D status”) (hereinafter “Holick (2006)”); *see also* Dror, D.K. & Allen, L.H., *Vitamin D inadequacy in pregnancy: biology, outcomes, and interventions*, 68(8) NUTR REV 465, 466 (2010) (hereinafter “Dror & Allen (2010)”).

<sup>12</sup> National Academy of Sciences, Institute of Medicine, *Dietary Reference Intakes for Calcium and Vitamin D*, (Washington D.C., The National Academies Press, 2011), at 13-14 (emphasis added), (available at <https://www.nap.edu/catalog/13050/dietary-reference-intakes-for-calcium-and-vitamin-d>) (hereinafter “2011 IOM DRI”).

<sup>13</sup> Holick, M.F., *et al.*, *Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline*, 96 J CLIN ENDOCRINOL METAB 1911, 1911 (2011) (hereinafter “Holick *et al.* (2011)”).

<sup>14</sup> Grant, C.C., *et al.*, *Vitamin D During Pregnancy and Infancy and Infant Serum 25-Hydroxyvitamin D Concentration*, 133(1) PEDIATRICS e143-e153 (2014) (hereinafter “Grant *et al.* (2014)”).

nmol/L) ( $p < 0.001$ ).<sup>15</sup> Importantly, Importantly, the researchers found that both 1,000 IU and 2,000 IU doses led to statistically-significant improvements in serum vitamin D compared to placebo ( $p < 0.001$ ).<sup>16</sup>

In Cooper *et al.*, researchers tested the effect of vitamin D<sub>3</sub> supplementation with 1,000 IU per day compared to placebo, on serum 25(OH)D levels and infant outcomes.<sup>17</sup> Researchers found that among the group receiving 1,000 IU per day there was a significantly lower number of women with 25(OH)D levels below 50 nmol/L [20 ng/mL] ( $p < 0.0001$ ), than the placebo group.<sup>18</sup> The authors concluded that “1000 IU of cholecalciferol daily is sufficient to ensure that most pregnant women are vitamin D replete, and it is safe.”<sup>18</sup>

In another double-blind randomized study, researchers compared the effectiveness of different doses of vitamin D<sub>3</sub> supplementation for raising pregnant women’s serum vitamin D levels to 80 nmol/L (32 ng/mL) or greater.<sup>19</sup> Researchers found that both 2,000 IU per day and 4,000 IU/day were significantly more effective than 400 IU/day at achieving a serum level of at least 80 nmol/L (32 ng/mL).<sup>20</sup> However, there was no significant difference between the effectiveness of 2,000 IU and 4,000 IU dosages.<sup>21</sup> This study demonstrates that pregnant women can achieve increased serum vitamin D levels with a dosage of vitamin D<sub>3</sub> (2,000 IU per day) that is far below the 4,000 IU tolerable upper limit (UL) set by the IOM. Therefore, while many of the studies discussed below provided supplementation at the 4,000 IU per day level, lower doses have been shown to also be effective in raising serum vitamin D levels out of the deficient range.

Accordingly, human clinical studies show that vitamin D<sub>3</sub> supplementation as low as 1,000 IU per day and as high as 4,000 IU per day is sufficient to justify the health claim being proposed in this petition. Vitamin D at this higher level – 4,000 IU per day – has been recognized as safe by the IOM, which set the tolerable upper limit (UL) for vitamin D at 4,000 IU per day persons aged 9 or older and for pregnant and lactating women.<sup>22</sup> However, we note that while IOM ultimately set the UL for vitamin D at 4,000 IU per day, it noted, after an extensive review of the available literature, that “there was no association between harm and intakes of 10,000 IU per day.”<sup>23</sup> The IOM further noted that available studies suggest that adverse events would be unlikely at daily intakes below 10,000 IU.<sup>24</sup> Importantly, too, the IOM noted that one of the key reasons for setting the upper-intake level below the amount that was shown as safe in the available literature (*i.e.*, 10,000 IU per day) was that upper intake levels are meant to “apply to long-term (essentially lifetime) exposures.”<sup>25</sup> We note that in the case of pregnant women, exposure time

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<sup>15</sup> *Id.*, at e151.

<sup>16</sup> *Id.*

<sup>17</sup> Cooper, C. & Harvey, N., *Maternal Gestational Vitamin D Supplementation and Offspring Bone Health (MAVIDOS): a Multicentre, Double-Blind, Randomised Placebo-Controlled Trial*, 4(5) LANCET DIABET ENDOCRINOL 393-402 (2016) (hereinafter “Cooper & Harvey (2016)”).

<sup>18</sup> *Id.*, at 393.

<sup>19</sup> Hollis, B. *et al.*, *Vitamin D Supplementation during Pregnancy: Double Blind, Randomized Clinical Trial of Safety and Effectiveness*, 26(10) J BONE MINER RES 2341-2357 (2011) (hereinafter “Hollis et al. (2011)”).

<sup>20</sup> *Id.*, at 2341.

<sup>21</sup> *Id.*

<sup>22</sup> 2011 IOM DRI, at 441; *see also Food Additives Permitted for Direct Addition to Food for Human Consumption; Vitamin D<sub>2</sub> and Vitamin D<sub>3</sub>*, 81 Fed. Reg. 46,578, 46,579 (July 18, 2016) (codified at 21 C.F.R. Part 172).

<sup>23</sup> 2011 IOM DRI, at 429

<sup>24</sup> *Id.*, at 430.

<sup>25</sup> *Id.*



would be in weeks or months, which is more akin to the length of time in the studies that indicated no harm likely at 10,000 IU per day rather than the lifetime exposure that is contemplated by the 4,000 IU per day upper intake level.<sup>26</sup>

Additional credible support in the literature for daily vitamin D intake above the IOM-established UL comes from Hathcock *et al.* (2007)<sup>27</sup>, who conducted a risk assessment for vitamin D<sub>3</sub>. The researchers determined that an appropriate UL for vitamin D<sub>3</sub> is 250 mcg or 10,000 IU per day. Review of available human clinical trials, which included vitamin D<sub>3</sub> supplementation as high as 2500 mcg (or 100,000 IU), led the authors to the conclusion that “[c]ollectively, the absence of toxicity in trials conducted in healthy adults that used vitamin D dose 250 µg /d (10 000 IU vitamin D<sub>3</sub>) supports the confident selection of this value as the UL.”<sup>28</sup> The 10,000 IU per day UL was based on combining results from “2 well-conducted studies, with the absence of toxicity in normal subjects exposed to a 5-fold dose [1250 µg vitamin D<sub>3</sub>/d],” which “warrants a high level of confidence in selection of 250 µg/d as the [no observed adverse event level or NOAEL] for vitamin D<sub>3</sub>.”<sup>29</sup> Notably, the serum 25(OH)D concentration associated with a critical effect (identified by the researchers as high serum calcium or hypercalcemia<sup>30</sup>) was consistently higher than the 25(OH)D serum level achieved with a 250 mcg (or 10,000 IU) daily dose.<sup>31</sup> Specifically, “the cases exhibiting toxicity all had serum 25(OH)D concentrations ranging from 700 to >1600 nmol/L,” which “increases the confidence in the NOAEL of 250 µg, because the 25(OH)D concentration typically achieved with that intake (220 nmol/L) are much lower.”<sup>32</sup> Additionally, there was “[n]o consistent or reproducible hypercalcemia or any other adverse effect from vitamin D [found] in well-conducted clinical trials at intakes up to 1250 µg.”<sup>33</sup> Ultimately, the researchers concluded that “vitamin D is not toxic at intakes much higher than previously considered safe.”<sup>34</sup>

The amount of vitamin D<sub>3</sub> that pregnant women would have to consume via supplementation in order to increase serum vitamin D levels is safe for pregnant women to consume. As indicated above, the upper intake level of vitamin D that IOM recommends is 4,000 IU per day for both the general adult population and pregnant and lactating women.<sup>35</sup> There are two potential dietary sources of vitamin D, intake through food and intake through supplementation. Even if we combine the average vitamin D intake through food consumption

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<sup>26</sup> *Id.* at 428-29 (10,000 IU per day studies between 4 weeks to 2.5 months).

<sup>27</sup> Hathcock J.N. *et al.*, *Risk assessment for vitamin D*, AM J CLIN NUTR; 85:6-18 (2007) (hereinafter “Hathcock *et al.* (2007)”).

<sup>28</sup> Hathcock *et al.* (2007), at 6

<sup>29</sup> Hathcock *et al.* (2007), at 10

<sup>30</sup> Hathcock *et al.* (2007), at 12-13. The risk assessment for the vitamin D<sub>3</sub> UL also included analysis of co-supplementation with calcium and the resultant effect on renal function, which led to the conclusion that “the literature at present does not appear to support the notion that supplemental vitamin D, including doses at and above the NOAEL identified here (250 µg) in persons consuming the recommended calcium intake, may increase the risk of renal stone formation in generally healthy adults.” Hathcock *et al.* (2007), at 13

<sup>31</sup> Hathcock *et al.* (2007), at 11

<sup>32</sup> *Id.* The reported adverse events caused by “apparent vitamin D intoxication” appear to be “accidental or uninformed consumption of very high doses of vitamin D,” and all of these consumption levels were “far above those administered in the clinical trials” discussed in the risk assessment. Additionally, cases in which the vitamin D over consumption is above 250 µg, “involved patients with compromised health or other confounding factors” and many of these cases involved vitamin D<sub>2</sub> rather than vitamin D<sub>3</sub>.

<sup>33</sup> Hathcock *et al.* (2007), at 14

<sup>34</sup> Hathcock *et al.* (2007), at 16

<sup>35</sup> 2011 IOM DRI. at 441.

with the amount of vitamin D through supplementation that would effectively increase serum 25(OH)D levels to a level that would decrease the risk of preterm birth, the total amount of vitamin D that pregnant women would potentially consume is still lower than the upper intake level of 4,000 IU established by the IOM.

Surveys of the dietary intake of Americans cited by the FDA in updating nutrition labeling regulations determined that 93.7 percent of the general adult population and 87.6 percent of pregnant or lactating women did not consume at least 10 mcg of vitamin D through food per day.<sup>36</sup> We note that 10 mcg is below the daily dietary intake recommended by IOM (600 IU per day, 15 mcg per day).<sup>37</sup> To attempt to address the issue of inadequate dietary intake, in the recent updates to the nutrition labeling rules, the FDA made vitamin D a mandatory disclosure and increased the RDI from 400 IU per day to 20 mcg per day (800 IU per day) for children four years of age and older and adults, and established the RDI for pregnant and lactating women at 15 mcg (600 IU per day).<sup>38</sup> Therefore, it is clear that dietary intake of vitamin D is not generally sufficient and leaves room for safe supplementation.

Together, the studies discussed above demonstrate that supplementing with vitamin D<sub>3</sub> at 2,000 IU or less is effective at raising the serum 25(OH)D levels of pregnant women in a manner that will help reduce the risk of preterm birth with no risk of adverse events. However, even at daily dosages up to 10,000 IU, there is evidence that supplementation would be safe.

3. **Vitamin D<sub>3</sub> is associated with a health-related condition (preterm birth) for which an identified U.S. population subgroup (pregnant women) is at risk.**

Vitamin D<sub>3</sub> is associated with preterm birth, for which pregnant women in the U.S. are at risk. The U.S. Centers for Disease Control (“CDC”) reported that, in 2015, the U.S. birth rate was 12.4 per 1,000 and there were almost 4 million births. The CDC also reports that approximately 1 in 10 births are preterm<sup>39</sup>, and each day in North America, more than 1,000 babies are born prematurely. According to Save the Children, the March of Dimes, and others, the United States is among the top 10 countries where preterm birth occurs, and 130 countries have a lower preterm birth rate than the United States.<sup>40</sup> Preterm (or premature) birth is an adverse pregnancy outcome that is the leading cause of perinatal morbidity and mortality.<sup>41</sup> Of particular concern is that 2016

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<sup>36</sup> *Food Labeling Revisions of the Nutrition and Supplement Facts Labels: Proposed Rule*, 79 Fed. Reg. 11,880, 11,924 and 11,945 (Mar. 3, 2014) (codified at 21 C.F.R. § 101.9).

<sup>37</sup> 2011 IOM DRI, at 363.

<sup>38</sup> 79 Fed. Reg. at 11,922, 11,931, 11,970.

<sup>39</sup> Preterm birth is generally defined as birth before 37 weeks of pregnancy are completed. Centers for Disease Control and Prevention, *Reproductive Health – Preterm Birth* (last updated Nov. 27, 2017), <https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm> (hereinafter “CDC Preterm Birth”).

<sup>40</sup> World Health Organization, *Born Too Soon: The Global Action Report on Preterm Birth* (Geneva, 2012), at 2 (hereinafter “WHO Born Too Soon Report”).

<sup>41</sup> Baczyńska-Strzecha, M. & Kalinka, J., *Assessment of Correlation between Vitamin D Level and Prevalence of Preterm Births in the Population of Pregnant Women in Poland*, 30(6) INT’L J OCCUPAT MED ENVIRON HEALTH, 933-941, 933 (2017) (hereinafter “Baczyńska-Strzecha, M. & Kalinka (2017)”; see also Bodnar, L. et al., *Early-Pregnancy Vitamin D Deficiency and Risk of Preterm Birth Subtypes*, 125(2) J OBSTETAND GYNECOL, 439-447 (2015) (hereinafter “Bodnar et al. (2015)”; McDonnell, S. et al., *Maternal 25(OH)D Concentrations ≥40 ng/mL Associated with 60% Lower Preterm Birth Risk Among General Obstetrical Patients at an Urban Medical Center*, 12(7) PLOS ONE, 1-12 (2017) (hereinafter “McDonnell et al. (2017)”; Bodnar, L.M., et al., *Maternal Vitamin D*

marked a second consecutive year of increasing preterm birth rates, and the trend is expected to increase once 2017 data is assessed.<sup>42</sup> In 2015, the CDC reported that preterm birth and low birth weight were responsible for approximately 17% of infant deaths.<sup>43</sup> Preterm birth is a leading cause of many long-term health-related conditions (e.g., neurological and respiratory disorders, learning difficulties, and behavioral challenges).<sup>44</sup> Preterm birth also has significant economic impacts (e.g., health care costs, lost income, special education services).<sup>45</sup>

While preterm birth is a heterogeneous health-related condition, several risk factors are known and are routinely addressed during antenatal care (e.g., age, economic status and workplace conditions, inflammation and infection, and diet and nutrition).<sup>46</sup> As diet and nutrition advice – including recommendations for dietary supplements – is routinely given to ensure maternal and fetal health with the goal of achieving a healthy full term pregnancy<sup>47</sup>, research has necessarily focused on better understanding the role of nutrients. Out of this research, vitamin D has emerged as an important nutrient for lowering the risk of preterm birth.

Despite the established RDI and though vitamin D may be synthesized in the dermis upon sun exposure and is found in some foods, recent reports<sup>48</sup> revealed that almost half of the U.S. population is deficient in vitamin D. The report found that the prevalence of vitamin D deficiency is even higher in certain subgroups of the U.S. population – 74% among the elderly and 82% among Americans with dark skin.<sup>49</sup> There is also vitamin D deficiency among pregnant women

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*Status and Spontaneous Preterm Birth by Placental Histology in the US Collaborative Perinatal Project*, 179(2) AM J EPIDEMIOLOG 168-176 (2014) (hereinafter “Bodnar et al. (2014)”).

<sup>42</sup> CDC Preterm Birth.

<sup>43</sup> *Id.*

<sup>44</sup> *Id.*; see March of Dimes, *Long-Term Health Effects of Premature Birth* (last reviewed Oct. 2013), <https://www.marchofdimes.org/complications/long-term-health-effects-of-premature-birth.aspx>; see also March of Dimes, *Premature Babies* (last reviewed Oct. 2013), <https://www.marchofdimes.org/complications/premature-babies.aspx>.

<sup>45</sup> March of Dimes, *The Impact of Premature Birth on Society*, (last reviewed Oct. 2015), <https://www.marchofdimes.org/mission/the-economic-and-societal-costs.aspx>; see WHO Born Too Soon Report at 12.

<sup>46</sup> Kirkham, C., et al., *Evidence-Based Prenatal Care: Part I. General Prenatal Care and Counseling Issues*, 71(7) AM FAM PHYSICIAN 1307-1316 (2005); Kirkham, C., et al., *Evidence-Based Prenatal Care: Part II. Third-Trimester Care and Prevention of Infectious Diseases*, 71(8) AM FAM PHYSICIAN 155-1560 (2005); see also Farahi N. and Zolotor A., *Recommendations for Preconception Counseling and Care*, 88(8) AM FAM PHYSICIAN 499-506 (2013).

<sup>47</sup> See American College of Obstetricians and Gynecologists, *Frequently Asked Questions, Pregnancy* (FAQ001, February 2018), <https://www.acog.org/Patients/FAQs/Nutrition-During-Pregnancy>; American College of Obstetricians and Gynecologists, *Frequently Asked Questions, Healthy Eating*, (FAQ130, November 2013) <https://www.acog.org/Patients/FAQs/Healthy-Eating>; Barry, K.A., *Impact of Antenatal Dietary Education and Supplementation on Maternal and Infant Health Outcomes*, 93(7) AM FAM PHYSICIAN 557-558 (2016); see also American Academy of Family Physicians, *Pregnancy: Keeping Yourself and Your Baby Healthy*, 71(7) AM FAM PHYSICIAN 1321-1322(2005).

<sup>48</sup> Jordan Lite, *Vitamin D deficiency soars in the U.S., study says*, Scientific American (Mar. 23, 2009), <https://www.scientificamerican.com/article/vitamin-d-deficiency-united-states/> (hereinafter “Scientific American 2009”); see also 81 Fed. Reg. 33,742, at 33,890 (FDA commenting that vitamin D intake levels are below the Estimated Average Requirement (EAR) identified in the 2015 Scientific Report of the 2015 Dietary Guidelines Advisory Committee, and that it considers vitamin D a nutrient of public health concern for the general population).

<sup>49</sup> Scientific American 2009; see also Holick (2006), at 356; Dror & Allen (2010), at 470.

in the U.S.<sup>50</sup>, and this has serious consequences for pregnancy outcomes.<sup>51</sup> Among black American women of child-bearing age, the prevalence of vitamin D deficiency has been shown to be as high as 42%.<sup>52</sup> Many Americans limit sun exposure because of the well-known serious health-related outcomes. Sunscreen, which is consistently recommended to mitigate the harmful effects of sun exposure, may also limit the body's ability to absorb the sunlight needed for vitamin D synthesis.<sup>53</sup> Skin pigmentation has a limiting effect on vitamin D synthesis in the dermis, and it is thought to be the main reason for a higher proportion of vitamin D deficiency among dark-skinned people.<sup>54</sup> That the U.S. is in a temperate region also impacts sun exposure levels and therefore the body's ability to synthesize its own vitamin D.<sup>55</sup> As for other sources of vitamin D<sub>3</sub>, few foods are good sources of vitamin D.<sup>56</sup> Fatty fish, egg yolks, beef liver, and fortified dairy and cereals are commonly available sources of vitamin D<sub>3</sub>, but a serving of many of these foods does not provide the currently-established or previous RDI.<sup>57</sup> Other well-known and frequently recommended sources of vitamin D<sub>3</sub> are, in fact, dietary supplements such as fish liver oils.

Pregnant women in the U.S. are often advised by health care professionals to restrict consumption of certain foods, including fish, because of concerns about contamination with heavy

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<sup>50</sup>See American College of Obstetricians and Gynecologists, Committee on Obstetric Practice, *Committee Opinion - Vitamin D: Screening and Supplementation During Pregnancy* (No. 495, July 2011); Looker, A.C., et al., *Data Brief - Vitamin D Status: United States, 2001-2006*, Centers for Disease Control and Prevention National Center for Health Statistics, *NCHS* (No. 59, Mar. 2011); American Academy of Pediatrics and American College of Obstetricians and Gynecologists, *Guidelines for Perinatal Care*, at 133 (7th ed., Oct. 2012), (available at <http://www.countycare.com/Media/Default/pdf/GuidelinesforPerinatalCare%207thed.pdf>) (hereinafter "American Academy of Pediatrics Perinatal Guidelines"); see also Bodnar, L.M., et al., *High Prevalence of Vitamin D Insufficiency in Black and White Pregnant Women Residing in the Northern United States and Their Neonates*, 137(2) *J NUTR* 447-452 (2007) (finding a high prevalence of vitamin D insufficiency and deficiency in black and white women in Pittsburgh, Pennsylvania. Specifically, there was a "remarkably high proportion of vitamin D deficiency and insufficiency among mothers throughout gestation and among their infants at birth." There were low concentrations of 25(OH)D despite more than 90% of the study participants reporting dietary supplement use in the last trimester of their pregnancies and 45% reporting regular dietary supplement use during the "preconception period." Dietary intake was not recorded during this study, but the study was conducted when the FDA-set RDI for pregnant women was 400 IU per day.) (hereinafter "Bodnar et al. (2007)"); Holick (2006) (discussing in detail the high prevalence of vitamin D inadequacy); Johnson et al. (2011), at 9 (concluding that the study "clearly demonstrates a high incidence of vitamin D deficiency and insufficiency and in women during their first trimester of pregnancy in a city in the United States with a high UV index.").

<sup>51</sup> Dror & Allen (2010), at 472 (discussing the public health implications of the "alarming prevalence of vitamin D insufficiency during pregnancy").

<sup>52</sup> Liu & Hewison (2012), at 37 (citing the 1988-1994 National Health and Nutrition Examination Survey (NHANES III). NHANES III defined deficiency as "serum levels of the main circulating form of vitamin D less than 37.5 nM").

<sup>53</sup> De-Regil et al. (2016), at 7 (explaining that UV rays are filtered by melanin thereby limiting the ability of the skin to synthesize vitamin D. Sunscreen acts in a similar fashion, as a filter and protectant against UV rays and so will inhibit the skin's ability to absorb the requisite UV rays needed to synthesize vitamin D); see also Holick (2006), at 356-357; Dror & Allen (2010), at 470; and, Johnson et al. (2011), at 8.

<sup>54</sup> Bodnar, L.M. & Simhan, H.N., *Vitamin D may be a link to black-white disparities in adverse birth outcomes*, 65(4) *OBSTET GYNECOL SURV* 273-284, at 2-3 (2010); Holick (2006), at 354; see also Johnson et al. (2011), at 10; Yu, C.K.H. et al., *Vitamin D Deficiency and Supplementation during Pregnancy*, 70(5) *J CLIN ENDOCRINOL* 685-690, 685 (2009) (commenting that certain ethnic groups with darker skin – from the "Indian subcontinent and Middle East – are at risk for vitamin D deficiency) (hereinafter "Yu et al. (2009)").

<sup>55</sup> See De-Regil et al. (2016), at 7; see also Bodnar et al. (2007) (discussing variability of vitamin D status according to season); Dror & Allen (2010), at 470.

<sup>56</sup> NIH Vitamin D Factsheet.

<sup>57</sup> NIH Vitamin D Factsheet.

metals.<sup>58</sup> Pregnant women may also be advised to limit sun exposure because of increased skin sensitivity that can cause dermatitis or discoloration.<sup>59</sup> Within this context, then, dietary supplements are clearly an important way for the general U.S. population, and pregnant women in particular, to get necessary amounts of vitamin D<sub>3</sub>. Indeed, researchers, health care professionals, and the U.S. federal government's own Dietary Guidelines generally accept – and recommend – dietary supplements as an affordable and accessible way to ensure appropriate nutrient intake.<sup>60</sup> Moreover, consumption of vitamin D<sub>3</sub> supplements will be an important way for certain segments of the subpopulation of pregnant women (*e.g.*, low income women or women of color) who may be more at risk for preterm birth to easily access an affordable means of improving nutrient intake. Supplementation with vitamin D<sub>3</sub> – a commonly available and relatively cheap nutrient already recognized by FDA as an essential nutrient and a nutrient of concern – is an efficient<sup>61</sup> and accessible way for pregnant women to increase their serum vitamin D levels, thereby decreasing the risk of experiencing a preterm birth.

A health claim about the role of vitamin D<sub>3</sub> supplementation in lowering the risk of preterm birth, a serious health-related condition, is an important and prudent step for maternal and child health. The health claim will emphasize for pregnant women the importance of vitamin D<sub>3</sub> for their health and their child's health, and it is consistent with current recommendations given during antenatal care. The March of Dimes, which is dedicated to the “health of all moms and babies,” specifically has a campaign dedicated to addressing preterm birth.<sup>62</sup> Among the information it provides is the importance of a healthy diet, and vitamin D<sub>3</sub> is highlighted as an important nutrient for achieving a successful full term pregnancy.<sup>63</sup> This kind of campaign and information is consistent with the information from other federal agencies, such as the CDC.

Serum vitamin D levels are a modifiable risk factor that can influence maternal and perinatal outcomes. Vitamin D supplements are generally affordable, safe, and, as discussed below, effective for modifying maternal serum vitamin D levels to levels that improve pregnancy outcomes. A health claim about vitamin D<sub>3</sub> supplementation as part of a healthy maternal diet, and the impact that supplementation could have on lowering the risk of preterm birth, is a relatively low cost way to have significant impact on overall U.S. maternal health and pregnancy outcomes.

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<sup>58</sup> See Food and Drug Administration, HHS, *Advice About Eating Fish, From the Environmental Protection Agency and Food and Drug Administration; Revised Fish Advice*, 82 Fed. Reg. 6571 (Jan. 19, 2017), <https://www.fda.gov/Food/ResourcesForYou/Consumers/ucm393070.htm>; see also Environmental Protection Agency, *Choose Fish and Shellfish Wisely* (last updated Feb. 23, 2017), <https://www.epa.gov/choose-fish-and-shellfish-wisely>.

<sup>59</sup> American Pregnancy Association, *Tanning During Pregnancy* (last updated July, 2017), <http://americanpregnancy.org/pregnancy-health/tanning-during-pregnancy/>; Jessie Wohlgemuth, *5 Pregnancy Sun Protection Tips*, Parents (last visited Mar. 24, 2018), <https://www.parents.com/pregnancy/pregnancy-sun-protection/>.

<sup>60</sup> NIH Vitamin D Factsheet; American Academy of Pediatrics Perinatal Guidelines, at 294; USDA 2015-2020 Dietary Guidelines, at 11, 16, and 60.

<sup>61</sup> Yu *et al.* (2009) (concluding that “single or daily dose” vitamin D supplementation improved 25(OH)D levels “significantly.” Specifically, with supplementation the researchers shows that vitamin D sufficiency of “> 50 nmol/L” could be achieved. The supplementation also improved vitamin D levels across all ethnic groups (as compared to the no treatment group).

<sup>62</sup> March of Dimes, *Prematurity Campaign: Activities and Milestones* (last reviewed Oct. 2015), <https://www.marchofdimes.org/mission/march-of-dimes-prematurity-campaign.aspx>.

<sup>63</sup> March of Dimes, *Vitamins and Other Nutrients During Pregnancy* (last reviewed Feb. 2018), <https://www.marchofdimes.org/pregnancy/vitamins-and-other-nutrients-during-pregnancy.aspx>



## B. SUMMARY OF SCIENTIFIC DATA

The understanding of vitamin D's role in many important body processes is the focus of ongoing research, but much is known. As discussed above, vitamin D has an immunomodulatory effect in the body, playing an important role in the body's response to infection and inflammation.<sup>64</sup> Preventing infection and inflammation during pregnancy is important not only for overall maternal and fetal health, but also, specifically, for preventing preterm birth.<sup>65</sup> Vitamin D plays an important role in cell formation; embryo implantation; and placenta formation, maintenance, and function.<sup>66</sup> Liu and Hewison (2012), for example, describe the mechanisms by

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<sup>64</sup> Liu, N., *et al.* showed that vitamin D plays a role in the immune response processes that take place in the placenta. The researchers concluded that the “data highlight a role for vitamin D as a potent regulator of inflammation in the placenta, and [that] this may be a key factor linking vitamin D with pathological conditions such as pre-eclampsia.” They also noted that vitamin D appears to stimulate other immune responses, including “the stimulation of antibacterial innate immune response.” Liu, N.Q., *et al.*, *Vitamin D and the Regulation of Placental Inflammation*, 186 J IMMUN 5968-5974 (2011).

Shin *et al.*, describes in detail the role vitamin D plays in the innate and adaptive immune responses, cell proliferation and differentiation, and, among other pregnancy processes, calcium absorption by the fetus. The researchers also conclude that vitamin D “supports fetal growth through delivery of calcium, controls secretion of multiple placental hormones, and limits production of proinflammatory cytokines.” Shin, J.S., *et al.*, *Vitamin D Effects on Pregnancy and the Placenta*, 31(12) PLACENTA 1027-103, at 407 (2010) (hereinafter “Shin *et al.* (2010)”).

<sup>65</sup> For example, bacterial vaginosis has been identified as a cause of pregnancy complications, including leading to preterm birth and other adverse pregnancy outcomes. *See, e.g.*, Kaushal, M. & Magon, N., *Vitamin D in pregnancy: A metabolic outlook*, 17(1) INDIAN J ENDOCRINOL METAB 76-82, 79 (2013) (hereinafter “Kaushal & Magon (2013)”); Heyden & Wimalawansa (2017).

Tamblyn *et al.* also describe how vitamin D acts as an immunomodulatory at the placenta. The researchers conclude that “[s]uccessful maintenance of [the] complex decidual immune system requires an equally complex set of regulatory factor[s] and, in this setting, vitamin D may play a highly versatile role by promoting antibacterial innate immune responses to infection while suppressing adverse inflammatory adaptive immunity.” The researchers note that “the placenta is one of the principal sites for extra-renal synthesis of 1,25(OH)<sub>2</sub>D, with both the maternal and fetal sides of the placenta cooperating to maintain high localized tissue levels of this hormone” and that the “success of these decidual responses to vitamin D will be dependent on the availability of substrate 25OHD, so that tissue-specific levels of 1,25(OH)<sub>2</sub>D may be compromised under conditions of vitamin D-insufficiency.” Tamblyn, J.A., *et al.*, *Immunological role of vitamin D at the maternal-fetal interface*, 244(3) J ENDOCRINOL R107-R121, R108-110 (2015).

<sup>66</sup> Cleal *et al.* explored the role vitamin D plays in placental amino acid transport, which is a critical process for placenta formation, implantation, and maintenance. Specifically, “[p]lacental amino acid transport is important for foetal growth and development” because it is integral to “foetal bone development.” By studying data and samples from a cohort study of 3158 pregnancies, the researchers determined that “[m]aternal 25(OH)D and [vitamin D binding protein] levels were positively associated with placental expression of genes involved in amino acid transport[, which] suggests that maternal vitamin D status may regulate the expression of placental amino acid transporters and potentially influence the transfer of amino acids to the fetus and subsequent foetal growth.” Cleal, J.K., *et al.*, *Placental amino acid transport may be regulated by maternal vitamin D and vitamin D-binding protein: results from the Southampton Women's Survey*, 113 BRIT J NUTR 1903-1910, 1907 (2015).

Meanwhile, Chen *et al.*, showed the mechanism by which vitamin D affects placental amino acid transport. The researched observed “placental amino acid transport activity increased after 18 hours of treatment, suggesting that regulation of placental amino acid transporter activity by 1,25-dihydroxy vitamin D<sub>3</sub> is likely to be mediated by transcriptional regulation via genomic actions rather than the rapid non-transcriptional actions.” The researchers concluded that these results were “consistent with the possibility that the improved vitamin D status through supplementation may be a potential strategy for reducing the risk of [fetal growth restriction] by increasing amino

which vitamin D exhibits immunomodulatory effects at various stages of a woman's reproductive cycle, including at conception and fertility, as well as during placental metabolism, implantation, and anti-inflammatory action.<sup>67</sup> This study details the impact of substrates and metabolites involved in vitamin D metabolism in various processes crucial to pregnancy, thereby demonstrating that vitamin D is involved in more than just maintenance of skeletal health. The conclusion reached by the researchers is instructive for the context of this health claim petition: "There is now increasing evidence that vitamin D exerts diverse effects during pregnancy. In its classical endocrine setting vitamin D remains an important component of maternal calcium homeostasis. However, it is now clear that the actions of vitamin D are likely to extend far beyond this, most notably on infection and immunity during pregnancy."<sup>68</sup>

With these mechanisms of action in mind, researchers have investigated the various impacts of vitamin D on pregnancy outcomes.<sup>69</sup> Current research shows a definite association between serum vitamin D levels and the incidence of preterm birth. The research also suggests that high serum vitamin D levels and vitamin D<sub>3</sub> supplementation can make a difference between an early preterm (generally at or before 34 weeks) or a late preterm birth (generally between 34

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acid transport across the placenta." Chen, Y.-Y., *et al.*, *1,25-dihydroxy vitamin D<sub>3</sub> stimulates System A amino acid transport in primary human trophoblast cells*, 442 *MOL CELL ENDOCRINOL* 90-97 (2017).

Among the conclusions by Shin *et al.* is that data support the role vitamin D plays in implantation and maintaining a normal pregnancy. Shin *et al.* (2010), at 6. Its role in reducing the risk of or helping to modulate the several harmful conditions for pregnant women (*e.g.*, pre-eclampsia, insulin resistance, and bacterial vaginosis) are also described by the researchers. *Id.*; see also Ganguly, A., *et al.*, *Vitamin D, the placenta and early pregnancy: effects on trophoblast function*, 236(2) *J ENDOCRINOL* R93-R103 (2018) (providing overview of vitamin D's effects in early pregnancy, including its role in placenta implantation and development).

<sup>67</sup> See Liu & Hewison (2012).

<sup>68</sup> *Id.*, at 45.

<sup>69</sup> Vitamin D has also been associated with pre-eclampsia, a pregnancy disorder that causes complications for safe and full-term delivery. For example, Wei *et al.* *BJOG* (2012) found that "lower maternal 25(OH)D levels at late mid-trimester were associated with an increased risk of pre-eclampsia." Wei, S.Q., *et al.*, *Longitudinal vitamin D status in pregnancy and the risk of pre-eclampsia*, 119(7) *BJOG* 832-839 (2012). The association was deemed statistically significant when comparing the mean 25(OH)D concentrations at 24-36 weeks of women who developed pre-eclampsia and those who did not (p=0.03). *Id.* Low 25(OH)D concentrations were assessed as < 50 nmol/L. The researchers concluded that because of "the high prevalence of vitamin D in pregnant women, it could be a modifiable risk factor with important public-health implications." *Id.* at 837.

Another adverse pregnancy outcome is recurrent pregnancy loss (RPL) or miscarriage, and vitamin D deficiency is a risk factor for RPL. Ota (2014) reported "a high proportion of women with RPL have vitamin D deficient, which is associated with increased cellular and autoimmunity." Ota, K., *et al.*, *Vitamin D deficiency may be a risk factor for recurrent pregnancy losses by increasing cellular immunity and autoimmunity*, 29 *HUM REPRO* 208-219 (2014). Ota *et al.* also concluded that vitamin D has "immunological implications in RPL" and that "vitamin D could be available as a new therapeutic option for reproductive failure." *Id.* at 217. Additionally, Wang *et al.* showed that there is likely an association between recurrent miscarriage and vitamin D levels. Wang, L-Q., *et al.*, *Women with Recurrent Miscarriage Have Decreased Expression of 25-Hydroxyvitamin D<sub>3</sub>-1 $\alpha$ -Hydroxylase by the Fetal-Maternal Interface*, 2016 *PLoS ONE* 1-12 (2016). See also Al-Shaikh, G.K., *et al.*, *Impact of vitamin D deficiency on maternal and birth outcomes in the Saudi population: a cross-sectional study*, 16 *BMC PREG AND CHILDBIRTH* 119-127 (2016) (concluding that there is a high prevalence of hypovitaminosis D among women in Riyadh, Saudi Arabia and that there was a "higher prevalence of miscarriage in women with low 25(OH)D."); Andersen, L.B., *et al.*, *Vitamin D insufficiency is associated with increased risk of first trimester miscarriage in the Odense Child Cohort*, 102 *AM J CLIN NUTR* 633-638 (2015) (concluding that "vitamin D is a modifiable risk factor for miscarriage" after finding an "association between 25(OH)D and first-trimester miscarriages").



and 37 weeks). This is an important finding, as an extra week or two weeks of gestation can have a significant and positive impact on the health of the mother and her newborn.

Studies – including many recent studies – have consistently found a relationship between maternal circulating vitamin D levels, which is best indicated by measuring serum levels of 25-hydroxyvitamin D (25(OH)D), and the risk of preterm birth. Specifically, higher levels of maternal circulating 25(OH)D are consistently associated with fewer preterm births. Among the research done into the effect of vitamin D on preterm birth are several human clinical trials investigating the association between maternal serum vitamin D levels and pregnancy outcomes, including preterm birth. Based on the totality of publicly-available scientific evidence, there is significant scientific agreement among experts qualified by scientific training and experience that vitamin D is associated with a decreased risk of preterm birth.

### **1. Higher serum vitamin D levels are associated with a lower risk of preterm birth.**

There is significant scientific agreement among experts qualified by scientific training and experience that higher serum vitamin D levels are associated with a decreased risk of preterm birth. Indeed, intervention trials show that vitamin D<sub>3</sub> supplementation effectively raises maternal circulating vitamin D levels and that higher levels of maternal circulating vitamin D are associated with a reduced risk of preterm birth. Singh *et al.* (2015)<sup>70</sup> examined the effect of supplementation with 2,000 IU vitamin D<sub>3</sub> on preterm birth in a randomized control study involving 100 pregnant women. Supplementation began as early as 12 weeks' gestation and continued through to delivery, and 25(OH)D serum levels were measured in blood samples that were taken at enrollment (baseline) and at the time of delivery.<sup>71</sup> Pregnant women in the control group were not given any vitamin D supplements. Results showed a statistically-significant relationship (p=0.001) between vitamin D deficiency (serum 25(OH)D levels <20 ng/mL or <50 nmol/L) and premature birth, specifically that “[v]itamin D deficiency increases the risk for preterm birth.”<sup>72</sup> The results of this study also showed that vitamin D<sub>3</sub> supplementation can improve maternal circulating vitamin D levels. The researchers concluded that vitamin D sufficiency (25(OH)D >50 nmol/L) “significantly reduces the risk for preterm birth.”<sup>73</sup>

A two-year randomized, controlled clinical trial conducted by Sablok *et al.* (2015)<sup>74</sup> showed that vitamin D<sub>3</sub> supplementation at higher than currently-recommended doses “reduces risk of maternal comorbidities and helps improve neonatal outcomes.”<sup>75</sup> The study involved 180 women randomized into control and treatment groups, with those in the treatment group given vitamin D<sub>3</sub> supplements depending on their baseline serum 25(OH)D levels.<sup>76</sup> The study's main

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<sup>70</sup> Singh, J. *et al.*, *Role of Vitamin D in Reducing the Risk of Preterm Labour*, 4(1) INT'L J OF REPRO CONTRA OBSTET GYNECOL 86-93 (2014) (hereinafter “Singh *et al.* (2014)”).

<sup>71</sup> Singh *et al.* defined vitamin D deficiency as < 30 nmol/L for the study and control groups, vitamin D inadequacy as 30-49.99 nmol/L, and vitamin D sufficiency as 50-74.99 nmol/L. These cut-off levels are consistent with current IOM recommendations.

<sup>72</sup> Singh *et al.* (2014), at 90.

<sup>73</sup> Singh *et al.* (2014), at 91.

<sup>74</sup> Sablok, A. *et al.*, *Supplementation of Vitamin D in Pregnancy and its Correlation with Feto-Maternal Outcome*, 83(4) J CLIN ENDOCRINOL, 536-541 (2015) (hereinafter “Sablok *et al.* (2015)”).

<sup>75</sup> Sablok *et al.* (2015), at 536.

<sup>76</sup> Sablok *et al.* (2015), at 537 (explaining that at baseline, women in the treatment group were classified according to their serum 25(OH)D levels, and were given vitamin D supplements as follows: one dose of 60,000 IU at 20

outcome measures included preterm labor, preeclampsia, and low birth weight. Each pregnant women in the treatment group showed an increase in serum 25(OH)D levels after supplementation, demonstrating that vitamin D<sub>3</sub> supplementation effectively increases circulating maternal vitamin D levels. Comparison between the groups revealed that women in the treatment group were less likely to experience preterm labor (21.1% vs. 8.3%), and the difference between the groups regarding this measure was statistically significant (p=0.02). None of the women developed hypervitaminosis D.

Several observational studies and secondary data analyses confirm the results from these intervention trials. After the Wagner (2013) and Hollis (2011) clinical trials, which are discussed in detail below, the Medical University of South Carolina (MUSC) implemented new guidelines for pregnant women; those guidelines included routine vitamin D supplementation. MUSC is a “comprehensive, urban medical center treating a large, diverse population of women (~ 3000 deliveries/year).”<sup>77</sup> To investigate the effect of these new vitamin D supplementation guidelines, McDonnell *et al.* (2017) analyzed medical data from 1,064 pregnant women treated at MUSC between September 2015 and December 2016 and who had at least one serum 25(OH)D test. Based on analyses of these data, the researchers concluded that maternal circulating serum 25(OH)D levels of  $\geq 40$  ng/mL (100 nmol/L) were associated with “substantial reduction”<sup>78</sup> in the risk of preterm birth. Specifically, at  $\geq 40$  ng/mL (100 nmol/L) 25(OH)D, there was a 62% lower risk of preterm birth as compared to those with a serum 25(OH)D concentration of  $< 20$  ng/mL (50 nmol/L) (p<0.0001).<sup>79</sup> Subgroup analysis of the data revealed similar magnitudes of risk with serum 25(OH)D concentrations  $\geq 40$  ng/mL (100 nmol/L): for spontaneous preterm birth<sup>80</sup>, there was a 58% reduced risk, and for indicated preterm birth, there was a 61% reduced risk. The researchers concluded that the study findings indicated that a “higher vitamin D status is significantly associated with lower [preterm birth] risk for both [preterm birth] subtypes and that vitamin D plays an important role in the underlying causes of indicated [preterm birth] including maternal hypertension, pre-existing diabetes, and non-reassuring fetal status.”<sup>81</sup> The researchers also concluded that the findings showed the importance of achieving maternal circulating serum 25(OH)D concentrations “substantially above” 20 ng/mL<sup>82</sup> for effective preterm birth prevention. Indeed, there “were significant decreases in [preterm birth] risk for 40 ng/mL vs.  $< 20$  ng/mL for both white (65%) and non-white women (68%).”<sup>83</sup>

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weeks if sufficient serum 25(OH)D ( $> 50$  nmol/L); two doses of 120,000 IU at 20 and 24 weeks if insufficient serum 25(OH)D (25-50 nmol/L); and four doses of 120,000 IU at 20, 24, 28, and 32 weeks if deficient serum 25(OH)D ( $< 25$  nmol/L)).

<sup>77</sup> McDonnell *et al.* (2017).

<sup>78</sup> McDonnell *et al.* (2017), at 2.

<sup>79</sup> McDonnell *et al.* (2017), at 6.

<sup>80</sup> Spontaneous preterm births are generally characterized as those during which, among other things, a woman’s water breaks or her cervix opens with no contractions. In contrast are indicated preterm births, which are planned because of a medical need, usually an imminent risk to the fetus or mother.

<sup>81</sup> McDonnell *et al.* (2017), at 9. These conclusions are supported by the data analyses conducted by Perez-Ferre *et al.*, which is discussed below. That 2012 study focused on the link between vitamin D status and glucose levels, which tends to indicate gestational diabetes, and found that low vitamin D levels were associated with “disorders in glucose homeostasis and adverse obstetric and newborn outcomes.”

<sup>82</sup> McDonnell *et al.* (2017), at 10

<sup>83</sup> McDonnell *et al.* (2017), at 9

A 2016 *post-hoc* analysis of Hollis (2011) and Wagner (2013) found a “clear association between 25(OH)D serum concentration within six weeks of delivery and preterm birth.”<sup>84</sup> This analysis found that pregnant women with a 25(OH)D serum concentration of “ $\geq 40$  ng/mL [100 nmol/L] within 6 weeks of delivery had a 57% lower risk of preterm birth as compared to those with concentrations  $\leq 20$  ng/mL [50 nmol/L].”<sup>85</sup> Of the pregnant women who began each study with a  $\leq 20$  ng/mL 25(OH)D serum concentration, those whose serum levels rose to  $\geq 40$  ng/mL (100 nmol/L) within 6 weeks of delivery “had 78% lower risk of preterm birth”<sup>86</sup> as compared to those who did not. Additionally, after adjusting for certain confounding socioeconomic factors, the positive effect of high circulating maternal vitamin D remained, as those with “ $\geq 40$  ng/mL [100 nmol/L] had a 59% lower risk of preterm birth.”<sup>87</sup> The researchers further observed that “the reduction in risk was most notable among those with baseline 25(OH)D  $\leq 20$  ng/mL [50 nmol/L] and among Hispanic women,” which they conclude support “the importance of vitamin D status during pregnancy.” The conclusion of this analysis was that that 25(OH)D levels of “40 ng/mL [100 nmol/L] and above are needed to significantly reduce the risk of preterm birth.”<sup>88</sup> Specifically, they concluded that “[r]eaching 40 ng/mL [100 nmol/L] would achieve the optimal conversion of 25(OH)D to 1,25(OH)<sub>2</sub>D and lower preterm birth risk.”<sup>89</sup>

In 2015, Wagner *et al.*<sup>90</sup> conducted a separate *post-hoc* analysis of the Hollis (2011) and Wagner (2013) clinical trials, focusing specifically on three important time points during pregnancy. This 2015 analysis found an association between late-term vitamin D<sub>3</sub> supplementation and a reduced risk of preterm birth. Specifically, “at baseline, those who had serum concentrations  $< 50$  nmol/L (20 ng/mL) had 3.3 times of odds of a preterm birth compared to those with serum concentrations  $\geq 100$  nmol/L (40 ng/mL;  $p = 0.27$ ). At 2nd trimester, the odds were 2.0 fold ( $p = 0.21$ ) and at the end of pregnancy, the odds were 3.8 fold ( $p = 0.01$ ).”<sup>91</sup> Indeed, “a serum concentration of 100 nmol/L (40 ng/mL) in the 3rd trimester was associated with a 47% reduction in preterm births.”<sup>92</sup> The analysis of data from almost 500 pregnant women focused on maternal circulating vitamin D levels at  $< 16$  weeks, 16-26 weeks, and  $\geq 27$  weeks and the association with preterm birth. Analysis showed that “maternal vitamin D status closest to delivery date was most closely associated with preterm birth and gestational age at delivery,”<sup>93</sup> leading to the conclusion that “intervention with vitamin [D<sub>3</sub>] supplementation throughout pregnancy but even given as ‘rescue therapy’ may impact vitamin D status and pregnancy outcome.”<sup>94</sup> As with other studies about vitamin D<sub>3</sub> supplementation and its effect on pregnancy outcomes, vitamin D levels were measured by the serum concentration of 25(OH)D, and no adverse effects were noted.

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<sup>84</sup> Wagner, C.L. *et al.*, *Post-hoc Analysis of Vitamin D Status and Reduced Risk of Preterm Birth in Two Vitamin D Pregnancy Cohorts Compared with South Carolina March of Dimes 2009-2011 Rates*, 155(B) J STEROID BIOCHEM MOL BIOL 245-251, 248 (2016) (hereinafter “Wagner *et al.* (2016)”, at 248).

<sup>85</sup> Wagner *et al.* (2016), at 247.

<sup>86</sup> *Id.*

<sup>87</sup> *Id.*

<sup>88</sup> *Id.* at 249.

<sup>89</sup> *Id.* at 250.

<sup>90</sup> Wagner, C.L. *et al.*, *Post-hoc Comparison of Vitamin D Status at Three Timepoints during Pregnancy Demonstrates Lower Risk of Preterm Birth with Higher Vitamin D Closer to Delivery*, 148 J STEROID BIOCHEM MOL BIOL 256-260 (2015) (hereinafter “Wagner *et al.* (2015)”).

<sup>91</sup> Wagner *et al.* (2015), at 256.

<sup>92</sup> *Id.*; see also *id.*, at 258.

<sup>93</sup> *Id.* at 256.

<sup>94</sup> *Id.* at 259.

A 2013 combined analysis<sup>95</sup> of the Hollis (2011) and Wagner (2013) clinical trials focused on the broader category of maternal comorbidities of pregnancy (COP). This 2013 analysis revealed that as vitamin D<sub>3</sub> supplementation dosage increased, there “was a trend toward lower rates of COP.”<sup>96</sup> The analysis defined sufficient vitamin D as a serum level of 32 ng/mL (80 nmol/L) and found that at this level, “there were clear differences in the rates of comorbidities for infection, hypertensive disorders of pregnancy, preterm birth without preeclampsia, and combined comorbidities.”<sup>97</sup> Additionally, a more detailed analysis of the data from these clinical trials revealed that “every 10ng/mL increase in maternal serum 25(OH)D at delivery resulted in reduced odds of infection and preterm birth without preeclampsia.”<sup>98</sup> Here, again, a beneficial association between vitamin D<sub>3</sub> supplementation, serum 25(OH)D concentration, and pregnancy outcomes was found.

In a case-cohort study<sup>99</sup> that evaluated 1,126 serum samples gathered at or before 20 weeks’ gestation from pregnant women in Pittsburgh, Pennsylvania, Bodnar *et al.* (2015) demonstrated that there was a relationship between serum 25(OH)D levels and the incidence of preterm birth, and that the risk of preterm birth significantly decreased as serum 25(OH)D concentrations increased. Even after adjusting for confounding socioeconomic and other risk factors, “the risk of preterm birth at less than 37 weeks of gestation significantly decreased as 25-hydroxyvitamin D increased to approximately 90 nmol/L [36 ng/mL] and then plateaued (test of nonlinearity  $P < .01$ ).”<sup>100</sup> Moreover, the “incidence of preterm birth at less than 37 weeks of gestation was 8.6% overall and 11.3%, 8.6%, and 7.3% among mothers with serum 25-hydroxyvitamin D less than 50, 50–74.9, and 75 nmol/L or greater [less than 20, 20–30, and 30 or greater ng/mL], respectively ( $P < .01$ ).”<sup>101</sup> Based on these data, the researchers concluded that “confounder-adjusted risk of preterm birth was highest when serum [25(OH)D] was less than 50 nmol/L [20 ng/mL];” the findings were similar for spontaneous or medically indicated preterm birth, as well as for preterm birth less than 34 weeks’ gestation.<sup>102</sup>

In another analysis of the association between pregnant women’s serum 25(OH)D concentrations and preterm birth, Bodnar *et al.* (2013) found that “serum vitamin D concentrations measured at 24–28 weeks of gestation were inversely associated with the risk of preterm birth at less than 35 weeks of gestation and at less than 32 weeks of gestation and with spontaneous preterm birth at less than 35 weeks of gestation, even after adjusting for covariates such as prepregnancy BMI, race and ethnicity, and season.”<sup>103</sup> Specifically, preterm birth “at less than 35 weeks of gestation occurred in 49.4% of women with [25(OH)D] concentrations less than 75 nmol/L [30 ng/mL] compared with 26.2% among those with concentrations of 75 nmol/L [30 ng/mL] or more

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<sup>95</sup> Wagner, C.L. *et al.*, *Health Characteristics and Outcomes of Two Randomized Vitamin D Supplementation Trials during Pregnancy: A Combined Analysis*, 136 J STEROID BIOCHEM MOL BIOL 313-320 (2013) (hereinafter “Wagner *et al.* (2013) combined analysis”).

<sup>96</sup> Wagner *et al.* (2013) combined analysis, at 313.

<sup>97</sup> *Id.*, at 318-319.

<sup>98</sup> *Id.*, at 319. The researchers also concluded that “[w]hen the four main comorbidities of pregnancy were combined, for every 10 ng/mL increase in maternal 25(OH)D at delivery, the odds ratio was reduced to 0.84 ( $p = 0.006$ ).”

<sup>99</sup> Bodnar *et al.* (2015).

<sup>100</sup> *Id.*, at 439.

<sup>101</sup> *Id.*

<sup>102</sup> *Id.*, at 444.

<sup>103</sup> Bodnar, L.M., *et al.*, *Maternal 25-Hydroxyvitamin D and Preterm Birth in Twin Gestations*, 122(1) OBSTET GYNECOL 91-98, at 95 (2013) (hereinafter “Bodnar *et al.* (2013)”).

( $P < .001$ ).<sup>104</sup> Even after adjusting for several socioeconomic and lifestyle factors, “maternal [25(OH)D] concentration of 75 nmol/L [30 ng/mL] or more was associated with a 60% reduction in the odds of preterm birth compared with concentrations less than 75 nmol/L [30 ng/mL] (adjusted odds ratio [OR] 0.4, 95% confidence interval [CI] 0.2–0.8).”<sup>105</sup> Moreover, a “similar protective association was observed when studying preterm birth at less than 32 weeks of gestation (OR 0.2, 95% CI 0.1–0.6) and after confounder adjustment.”<sup>106</sup> The authors noted that their “finding that poor vitamin D status is associated with early preterm birth suggests that the anti-inflammatory and immunomodulating roles of vitamin D may be relevant.”<sup>107</sup> They concluded that “[I]ate second-trimester maternal [25(OH)D] concentrations less than 75 nmol/L [30 ng/mL] are associated with an increase in the risk of preterm birth in this cohort of twin pregnancies.”<sup>108</sup>

The importance of higher maternal circulating serum 25(OH)D concentrations has been highlighted in other studies. In a prospective cohort study<sup>109</sup> of 1,810 women, in which serum 25(OH)D was measured in the first and third trimesters, Bärebring *et al.* (2018) showed that vitamin D “status trajectory from early to late pregnancy was inversely associated with...preterm delivery with the lowest odds among women with the highest increment” of 25(OH)D.<sup>110</sup> They concluded that lower vitamin D status in early pregnancy is related to pregnancy loss,<sup>111</sup> and that “the lowest odds [were] for women with an increment in [25(OH)D]  $\geq 30$  nmol/L [12 ng/mL].”<sup>112</sup>

Meanwhile, a retrospective cohort analysis by Dziadosz *et al.* (2014)<sup>113</sup> of 750 women showed that serum vitamin D levels at  $<20$  ng/mL (50 nmol/L) in early pregnancy led to an increased risk of preterm birth between 23 and 37 weeks. Based on this outcome of their analysis, the researchers hypothesized that vitamin D deficiency and preterm birth were related because of the “known anti-inflammatory and bacteriostatic properties inherent to vitamin D.” The researchers concluded that there was a relationship between vitamin D deficiency and preterm birth, with higher maternal circulating levels making preterm birth less likely.

Another study by Baczyńska-Strzecha and Kalinka (2017)<sup>114</sup> of 201 women – 100 of whom experienced spontaneous preterm birth and 101 of whom experienced a full-term birth (the control group) – found that while serum vitamin D deficiency ( $<30$  ng/mL or  $<75$  nmol/L) was common in both groups, women who experienced preterm birth had “severe vitamin D deficiency” more often than women in the control group. For this study, a severe vitamin D deficiency was defined as  $<10$  ng/mL (25 nmol/L) serum 25(OH)D. Additionally, based on analysis of each woman’s medical history, the researchers found that preterm births were more common in women who only

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<sup>104</sup> Bodnar *et al.* (2013), at 91

<sup>105</sup> Bodnar *et al.* (2013), at 91-92

<sup>106</sup> Bodnar *et al.* (2013), at 92

<sup>107</sup> Bodnar *et al.* (2013), at 96

<sup>108</sup> Bodnar *et al.* (2013), at 92

<sup>109</sup> Bärebring, L. *et al.*, *Trajectory of Vitamin D Status during Pregnancy in Relation to Neonatal Birth Size and Fetal Survival: a Prospective Cohort Study*, 18(51) BMC PREG AND CHILDBIRTH, 1-7 (2018) (hereinafter “Bärebring *et al.* (2018)”).

<sup>110</sup> Bärebring (2018), at 1.

<sup>111</sup> *Id.*, at 5.

<sup>112</sup> *Id.*, at 6.

<sup>113</sup> Dziadosz, M. *et al.*, *Vitamin D Deficiency in Early Gestation and Rates of Preterm Birth: A Retrospective Cohort*, 210(1) J OBSTET & GYN S391 (2014).

<sup>114</sup> Baczyńska-Strzecha & Kalinka (2017).

periodically supplemented with vitamin D during their pregnancy. Subgroup analysis also showed that the average level of maternal circulating vitamin D was lower in women who experienced an early preterm birth (before 34 weeks) than in women who experienced a late preterm birth (34-36.6 weeks). This study demonstrates the association between severe vitamin D deficiency (which the researchers defined as < 10 ng/mL or <25 nmol/L)<sup>115</sup> and increased risk of preterm birth, and that an earlier birth – even an earlier preterm birth – correlates with a lower vitamin D level.<sup>116</sup> Notable, too, is that the “percentage of patients with normal vitamin D levels [defined in the study as > 30 ng/mL or > 75 nmol/L] was higher for the term birth group than for the preterm birth group.”<sup>117</sup>

Tabatabaei *et al.* (2017)<sup>118</sup> found that an insufficient level of vitamin D is associated with an increased risk of preterm birth. This case control study focused on minority women and included 120 cases of preterm birth and 360 full-term births (the control group). Specifically, the study found that serum 25(OH)D concentrations of 30 nmol/L (12 ng/mL) were associated with “4.05 times the risk of preterm birth”<sup>119</sup> in the total population studied, relative to participants with a serum 25(OH)D concentration of 75 nmol/L (30 ng/mL). The researchers also observed that the proportion of preterm birth (overall and spontaneous) in this study “decreased progressively as maternal vitamin D status increased but only in ethnic minority women.”<sup>120</sup> Ultimately, the researchers concluded that “[v]itamin D insufficiency [plasma 25(OH)D <75 nmol/L [<30 ng/mL]] at early gestation is associated with an increased risk of preterm birth in ethnic minority women.”<sup>121</sup> Similar results indicating a link between ethnicity, serum vitamin D levels, and the risk of preterm birth were observed in the Wagner and Hollis intervention trials (discussed below), the secondary analyses of those trials, and in the McDonnell *et al.* analysis of those trials, which are discussed above.

Zhu *et al.* (2015)<sup>122</sup> found that mothers who gave birth to babies delivered before 31 weeks had “significantly lower vitamin D level[s] than those who delivered after 31 weeks of gestation.”<sup>123</sup> Despite not observing a difference in vitamin D levels (measured by serum 25(OH)D concentration) between the 31-week preterm births and those who were delivered at 32 – 37 weeks, the researchers concluded that low maternal vitamin D levels were associated with preterm births at least before 31 weeks.<sup>124</sup>

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<sup>115</sup> *Id.* at 935.

<sup>116</sup> *Id.* at 933.

<sup>117</sup> *Id.* at 935.

<sup>118</sup> Tabatabaei, N. *et al.*, *Maternal Vitamin D Insufficiency Early in Pregnancy is Associated with Increased Risk of Preterm Birth in Ethnic Minority Women in Canada*, 147(6) J NUTR 1145-1151 (2017) (hereinafter “Tabatabaei, N. *et al.* (2017)”).

<sup>119</sup> Tabatabaei, N. *et al.* (2017), at 1148

<sup>120</sup> *Id.*

<sup>121</sup> *Id.*

<sup>122</sup> Zhu, T. *et al.*, *High Prevalence of Maternal Vitamin D Deficiency in Preterm Births in Northeast China*, *Shenyang*, 8(2) INT’L J CLIN EXPER PATH 1459-1465 (2015) (hereinafter “Zhu *et al.* (2015)”).

<sup>123</sup> Zhu *et al.* (2015), at 1463.

<sup>124</sup> Zhu *et al.* (2015) (commenting on a seasonal impact of vitamin D deficiency, finding that the deficiency was most severe in late spring and least severe in the summertime). This finding corresponds with the general understanding of the effect of season and latitude on the body’s ability to synthesize vitamin D because of the varying availability of sunlight. This is particularly important for the population of pregnant women in the U.S. because of U.S. geography and climate. *Id.*

As mentioned above, vitamin D is known to have an immunomodulatory effect in the body.<sup>125</sup> As inflammation and infection are known causes of preterm birth and other adverse pregnancy outcomes, the underlying mechanism driving the well-established association described above between vitamin D supplementation and high maternal circulating vitamin D and a lower risk of preterm birth may be this immunomodulatory effect.

One prospective case-control study by Fischer-Suárez *et al.* (2016)<sup>126</sup> measured C-reactive protein (CRP) and vitamin D levels in 123 pregnant women – 59 women were experiencing threatened preterm labor (the case group) and 64 were experiencing a normal pregnancy (the control group). CRP is an accepted indicator of “systemic inflammation” that is “found in maternal blood at higher levels in conditions such as preeclampsia, preterm birth or intrauterine growth restrictions.”<sup>127</sup> The researchers measured CRP and vitamin D levels (using serum 25(OH)D concentrations) in both groups. Comparison of the two groups showed that while the mean serum 25(OH)D concentrations were similar in both groups,<sup>128</sup> subgroup analysis showed that women who actually delivered preterm had higher CRP, *lower* 25(OH)D levels, higher diastolic blood pressures, and shorter cervical lengths than the pregnant women in the control group.<sup>129</sup> They hypothesized that the link between preterm delivery and serum 25(OH)D levels is explained “by the effect that vitamin D has over the immune system and/or a direct effect over the myometrium.”<sup>130</sup> The researchers also commented that there was a “trend among those not receiving vitamin D supplements toward lower levels observed in the third as compared to the first trimester of pregnancy.”<sup>131</sup>

An earlier study by Shibata *et al.* (2011)<sup>132</sup> evaluated the serum 25(OH)D levels<sup>133</sup> of 93 pregnant women after 30 weeks’ gestation. The women were selected during a routine obstetric visit and had “biochemical parameters...checked in March, June, September, and December.”<sup>134</sup> The researchers concluded that “a high prevalence of hypovitaminosis D” in the study population “seems...to be associated with the threat of premature delivery.”<sup>135</sup> Specifically, analyses of the serum 25(OH)D levels showed that pregnant women “with threatened premature delivery [or

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<sup>125</sup> See discussion at the beginning of Section B.

<sup>126</sup> Fischer-Suárez, N. *et al.*, *Maternal Serum 25-Hydroxyvitamin D and C-Reactive Protein Levels in Pregnancies Complicated with Threatened Preterm Labour*, 32(9) J GYN ENDOCRINOL 777-781 (2016) (hereinafter “Fischer-Suarez *et al.* (2016)”).

<sup>127</sup> Fischer-Suarez *et al.* (2016), at 777.

<sup>128</sup> *Id.*, at Table 1 at 779 (showing the demographic and antenatal characteristics of women in the threatened preterm labor (TPL) and control groups). The table shows that the mean serum 25(OH)D levels between the TPL and control groups were similar, at 25.8 ng/mL and 25.0 ng/mL, respectively. A possible explanation for this may be the distribution of women classified as deficient, insufficient, and sufficient in the TPL versus the control groups. Women classified into each category were more evenly distributed in the control group than in the TPL group. *Id.*

<sup>129</sup> *Id.*, at 778.

<sup>130</sup> *Id.*, at 780.

<sup>131</sup> *Id.*, at 778.

<sup>132</sup> Shibata, M., *et al.*, *High prevalence of hypovitaminosis D in pregnant Japanese women with threatened premature delivery*, 29 J BONE MINER METAB 615-620 (2011) (hereinafter “Shibata *et al.* (2011)”).

<sup>133</sup> Shibata *et al.* (2011), at 615, 619 (defines vitamin D deficiency as serum 25(OH)D less than 10 ng/mL and hypovitaminosis D as serum 25(OH)D less than 20 ng/mL).

<sup>134</sup> *Id.*, at 616.

<sup>135</sup> *Id.*, at 619-620.

preterm birth] had significantly lower 25-OHD levels ( $11.2 \pm 3.2$  ng/ml) than those in mothers with normal delivery ( $15.6 \pm 5.1$  ng/ml).”<sup>136</sup>

Perez-Ferre *et al.* (2012)<sup>137</sup> showed an association between low serum vitamin D levels and high fasting glucose levels, the latter being a marker for gestational diabetes, which is known to make preterm birth more likely. Data analyses also showed that with “a 25(OH)D concentration less than 20 ng/mL, the odds ratios were 3.31 for premature birth” ( $p < 0.02$ ).<sup>138</sup> As compared to women with greater than 20 ng/mL serum 25(OH)D, women with less than 20 ng/mL serum 25(OH)D “presented more frequently [with] premature birth. ( $P < 0.001$ ).”<sup>139</sup> This study evaluated serum 25(OH)D and fasting glucose levels in 266 pregnant women and then evaluated delivery and newborn outcomes. The researchers concluded that vitamin D deficiency ( $< 20$  ng/mL or 50 nmol/L) was “very common during pregnancy”<sup>140</sup> in the study population, and that lower levels of 25(OH)D were associated with “disorders of glucose homeostasis and adverse obstetric and newborn outcomes.”<sup>141</sup> The researchers also commented that vitamin D status has been linked to immune status, and that “certain infections have been associated with preeclampsia.”<sup>142</sup> A compromised immune system or infection during pregnancy has been shown to increase the risk of preterm birth. Perez-Ferre *et al.* also mention that “[v]itamin D deficiency has been associated with proximal muscle weakness and suboptimal muscle performance and strength, thus having a role in the initiation of early labor”<sup>143</sup> which could lead directly to preterm birth.

Another study of women experiencing high risk pregnancy confirmed that low serum vitamin D levels is associated with lower preterm birth risk. This secondary analysis by Gernand *et al.* (2016)<sup>144</sup> is important because it demonstrates that the association between serum vitamin D levels and lower preterm birth risk is constant in a high-risk pregnant population. The study analyzed the serum 25(OH)D concentrations in 822 geographically- and racially-diverse women who underwent a low-dose aspirin trial. Analysis of the data showed that low serum vitamin D levels were related to the risk of “preeclampsia and preterm birth at  $< 35$  weeks in high risk pregnancies.”<sup>145</sup> Specifically, “vitamin D status was associated with risk of preterm birth at  $< 35$  weeks’ gestations – an association driven by indicated deliveries, many of which were medically necessary due to hypertensive disorders.”<sup>146</sup> The results led these researchers to conclude that there was a link between maternal circulating vitamin D and preterm birth at  $< 35$  weeks.

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<sup>136</sup> *Id.*, at 615.

<sup>137</sup> Perez-Ferre, N. *et al.*, *Association of Low Serum 25-Hydroxyvitamin D Levels in Pregnancy with Glucose Homeostasis and Obstetric and Newborn Outcomes*, 18(5) *AACE J ENDOCRIN PRACT* 676-684 (2012) (hereinafter “Perez-Ferre *et al.* (2012)”).

<sup>138</sup> Perez-Ferre *et al.* (2012), at 676.

<sup>139</sup> *Id.*, at 678.

<sup>140</sup> *Id.*, at 676.

<sup>141</sup> *Id.*,

<sup>142</sup> *Id.*, at 680.

<sup>143</sup> *Id.*,

<sup>144</sup> Gernand, A.D. *et al.*, *Vitamin D, Pre-Eclampsia, and Preterm Birth Among Pregnancies at High Risk for Pre-Eclampsia: An Analysis of Data from a Low-Dose Aspirin Trial*, 124(12) *INT’L J OBSTET GYN* 1874-1882 (2016) (hereinafter “Gernand *et al.* (2016)”).

<sup>145</sup> Gernand *et al.* (2016), at 1874.

<sup>146</sup> *Id.* at 1879.



Another mechanism by which vitamin D works to improve pregnancy outcomes is its involvement in placenta formation and maintenance. Mohamed *et al.* (2017)<sup>147</sup> showed an association between maternal circulating vitamin D and corticotropin-releasing hormone (CRH) levels. CRH is produced and released by the placenta, and maternal circulating levels increase throughout gestation. It has been observed that the “rise of maternal CRH occurs earlier and more rapidly in women who deliver preterm compared to women who deliver at term.”<sup>148</sup> Based on this study of 97 women (15 early-preterm, 31 late-preterm, 21 early-term, and 30 term births)<sup>149</sup>, the researchers concluded that early-preterm birth was associated with high maternal CRH and low serum vitamin D levels. Specifically, for preterm births “without other pregnancy complications,” the women with serum 25(OH)D levels below 30 ng/mL had higher circulating CRH (p=0.016).<sup>150</sup> Notably, most of the women who experienced an early preterm birth (73.3%) and almost half of those who experienced a late preterm birth (45.2%) had 25(OH)D levels below 30 ng/mL, compared to 25.5% of term births; the difference was statistically significant (p=0.003).<sup>151</sup> Overall, these researchers concluded that the results indicate a link between circulating maternal 25(OH)D levels and pregnancy outcomes, “with low vitamin D status linked with poorer outcomes.”<sup>152</sup> They also concluded that these data support the conclusion that “vitamin D regulates CRH through effects on inflammatory mechanisms.”<sup>153</sup>

Meta-analyses and review articles also confirm the association between vitamin D and preterm birth, specifically that higher levels of serum 25(OH)D are associated with a lower risk of preterm birth. Zhou *et al.* (2017)<sup>154</sup> reviewed 24 studies, which included 6 randomized control trials (RCTs) and 18 observational studies, and found that vitamin D deficiency (<50 nmol/L [20 ng/mL] 25(OH)D) was associated with an increased risk of preterm birth. The analysis of the RCTs (totaling 1687 women<sup>155</sup>) – in which oral vitamin D supplementation ranged from 400 IU to 120,000 IU<sup>156</sup> – found that studies with sample sizes exceeding 100, a low risk bias, and single-dose vitamin D supplementation demonstrated that vitamin D was “significantly associated” with preterm birth.<sup>157</sup> Further, this meta-analysis found that supplementation alone could reduce this preterm birth risk. Amegah *et al.* (2017)<sup>158</sup> reviewed eighteen studies and found that serum 25(OH)D levels of <75 nmol/L [30 ng/mL] were associated with an 83% increased risk of preterm birth at <32-34 weeks and a 13% increased risk of preterm birth at <35-37 weeks. An inverse dose relationship was also observed for both of these preterm birth outcomes. The results for every study included in this meta-analysis were obtained at health facilities, and the authors found that

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<sup>147</sup> Mohamed, S. et al., *Vitamin D and Corticotropin-Releasing Hormone in Term and Preterm Birth: Potential Contributions to Preterm Labor and Birth Outcome*, 2017 J MATERNAL-FETAL & NEONATAL MED 1-7 (2017) (hereinafter “Mohamed *et al.* (2017)”).

<sup>148</sup> Mohamed *et al.* (2017), at 2.

<sup>149</sup> In this study, early-preterm birth was defined as delivery before 34 weeks and early-term birth was defined as delivery between 37 and 38 weeks. *See id.*

<sup>150</sup> *Id.*, at 5.

<sup>151</sup> *Id.*, at 4.

<sup>152</sup> *Id.*, at 5.

<sup>153</sup> *Id.*, at 6.

<sup>154</sup> Zhou, S. et al., *Vitamin D and Risk of Preterm Birth: Up-to-Date Meta-Analysis of Randomized Controlled Trials and Observational Studies*, 43(2) J OBSTET GYNECOL RES 247-256 (2017) (hereinafter “Zhou *et al.* (2017)”).

<sup>155</sup> Zhou *et al.* (2017), at 254.

<sup>156</sup> Vitamin D<sub>3</sub> was used for oral supplementation in 5 of the 6 RCTs reviewed in by Zhou. *Id.* at 250-251.

<sup>157</sup> *Id.* at 251.

<sup>158</sup> Amegah, A. K. et al., *Maternal Vitamin D Insufficiency and Risk of Adverse Pregnancy and Birth Outcomes: A Systematic Review and Meta-analysis of Longitudinal Studies*, 12(3) PLoS ONE 1-22 (2017).

the potential for information bias was unlikely. Qin *et al.* (2016)<sup>159</sup> analyzed 10 studies including 10,098 participants and determined that pregnant women with a vitamin D deficiency (*i.e.*, 25(OH)D <20 ng/mL) had a significantly increased risk of preterm birth.

While we acknowledge that many of the studies cited in these meta-analyses do not show an association between vitamin D deficiency and risk of preterm labor,<sup>160</sup> there are a number of potential factors that indicate that, in the case of the association between preterm delivery and vitamin D levels, pooled data in meta-analyses offers an advantage over, or at least addresses some of the potential weaknesses of, the individual studies.

First, the pooled data across many different studies helps to address potential issues caused by differences in serum vitamin D levels due to geography. For example, one study notes that a potential reason why the study did not detect statistically-significant links between vitamin D deficiency and pregnancy outcomes was “perhaps due to the low prevalence (1.6% of the cohort) of severe maternal vitamin D deficiency (defined as < 30.0 nmol/l [12 ng/mL]) in our population,” with a total percent of the study population that is deficient at only 13.2%.<sup>161</sup> Even studies conducted in different parts of the United States reported different prevalence of vitamin D deficiency in sites in the Northern versus the Southern USA.<sup>162</sup> By pooling data from studies conducted in multiple different localities, these meta-analyses can help diminish the unique effects that a specific local climate or diet might have on issues similar to those referenced in Ong, *et al.*

Second, pooled data can help address issues of individual studies being insufficiently powered to detect significant differences in such a rare endpoint. A number of the studies mentioned the difficulties posed by the relative rarity of preterm birth or a small instance of severe vitamin D deficiency in a study population and how that can affect whether a study is sufficiently powered to detect effects of vitamin D deficiency on preterm delivery.<sup>163</sup> For example, in Flood-Nichols *et al.*, researchers investigated whether there was a link between vitamin D deficiency and a composite of multiple negative pregnancy outcomes (*e.g.*, preeclampsia, growth restriction, gestational diabetes, preterm labor, and spontaneous abortion).<sup>164</sup> The study authors note that a

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<sup>159</sup> Qin, L. *et al.*, *Does Maternal Vitamin D Deficiency Increase the Risk of Preterm Birth: A Meta-Analysis of Observational Studies*, 8(5) NUTRIENTS 1-10 (2016).

<sup>160</sup> We note that while numerous studies did not independently find a statistically-significant association between preterm birth and vitamin D deficiency, there was only one study, Zhou, *et al.* (2014), that found an association between preterm delivery and higher levels of vitamin D. However, the study authors dismissed this results, as the study failed to control for age and BMI of the mother, two factors that are also associated with preterm birth and were higher in the high vitamin D group. Zhou, J., *et al.*, *Associations between 25-hydroxyvitamin D levels and pregnancy outcomes: a prospective observational study in southern China*, 68 Euro J Clin Nutr 925-930, 925 (2014) (cited in Amegah, *et al.*, 2017).

<sup>161</sup> Ong, Y.L., *et al.*, *The association of maternal vitamin D status with infant birth outcomes, postnatal growth and adiposity in the first 2 years of life in a multi-ethnic Asian population: the Growing Up in Singapore Towards healthy Outcomes (GUSTO) cohort study*, 116 BRIT J NUTR 612-631 (2016) (hereinafter “Ong *et al.* (2016)”).

<sup>162</sup> Thorp, J.M., *et al.*, *Vitamin D status and recurrent preterm birth: a nested case-control study in high-risk women*, 119(13) BJOG 1617-1623 (2012).

<sup>163</sup> See, *e.g.*, Ong *et al.* (2016), at 621 (noting low prevalence of vitamin D deficiency and severe vitamin D deficiency); Møller, U.K., *et al.*, *Effects of 25OHD concentrations on chances of pregnancy and pregnancy outcomes: a cohort study in healthy Danish women*, 66 Euro J CLIN NUTR 862-868, 867 (2012) (“As only few of our included women had severe vitamin D deficiency, our study does not allow for conclusions on effects of very low P-25OHD concentrations. Moreover, our study does not exclude minor effects of P-25OHD insufficiency that we may not have been able to detect because of the relative small size of our study.”).

<sup>164</sup> Flood-Nichols, S.K., *et al.*, *Vitamin D Deficiency in Early Pregnancy*, 10(40) PLOS ONE e0123763 (2015).

study population of n=235 “was not powered to detect associations between vitamin D status and these individual complications of pregnancy.”<sup>165</sup> In an even larger observational study (n > 2300), Rodriguez *et al.*, study authors noted “the small rate of some adverse pregnancy outcomes may limit the statistical power to detect significant differences.”<sup>166</sup>

Lastly, some of the studies distinguished between spontaneous preterm birth and medical conditions that are linked to and may necessitate medically-induced preterm delivery (*e.g.*, preeclampsia), with some studies performing different statistical analyses for each outcome<sup>167</sup> and others simply measuring only spontaneous preterm birth.<sup>168</sup> Therefore, studies that measured only spontaneous preterm birth may have been under inclusive of the number of actual or threatened preterm deliveries. In either scenario, considering separately or not measuring physician-induced preterm delivery due to pregnancy complications, the prevalence of the preterm birth outcomes could have been under reported, potentially exacerbating issues relating to underpowered studies. Again, by pooling the data and increasing the sample size, the meta-analyses can help address issues relating to insufficiently powered studies to detect statistically-significant associations between vitamin D deficiency and preterm delivery.

These studies and analyses show that a higher serum vitamin D level is associated with a significant and beneficial effect on the incidence of preterm birth. It is also important that no adverse events were reported in the studies discussed above.

## **2. Supplementation with vitamin D<sub>3</sub> increases the serum vitamin D levels in pregnant women.**

Multiple studies have also shown that supplementation with vitamin D<sub>3</sub> increases serum 25(OH)D levels in pregnant women. Wagner *et al.* (2013)<sup>169</sup> showed that daily vitamin D<sub>3</sub> supplementation at 2,000 IU and 4,000 IU improved maternal and neonatal vitamin D status in a diverse group of subjects. By 10 weeks’ gestation, pregnant women were enrolled in this randomized, double-blinded study, and supplementation with either 2,000 IU or 4,000 IU (vitamin D<sub>3</sub>) began no earlier than 12 weeks’ gestation. The women were observed and given daily vitamin D<sub>3</sub> supplements throughout the remainder of their pregnancies; blood samples were collected at baseline, at alternating obstetric visits, and at the time of delivery so that the researchers were able to track serum 25(OH)D levels throughout the pregnancy. Urine samples were collected at each obstetric visit, and, at delivery, cord blood was collected (if no cord blood was available then blood samples were taken from the newborn within 2 weeks of delivery). Based on comparisons between dosage groups of serum 25(OH)D levels, Wagner *et al.* demonstrated that daily vitamin D<sub>3</sub> supplementation at 4,000 IU is better at raising maternal serum vitamin D levels over time than a daily 2,000 IU dose. This higher dosage level is also superior at achieving sufficient vitamin D

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<sup>165</sup> *Id.* at 11.

<sup>166</sup> Rodriguez, A., *et al.*, *Associations of maternal circulating 25-hydroxyvitamin D<sub>3</sub> concentration with pregnancy and birth outcomes*, 122 BJOG 1695-1704 (2015).

<sup>167</sup> See Schneuer, F.J., *et al.*, *Effects of maternal serum 25-hydroxyvitamin D concentrations in the first trimester on subsequent pregnancy outcomes in an Australian population*, 99 AM J CLIN NUTR 287-295 (2014) (distinguishing between spontaneous preterm birth and preeclampsia).

<sup>168</sup> See Baker, A.M., *et al.*, *A Nested Case-Control Study of First-Trimester Maternal Vitamin D Status and Risk for Spontaneous Preterm Birth*, 28(9) AM J PERINATOL 667-671, 668 (2011) (only including spontaneous preterm birth, specifically excluding iatrogenic (physician caused) preterm deliveries).

<sup>169</sup> Wagner, C.L. *et al.*, *A Randomized Trial of Vitamin D Supplementation in 2 Community Health Center Networks in South Carolina*, 208(2) AM J OF OBSTET GYNECOL 137.e1-137.e13 (2013) (hereinafter Wagner *et al.* (2013)).

levels in newborns. Importantly, no adverse effects (including hypervitaminosis, hypercalciuria, and hypercalcemia) were observed or reported at either dosage level.

Another randomized, controlled, double-blinded clinical trial investigated the safety and efficacy of 400 IU compared to higher doses (2,000 IU and 4,000 IU) of vitamin D<sub>3</sub>.<sup>170</sup> The study found that the higher doses were safe and more effective at increasing maternal circulating 25(OH)D levels, regardless of race.”<sup>171</sup> Four hundred ninety-four women were enrolled in the study (350 remained in the study until delivery), and twice daily oral supplementation of vitamin D<sub>3</sub> began around 12-16 weeks’ gestation; the primary outcome measured was circulating maternal 25(OH)D at delivery and a secondary outcome measure included serum 25(OH)D ≥80 nmol/L [32 ng/mL]. Blood samples were taken at an initial visit and then each month through to delivery (monthly collections coincided with a routine obstetric visit). No adverse events attributable to supplementation were reported in this study. Because this study included high dosages of vitamin D<sub>3</sub>, the researchers were able to test the effectiveness of the dosage commonly found in prenatal supplements (400 IU). They concluded that the lower dose of 400 IU was not as effective at achieving “adequate circulating 25(OH)D especially in African Americans.”<sup>172</sup>

Sablok *et al.* (2015),<sup>173</sup> which is discussed in detail above, demonstrated that vitamin D<sub>3</sub> supplementation at high doses was not harmful (none of the women developed hypervitaminosis D<sup>174</sup>) and increased circulating maternal vitamin D levels in all 4 intervention groups. Specifically, pregnant women were given one dose of 60,000 IU at 20 weeks if they had sufficient serum 25(OH)D (>50 nmol/L [20 ng/mL]); two doses of 120,000 IU at 20 and 24 weeks if they had insufficient serum 25(OH)D (25-50 nmol/L [10-20 ng/mL]); and four doses of 120,000 IU at 20, 24, 28, and 32 weeks if they were deficient in serum 25(OH)D (<25 nmol/L [<10 ng/mL])).

The Wagner (2016) *post-hoc* analysis supports the proposition that higher than currently-recommended daily vitamin D<sub>3</sub> supplementation is needed to support optimal maternal and fetal health. Specifically, the *post-hoc* analysis showed that only less than one-third (29%) of the participants achieved a serum 25(OH)D concentration of 40 ng/mL with the then-IOM recommendation of 400 IU vitamin D<sub>3</sub> per day, while over half (57%) of the women “in the 4000 IU treatment group” achieved serum 25(OH)D of 40 ng/mL.<sup>175</sup> Since this *post-hoc* analysis was completed, the IOM recommendation for pregnant women was increased to 600 IU per day. This level is still insufficient to provide full benefits to maternal and fetal health. The Wagner (2016) *post-hoc* analysis supports the conclusion that an “intake amount substantially higher than [400 IU per day]”<sup>176</sup> is necessary for pregnant women to achieve maternal circulating serum 25(OH)D concentrations of 40 ng/mL and above, which is the level associated with a reduction in the risk of preterm birth.

Similar to Hollis (2011) and Wagner (2013) discussed above, Dawodu *et al.* (2013)<sup>177</sup> also showed that vitamin D<sub>3</sub> supplementation at either 2,000 IU or 4,000 IU daily was safe during

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<sup>170</sup> Hollis *et al.* (2011).

<sup>171</sup> *Id.*, at 2.

<sup>172</sup> *Id.*

<sup>173</sup> Sablok *et al.* (2015).

<sup>174</sup> Wagner *et al.* (2016), at 250.

<sup>175</sup> *Id.*

<sup>176</sup> *Id.*

<sup>177</sup> Dawodu, A. *et al.*, *Randomized Controlled Trial (RCT) of Vitamin D Supplementation in Pregnancy in a Population with Endemic Vitamin D Deficiency*, 98(6) J CLIN ENDOCRINOL METAB 2337-2346 (2013).

pregnancy. One hundred ninety-two pregnant women in the second trimester were randomized into three groups receiving 400 IU (control group), 2,000 IU, or 4,000 IU of vitamin D<sub>3</sub> daily; the study was double-blinded. Again, vitamin D<sub>3</sub> supplementation at 4,000 IU was more effective at “optimizing serum 25(OH)D concentrations ( $\geq 85$ nmol/L [ $34$  ng/mL]) in mothers and their infants.”<sup>178</sup> No adverse effects were reported.

Grant *et al.* (2014) and Cooper & Harvey (2016), discussed above in Section A(2) also show that vitamin D<sub>3</sub> supplementation raises serum 25(OH)D concentrations in pregnant women. Grant *et al.* (2014) found that vitamin D<sub>3</sub> supplementation at 1,000 IU and 2,000 IU between 27 and 36 weeks of gestation led to a statistically-significant increase in the percentage of women with serum levels that were not deficient ( $\geq 20$  ng/mL or 50 nmol/L) and that were vitamin D sufficient ( $\geq 30$  ng/mL or 75 nmol/L) ( $p < 0.001$ ).<sup>179</sup> Both dosage levels caused statistically-significant improvements in serum vitamin D compared to placebo ( $p < 0.001$ ).<sup>180</sup> Similarly, Cooper *et al.* (2016), found that among the group of pregnant women receiving 1,000 IU per day there was a significantly lower percentage of women with serum 25(OH)D levels below 50 nmol/L (20 ng/mL) ( $p < 0.0001$ ), than the placebo group.<sup>181</sup> The authors concluded that “1000 IU of cholecalciferol daily is sufficient to ensure that most pregnant women are vitamin D replete, and it is safe.”<sup>182</sup>

Taken together, the Hollis *et al.* (2011), Wagner *et al.* (2013), Dawodu (2013), Grant *et al.* (2014), and Cooper *et al.* (2016) clinical trials and the analyses of the Hollis (2011) and Wagner *et al.* (2013) data show that vitamin D<sub>3</sub> supplementation at levels up to 4,000 IU has a beneficial impact on maternal circulating vitamin D. Additionally, and as importantly, none of these clinical trials reported any adverse effects at high levels of vitamin D<sub>3</sub> supplementation. These clinical trials show that vitamin D<sub>3</sub> supplementation is a practical, safe, and effective method of increasing serum vitamin D levels in pregnant women.

Human investigations or clinical trials included in this petition were conducted in compliance with the requirements for institutional review and oversight as required at 21 C.F.R. § 101.70(d). The authors of these studies<sup>183</sup> stated that the studies had been reviewed and approved by the relevant ethics, research, and institutional review boards. The authors of each of these studies also stated that subjects were informed about the study and provided written informed consent to participate in the study. Of particular note is that the human and clinical studies referenced in this section were all published in peer reviewed journals, requiring attestation as to institutional review and study participant informed consent.

### **3. Vitamin D<sub>3</sub> has a beneficial effect on maternal health and reduces the risk of preterm birth.**

The intervention trials discussed above demonstrate a clear relationship between increased maternal circulating vitamin D levels and a reduction in the risk of adverse pregnancy outcomes,

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<sup>178</sup> *Id.*, at 2337.

<sup>179</sup> Grant *et al.* (2014) at e151.

<sup>180</sup> *Id.*

<sup>181</sup> Cooper & Harvey (2016), at 399.

<sup>182</sup> Cooper & Harvey (2016), at 393.

<sup>183</sup> See Section F

including preterm birth. In addition, the studies show that supplementation with vitamin D<sub>3</sub> increases serum 25(OH)D levels in pregnant women. Finally, the studies show that vitamin D<sub>3</sub> supplementation at high levels is safe during pregnancy. Accordingly, the FDA should permit a health claim for the relationship between vitamin D and a decreased risk of preterm birth.

### C. Analytical Data per 21 C.F.R. § 101.70(f)(C)

The FDA requires that the petitioner provide analytical data that show the amount of the substance that is present in representative foods that would be candidates to bear the claim. For dietary supplements, vitamin D levels will vary from product to product, depending on product specifications. However, the level of vitamin D will be declared in the Supplement Facts panel, as mandated by 21 C.F.R. § 101.36(b)(2). In addition, given that FDA's Good Manufacturing Practice (GMP) regulations require that the finished product meets specifications<sup>184</sup>, the amount of vitamin D present in the dietary supplement must be the level declared in the Supplement Facts panel (with the exception of small intentional overages necessary to ensure that the nutrient remains at the declared level through the expiration date of the product). Accordingly, the amount of the substance that is present in dietary supplements is the amount declared on the product label in the Supplement Facts panel.

There are at least three validated AOAC testing methods that would potentially be applicable to dietary supplements, depending on the product formulation: AOAC method 975.42-1977 (Vitamin D in Vitamin Preparations - Colormetric Method); AOAC method 979.24-1980 (Vitamin D in Vitamin Preparations - Liquid Chromatographic Method); and AOAC method 980.26-1980 (Vitamin D in Multivitamin Preparations – Liquid Chromatographic Method). O&N proposes that the ultimate health claim require that supplements confirm the level of vitamin D3 in the product using one of these methods, if the testing method is appropriate for the product type.

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<sup>184</sup> 21 C.F.R § 111.75(c) (“For a subset of finished dietary supplement batches that you identify through a sound statistical sampling plan (or for every finished batch), you must verify that your finished batch of the dietary supplement meets product specifications for identity, purity, strength, composition, and for limits on those types of contamination that may adulterate or that may lead to adulteration of the finished batch of the dietary supplement. To do so: . . . (2) You must conduct appropriate tests or examinations to determine compliance with [specifications]...”).

#### **D. MODEL HEALTH CLAIMS**

Pregnant women who have higher serum vitamin D levels have a decreased risk of preterm birth. Adding a vitamin D<sub>3</sub> supplement to your healthy diet can help increase your serum vitamin D levels. Your healthcare practitioner can measure your serum vitamin D levels and determine the appropriate dosage of vitamin D<sub>3</sub> for you.



## E. PETITION ATTACHMENTS

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**F. REQUEST FOR CATEGORICAL EXCLUSION UNDER 21 C.F.R. § 25.32**

This petition is categorically excluded from the requirement to prepare an environmental assessment (EA) or an environmental impact statement (EIS) pursuant to 21 C.F.R. § 25.32(p) because this petition is a health claim petition that requests that the agency issue a regulation.