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## A.S.P.E.N. Position Paper: Recommendations for Changes in Commercially Available Parenteral Multivitamin and Multi-Trace Element Products

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### Abstract

The parenteral multivitamin preparations that are commercially available in the United States (U.S.) meet the requirements for most patients who receive parenteral nutrition (PN). However, a separate parenteral vitamin D preparation (cholecalciferol or ergocalciferol) should be made available for treatment of patients with vitamin D deficiency unresponsive to oral vitamin D supplementation. Carnitine is commercially available and should be routinely added to neonatal PN formulations. Choline should also be routinely added to adult and pediatric PN formulations; however, a commercially available parenteral product needs to be developed. The parenteral multi-trace element (TE) preparations that are commercially available in the U.S. require significant modifications. Single-entity trace element products can be used to meet individual patient needs when the multiple-element products are inappropriate (see Summary/A.S.P.E.N. Recommendations section for details of these proposed modifications). (*Nutr Clin Pract.* 2012;27:440-491)

### Keywords

mineral; trace elements; parenteral nutrition; parenteral nutrition solutions; vitamins

### Introduction/Background

Vitamins and trace elements (TEs) are required for specific metabolic functions. Vitamins are essential organic substances unable to be synthesized in the human body. TEs are minerals present at very low concentrations (equal to or less than 0.005% of body weight) in the human body. Appendix 1 lists each of the vitamins and TEs with their basic functions, and clinical sequelae of deficiency and toxicity.

In 1941, the U.S. National Academy of Sciences established the Food and Nutrition Board, which was responsible for the establishment of recommendations for standard oral daily allowances for each nutrient. The final set of guidelines was referred to as the Recommended Daily Allowances (RDA), which were then revised every 5–10 years. In 1997, the Institute of Medicine (IOM) of the U.S. National Academy of Sciences developed the Dietary Reference Intakes (DRIs), which expanded upon the RDAs. The current terms used for recommended oral nutrition intakes are described in Table 1.<sup>1</sup> In this position paper, the RDA was used to determine the daily oral vitamin and TE requirements; however, an RDA was not available for some vitamins and TEs, in which case the

Adequate Intake (AI) was used. However, it must be noted that the DRIs are for healthy individuals on a usual oral diet, so these must be extrapolated with care to patients on nutrition support with or without concurrent acute disease processes.

With the advent of parenteral nutrition (PN) in the 1960s, vitamins and TEs (collectively termed *micronutrients*) had to be provided intravenously. This represented a unique nutrient delivery system that required a reevaluation of nutrient requirements. While intravenously infused nutrients are 100% bioavailable, it was unknown whether metabolism would be affected by the bypass of normal hepatic first-pass

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**Table 1.** Current Terms Used to Describe Dietary Reference Intakes for Oral Requirements<sup>1</sup>

- **Estimated Average Requirement (EAR)**—the average daily intake expected to meet the needs of 50% of the healthy individuals in a particular life stage or gender group based on available scientific literature.
- **Recommended Dietary Allowance (RDA)**—the average daily dietary nutrient intake level that is sufficient to meet the nutrient requirements of nearly all (97%–98%) healthy individuals in a particular life stage and gender group. The RDA is calculated by adding 2 standard deviations to the EAR unless the requirement distribution is skewed, in which case the RDA is set between 97th and 98th percentile. If there is insufficient evidence to establish an EAR, then no RDA can be calculated.
- **Adequate Intake (AI)**—the recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group or groups of apparently healthy individuals that are assumed to be adequate. AI is used when an RDA cannot be determined.
- **Tolerable Upper Intake Level (UL)**—the highest average daily nutrient intake level that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects may increase.

**Table 2.** Historical Changes in Recommendations for Parenteral Trace Elements for Adults

Published Guidelines	Zinc, <sup>a</sup> mg	Copper, <sup>b</sup> mg	Manganese, <sup>b</sup> mcg	Chromium, mcg	Selenium, mcg
1979 NAG-AMA <sup>18,19</sup>	2.5–4	0.5–1.5	150–800	10–15	—
1984 AMA; NY Ac Med <sup>20</sup>	2.5–4	0.3–0.5	400–800	10–20	50–60
1994 9th ed Mod Nutr H-D <sup>21</sup>	2.5–4	0.3–0.5	60–100	10–15	40–80
1998 A.S.P.E.N. <sup>22</sup> and 2004 A.S.P.E.N. <sup>23</sup>	2.5–5	0.3–0.5	60–100	10–15	20–60

AMA, American Medical Association; A.S.P.E.N., American Society for Parenteral and Enteral Nutrition; Mod Nutr H-D, Modern Nutrition in Health & Disease; NAG-AMA, Nutrition Advisory Group of the American Medical Association; NY Ac Med, New York Academy of Medicine. Adapted from Buchman AL, Howard LJ, Guenter P, Nishikawa RA, Compher CW, Tappenden KA. Micronutrients in parenteral nutrition: too little or too much? The past, present, and recommendations for the future. *Gastroenterology*. 2009;137(5)(suppl):S1-S6 with permission from Elsevier.

<sup>a</sup>Increase with abnormal intestinal loss.

<sup>b</sup>Decrease or omit with increasing cholestasis.

metabolism. Therefore, it was unclear whether nutrient requirements would be reduced because of their increased bioavailability or increased due to altered metabolism and increased

urinary losses. In addition, difficulties were encountered in the development of safe and effective means for both the preparation of intravenous (IV) micronutrients, as well as their administration.<sup>2</sup> Subsequently, parenteral multivitamin and multi-TE products became commercially available. The importance of vitamins in the PN formulation was demonstrated by reports of significant complications and even deaths related to thiamine (also spelled as *thiamin*) and other vitamin deficiencies during national parenteral vitamin shortages in 1988 and 1996.<sup>3–8</sup> Moreover, zinc, copper, selenium, and chromium deficiencies have been reported when these TEs have been excluded from PN.<sup>9–12</sup>

In 1972, the U.S. Food and Drug Administration (FDA) declared parenteral multivitamin preparations as “ineffective as currently formulated” because they lacked certain essential vitamins and some vitamins were present in too high or too low concentrations.<sup>13</sup> In 1975, the Nutrition Advisory Group (NAG) of the Department of Food and Nutrition and the American Medical Association (AMA) proposed guidelines for 9 water-soluble (ascorbic acid, thiamine, riboflavin, niacin, pyridoxine, pantothenic acid, folate, cobalamin, and biotin) and 4 fat-soluble vitamins (vitamins A [retinol], D [cholecalciferol/ergocalciferol], E [ $\alpha$ -tocopherol], K [phyloquinone]) for adult and pediatric age groups.<sup>14,15</sup> The FDA accepted the adult formulation in 1979 and the pediatric formulation in 1981. In 1985, the FDA and AMA co-sponsored a workshop on parenteral multivitamins where increases in doses of ascorbic acid, thiamine, pyridoxine, and folate, as well as the addition of vitamin K to the adult formula, were recommended. However, these changes were not mandated by the agency until 2000.<sup>16</sup> In 1988, pediatric parenteral vitamin requirements were reevaluated by the Committee on Clinical Practice Issues of the American Society for Clinical Nutrition and modified according to input from the American Academy of Pediatrics and National Institute of Child Health and Development.<sup>17</sup>

In 1979, the NAG and AMA<sup>18,19</sup> recommended that 4 TEs, zinc, copper, manganese, and chromium, be provided in adult PN formulas; daily dose ranges were provided (Table 2). In 1984, recommendations were made to add selenium, decrease the dose range for copper, and increase the dose ranges for both manganese and chromium.<sup>20</sup> In 1994, the recommended dose range for selenium was increased and those for manganese and chromium were decreased.<sup>21</sup> These recommendations were reviewed by the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) in 1998<sup>22</sup> and 2004,<sup>23</sup> and a further recommendation was made to modestly decrease the dose range for selenium.

In February 2009, the annual A.S.P.E.N. Research Workshop focused on “Micronutrients in Parenteral Nutrition: Too Little or Too Much?”<sup>24</sup> At this workshop, a group of international experts reviewed the parenteral requirements of many of the vitamins and TEs as well as two related nutrients, carnitine and choline. The panel concluded that changes were needed in

**Table 3.** Review of the Literature for Vitamins and Trace Elements Provision in Parenteral Nutrition

Micronutrient	Source of Literature Review
Vitamin A	Working Group—see Appendix 2
Vitamin D	2009 A.S.P.E.N. Research Workshop—DeLuca <sup>25</sup>
Vitamin E	2009 A.S.P.E.N. Research Workshop—Biesalski <sup>26</sup>
Vitamin K	2009 A.S.P.E.N. Research Workshop—Shearer <sup>27</sup>
Vitamin B <sub>1</sub> (thiamine)	Working Group—see Appendix 3
Vitamin B <sub>2</sub> (riboflavin)	Working Group—see Appendix 4
Vitamin B <sub>3</sub> (niacin)	Working Group—see Appendix 4
Vitamin B <sub>5</sub> (pantothenic acid)	Working Group—see Appendix 5
Vitamin B <sub>6</sub>	Working Group—see Appendix 6
Vitamin B <sub>12</sub>	Working Group—see Appendix 7
Vitamin C	2009 A.S.P.E.N. Research Workshop—Berger <sup>28</sup>
Folate	Working Group—see Appendix 8
Biotin	Working Group—see Appendix 9
Carnitine	2009 A.S.P.E.N. Research Workshop—Borum <sup>29</sup>
Choline	2009 A.S.P.E.N. Research Workshop—Buchman <sup>30</sup>
Copper	2009 A.S.P.E.N. Research Workshop—Shike <sup>9</sup>
Chromium	2009 A.S.P.E.N. Research Workshop—Moukarzel <sup>10</sup>
Fluoride, boron, and silicone	2009 A.S.P.E.N. Research Workshop—Nielsen <sup>31</sup>
Iodine	2009 A.S.P.E.N. Research Workshop—Zimmermann <sup>32</sup>
Iron	2009 A.S.P.E.N. Research Workshop—Forbes <sup>33</sup>
Manganese	2009 A.S.P.E.N. Research Workshop—Hardy <sup>34</sup>
Molybdenum	Working Group—see Appendix 10
Selenium	2009 A.S.P.E.N. Research Workshop—Shenkin <sup>11</sup>
Zinc	2009 A.S.P.E.N. Research Workshop—Jeejeebhoy <sup>12</sup>

A.S.P.E.N., American Society for Parenteral and Enteral Nutrition.

the recommendations for the daily requirements for these micronutrients in PN, which would require significant changes in current commercially available products.

In May 2009, the A.S.P.E.N. Board of Directors formed the Novel Nutrient Task Force with a charge to assess the level of scientific evidence for the clinical use of several different parenteral nutrients and develop position statements for each nutrient. The position statements were to address evidence-based data on the use of these nutrients in clinical practice and to provide recommendations for changes in the products

available in the U.S. The task force was divided into working groups for each of these nutrients, one of which was the Parenteral Vitamin and TE Working Group.

### Issue/Problem Definition

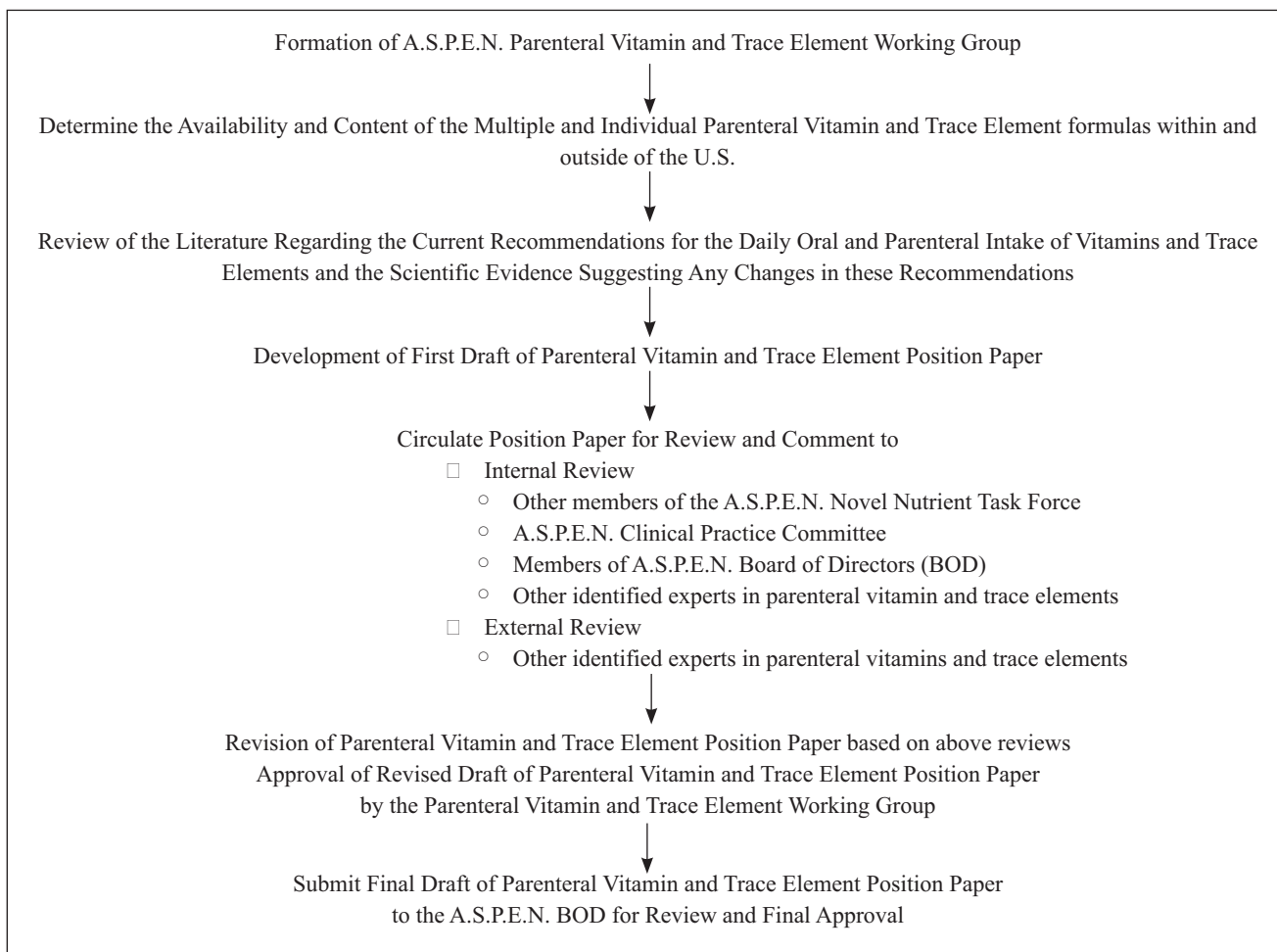
Recommendations for adult and pediatric patients are included in this position paper, and the pediatric patients are referred to as either neonates or pediatric (pediatric patients excluding neonates). The Working Group determined the procedure for development, review, and approval of this position paper (Figure 1). The literature review was primarily based on the review articles published from the 2009 A.S.P.E.N. Research Workshop. However, several vitamins and TEs were not reviewed as a part of the workshop, so Working Group members were assigned to complete literature reviews on these micronutrients (Table 3). Members of the Working Group with pediatric and neonatal expertise also conducted an additional literature review regarding recommendations for parenteral vitamin and TE supplementation in these patient populations.

The current adult, pediatric, and neonatal oral and parenteral daily recommendations for vitamins and TEs are shown in Tables 4–7. The commercially available multiple and individual parenteral vitamin and TE products available in the U.S. and in Europe are shown in Tables 8–13.

### Recommendations for Parenteral Vitamins

Based on the recommended doses for the current parenteral multivitamin products, the daily dose of the fat-soluble vitamins is approximately the same as the oral RDA or AI for these vitamins, even though the bioavailability should be much greater when these vitamins are administered intravenously. The rationale for providing a higher effective dose when given as part of PN therapy was that these patients had higher vitamin requirements due to malnutrition, baseline vitamin deficiencies, and metabolic changes secondary to acute and chronic illness.<sup>41</sup> The currently administered water-soluble vitamin daily parenteral doses are 2–5.5 times greater than the oral RDA or AI. The rationale for giving even higher relative doses for these vitamins was that in addition to the increased requirements, as discussed above, there is increased urinary excretion of water-soluble vitamins when administered intravenously.<sup>41</sup> These relatively high doses of vitamins have been used in PN therapy for over 30 years, and no toxicity has been described. Therefore, A.S.P.E.N. does not recommend any dose reductions in the parenteral multivitamin products.

The recommendations for daily oral intake of vitamin D were increased in 2010.<sup>42</sup> The IOM established RDAs for vitamin D that ranged from 400 International Units at birth to 800 International Units in the elderly (Tables 4 and 5). There is concern as to whether the daily dose of 200 International Units



**Figure 1.** Procedure for the development of the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) position paper on parenteral vitamin and trace elements.

per day of vitamin D in the current parenteral vitamin products is adequate for most patients that require long-term PN.

Compher et al<sup>43</sup> measured serum 25-hydroxyl vitamin D concentrations in 6 stable, intestinal failure patients on long-term PN, 2 males and 4 females, and all the patients were vitamin D deficient with concentrations ranging from 5–14 ng/mL (reference range, 20–100 ng/mL). Corey et al<sup>44</sup> measured serum 25-hydroxyl vitamin D concentrations in 35 patients that required home PN, all of whom had received parenteral multivitamin formulations that contained 200 International Units of cholecalciferol ( $D_3$ ) per day. This group consisted of 26 women and 9 men who used PN for a duration of 4 weeks to over 20 years, and all patients consumed some oral nutrition. Vitamin D deficiency, defined as 25(OH) vitamin D concentration <30 ng/mL, occurred in

77% of the patients. In a recent study, Thomson and Duerksen<sup>45</sup> reported vitamin D insufficiency in 27% and vitamin D deficiency in 68% of a group of 22 adult home patients who used PN for a duration of 1 month to over 14 years. Vitamin D insufficiency was defined as 25(OH) vitamin D >50 nmol/L (20 ng/mL) but <75 nmol/L (30 ng/mL), and vitamin D deficiency was defined as <50 nmol/L (20 ng/mL). Two of the patients in that study were taking oral vitamin D supplements; one took 2000 International Units cholecalciferol per day and was not deficient, and the other was taking 50,000 International Units ergocalciferol per week and was deficient. In an abstract published in 2009, doses of 40–75 mcg (1600–3000 International Units) of oral vitamin D per day failed to improve 25(OH) vitamin D levels in 5 out of a group of 10 home PN patients.<sup>46</sup>



**Table 4.** Current Recommended Adult Daily Oral and Parenteral Micronutrient Requirements

	Oral <sup>1,a</sup>	Parenteral <sup>2,3</sup>
<b>Fat-Soluble Vitamins</b>		
Vitamin A	M, 900 mcg or 3000 IU; F, 700 mcg or 2333 IU <sup>b</sup> 770 mcg (preg); 1300 mcg (lact)	990 mcg or 3300 IU <sup>b</sup>
Vitamin D	Age 19–70 y: 15 mcg or 600 IU <sup>c,35</sup> Age >70 y: 20 mcg or 800 IU <sup>35</sup>	5 mcg or 200 IU <sup>c</sup>
Vitamin E	15 mg; 19 mg (lact)	10 mg or 10 IU <sup>d</sup>
Vitamin K	M, 120 mcg; F, 90 mcg (AI)	150 mcg
<b>Water-Soluble Vitamins</b>		
Vitamin B <sub>1</sub> (thiamine)	M, 1.2 mg; F, 1.1 mg 1.4 mg (preg/lact)	6 mg
Vitamin B <sub>2</sub> (riboflavin)	M, 1.3 mg; F, 1.1 mg 1.4 mg (preg); 1.6 mg (lact)	3.6 mg
Vitamin B <sub>3</sub> (niacin)	M, 16 mg; F, 14 mg 18 mg (preg); 17 mg (lact)	40 mg
Vitamin B <sub>5</sub> (pantothenic acid)	5 mg; 6 mg (preg); 7 mg (lact) (AI)	15 mg
Vitamin B <sub>6</sub> (pyridoxine)	Age 19–50 y: 1.3 mg Age >51 y: M, 1.7 mg; F, 1.5 mg 1.9 mg (preg); 2.0 mg (lact)	6 mg
Vitamin B <sub>12</sub> (cyanocobalamin)	2.4 mcg; 2.6 mcg (preg); 2.8 mcg (lact)	5 mcg
Vitamin C (ascorbic acid)	M, 90 mg; F, 75 mg 85 mg (preg); 120 mg (lact)	200 mg
Folate	400 mcg; 600 mcg (preg); 500 mcg (lact)	600 mcg
Biotin	30 mcg; 35 mcg (lact) (AI)	60 mcg
<b>Other Nutrients</b>		
Choline	M, 550 mg; F, 425 mg 450 mg (preg); 550 mg (lact) (AI)	Not available for PN use
<b>Trace Elements</b>		
Copper	900 mcg 1000 mcg (preg); 1300 mcg (lact)	0.3–0.5 mg
Chromium	Age 19–50 y: M, 35 mcg; F, 25 mcg Age >51 y: M, 30 mcg; F, 20 mcg 30 mcg (preg); 45 mcg (lact) (AI)	10–15 mcg
Fluoride	M, 4 mg; F, 3 mg (AI)	Not routinely added in U.S. <sup>c</sup>
Iodine	150 mcg; 220 mcg (preg); 290 mcg (lact)	Not routinely added in U.S. <sup>c</sup>
Iron	Age 19–50 y: M, 8 mg; F, 18 mg Age >50 y: 8 mg 27 mg (preg); 9 mg (lact)	Not routinely added in U.S. <sup>c</sup> (given 25–50 mg/monthly as separate IV infusion when indicated)
Manganese	M, 2.3 mg; F, 1.8 mg 2.0 mg (preg); 2.6 mg (lact) (AI)	0.06–0.1 mg
Molybdenum	45 mcg; 50 mcg (preg/lact)	Not routinely added in U.S. <sup>c</sup>
Selenium	55 mcg; 60 mcg (preg); 70 mcg (lact)	20–60 mcg
Zinc	M, 11 mg; F, 8 mg 11 mg (preg); 12 mg (lact)	2.5–5 mg

Ranges include female (lower amounts) and male (higher amounts). This table does not include nutrient needs for pregnancy or lactation for ages <19 years. AI, Adequate Intake; F, female; IU, International Unit; IV, intravenous; lact, lactation; M, male; PN, parenteral nutrition; preg, pregnancy.

<sup>a</sup>Enteral recommendations are the Recommended Dietary Allowance (RDA) unless one is not established, in which case the AI is listed and so noted in the table.

<sup>b</sup>1 mcg RAE (retinol activity equivalent) = 1 mcg retinol = 12 mcg  $\beta$ -carotene = 24 mcg  $\alpha$ -carotene or  $\beta$ -cryptoxanthin.

<sup>c</sup>1 IU of retinol = 0.3 mcg retinol or 0.3 mcg RAE.

<sup>d</sup>To convert IU  $\alpha$ -tocopherol to mg: IU  $\times$  0.67 mg RRR- $\alpha$ -tocopherol, natural form (“d- $\alpha$ -tocopherol”) or IU  $\times$  0.45 mg all-rac- $\alpha$ -tocopherol, synthetic form (“dl- $\alpha$ -tocopherol”). dl- $\alpha$ -tocopheryl acetate (1 IU = 1 mg = 1 USP unit) is used in IV multivitamin preparation.<sup>36</sup>

<sup>e</sup>Fluoride (0.57–1.45 mg), iodine (10–130 mcg), iron (1–1.95 mg), molybdenum (10–25 mcg), and cobalt (0–1.47 mcg) are routinely added to PN products in Europe.<sup>37</sup>

**Table 5.** Daily Oral or Enteral Recommended Daily Allowances (RDA) for Pediatric Age Groups<sup>1</sup>

	Age Groups							
	0–6 mo	7–12 mo	1–3 y	4–8 y	9–13 y	14–18 y	<18 y Pregnant	<18 y Lactating
<b>Fat-Soluble Vitamins</b>								
Vitamin A, mcg <sup>a</sup>	400 <sup>b</sup>	500 <sup>b</sup>	300	400	600	M, 900; F, 700	750	1200
Vitamin D, mcg/IU <sup>35</sup>	10/400 <sup>b</sup>	10/400 <sup>b</sup>	15/600	15/600	15/600	15/600	15/600	15/600
Vitamin E, mg	4 <sup>b</sup>	5 <sup>b</sup>	6	7	11	15	15	19
Vitamin K, mcg	2 <sup>b</sup>	2.5 <sup>b</sup>	30 <sup>b</sup>	55 <sup>b</sup>	60 <sup>b</sup>	75 <sup>b</sup>	75 <sup>b</sup>	75 <sup>b</sup>
<b>Water-Soluble Vitamins</b>								
Vitamin B <sub>1</sub> (thiamine), mg	0.2 <sup>b</sup>	0.3 <sup>b</sup>	0.5	0.6	0.9	M, 1.2; F, 1.0	1.4	1.4
Vitamin B <sub>2</sub> (riboflavin), mg	0.3 <sup>b</sup>	0.4 <sup>b</sup>	0.5	0.6	0.9	M, 1.3; F, 1.0	1.4	1.6
Vitamin B <sub>3</sub> (niacin), mg	2 <sup>b</sup>	4 <sup>b</sup>	6	8	12	M, 16; F, 14	18	17
Vitamin B <sub>5</sub> (pantothenic acid), mg	1.7 <sup>b</sup>	1.8 <sup>b</sup>	2 <sup>b</sup>	3 <sup>b</sup>	4 <sup>b</sup>	5 <sup>b</sup>	6 <sup>b</sup>	7 <sup>b</sup>
Vitamin B <sub>6</sub> (pyridoxine), mg	0.1 <sup>b</sup>	0.3 <sup>b</sup>	0.5	0.6	1.0	M, 1.3; F, 1.2	1.9	2.0
Vitamin B <sub>12</sub> (cyanocobalamin), mcg	0.4 <sup>b</sup>	0.5 <sup>b</sup>	0.9	1.2	1.8	2.4	2.6	2.8
Vitamin C (ascorbic acid), mg	40 <sup>b</sup>	50 <sup>b</sup>	15	25	45	M, 753; F, 65	80	115
Folate, mcg	65 <sup>b</sup>	80 <sup>b</sup>	150	200	300	400	600	500
Biotin, mcg	5 <sup>b</sup>	6 <sup>b</sup>	8 <sup>b</sup>	12 <sup>b</sup>	20 <sup>b</sup>	25 <sup>b</sup>	30 <sup>b</sup>	35 <sup>b</sup>
Choline, mg	125 <sup>b</sup>	150 <sup>b</sup>	200 <sup>b</sup>	250 <sup>b</sup>	375 <sup>b</sup>	M, 550; F, 400 <sup>b</sup>	450 <sup>b</sup>	550 <sup>b</sup>
<b>Trace Elements</b>								
Copper, mcg	200 <sup>b</sup>	220 <sup>b</sup>	340	440	700	890	1000	1300
Chromium, mcg	0.2 <sup>b</sup>	5.5 <sup>b</sup>	11 <sup>b</sup>	15 <sup>b</sup>	M, 25; F, 21 <sup>b</sup>	M, 35; F, 24 <sup>b</sup>	29 <sup>b</sup>	44 <sup>b</sup>
Fluoride, mg	0.01 <sup>b</sup>	0.5 <sup>b</sup>	0.7 <sup>b</sup>	1 <sup>b</sup>	2 <sup>b</sup>	3 <sup>b</sup>	3 <sup>b</sup>	3 <sup>b</sup>
Iodine, mcg	110 <sup>b</sup>	130 <sup>b</sup>	90	90	120	150	220	290
Iron, mg	0.27 <sup>b</sup>	11	7	10	8	M, 11; F, 15	27	10
Manganese, mg	0.003 <sup>b</sup>	0.6 <sup>b</sup>	1.2 <sup>b</sup>	1.5 <sup>b</sup>	M, 1.9; F, 1.6 <sup>b</sup>	M, 2.2; F, 1.6 <sup>b</sup>	2 <sup>b</sup>	2.6 <sup>b</sup>
Molybdenum, mcg	2 <sup>b</sup>	3 <sup>b</sup>	17	22	34	43	50	50
Selenium, mcg	15 <sup>b</sup>	20 <sup>b</sup>	20	30	40	55	60	70
Zinc, mg	2 <sup>b</sup>	3	3	5	8	M, 11; F, 9	12	13

F, female; IU, International Unit; M, male.

<sup>b</sup>No Recommended Daily Allowance (RDA) available; Adequate Intake (AI) is listed.

<sup>1</sup>1 mcg RAE (retinol activity equivalent) = 1 mcg retinol = 12 mcg  $\beta$ -carotene = 24 mcg  $\alpha$ -carotene or  $\beta$ -cryptoxanthin; 1 IU of retinol = 0.3 mcg retinol or 0.3 mcg RAE.

Currently, no separate parenteral ergocalciferol or cholecalciferol product is commercially available. A.S.P.E.N. recommends a parenteral cholecalciferol or ergocalciferol vitamin D product be developed for use in PN-dependent patients that are vitamin D deficient and fail to respond to oral vitamin D supplementation.<sup>47</sup> There is some evidence to show that cholecalciferol may be more effective at increasing vitamin D levels.<sup>48</sup> Vitamin D supplementation in pediatric and neonatal PN patients is important, but there is insufficient evidence to develop definitive daily recommendations. It appears that the current parenteral form and dose of vitamin D supports adequate blood levels.<sup>49</sup>

A.S.P.E.N. also recommends that parenteral multivitamin products with and without vitamin K should continue to be available. This permits clinicians the option to withhold vitamin K when required, such as in the case of those patients who require warfarin therapy.

The scientific data supporting the current dose recommendations for pediatric and neonatal parenteral vitamin administration are very limited, so there are insufficient data to make any recommended changes in the current pediatric and neonatal parenteral multivitamin products.

### *Recommendations for Parenteral Carnitine and Choline*

Carnitine and choline are technically not vitamins, but their essentiality was considered by the Food and Nutrition Board of the IOM. Both of these nutrients either have been used in PN formulas or have been investigated for inclusion in PN formulas. Carnitine is a quaternary ammonium compound biosynthesized from the amino acids lysine and methionine. It is required for the transport of fatty acids from the cytosol into the mitochondria during the breakdown of lipids for the

**Table 6.** Current Daily Parenteral Recommendations for Infants and Children<sup>38</sup>

	Infants	Children
<b>Fat-Soluble Vitamins</b>		
Vitamin A <sup>a</sup>	150–300 mcg/kg/d	150 mcg/d
Vitamin D	0.8 mcg/32 IU per kg/d	10 mcg/400 IU per d
Vitamin E	2.8–3.5 mg/kg/d	7 mg/d
Vitamin K	10 mcg/kg/d	200 mcg/d
<b>Water-Soluble Vitamins</b>		
Vitamin B <sub>1</sub> (thiamine)	0.35–0.5 mg/kg/d	1.2 mg/d
Vitamin B <sub>2</sub> (riboflavin)	0.15–0.2 mg/kg/d	1.4 mg/d
Vitamin B <sub>3</sub> (niacin)	4.0–6.8 mg/kg/d	17 mg/d
Vitamin B <sub>5</sub> (pantothenic acid)	1–2 mg/kg/d	5 mg/d
Vitamin B <sub>6</sub> (pyridoxine)	0.15–0.2 mg/kg/d	1 mg/d
Vitamin B <sub>12</sub> (cyanocobalamin)	0.3 mcg/kg/d	1 mcg/d
Vitamin C (ascorbic acid)	15–25 mg/kg/d	80 mg/d
Folate	56 mcg/kg/d	140 mcg/d
Biotin	5–8 mcg/kg/d	20 mcg/d
<b>Trace Elements</b>		
Copper	20 mcg/kg/d (no max stated) <sup>b</sup>	20 mcg/kg/d (500 mcg/d max <sup>c,d</sup> ) <sup>b</sup>
Chromium	0.2 mcg/kg/d (max 5 mcg/d) <sup>e</sup>	0.2 mcg/kg/d (max 5 mcg/d) <sup>e</sup>
Fluoride	No recommendations	No recommendations
Iodine	1 mcg/d <sup>f</sup>	1 mcg/d <sup>f</sup>
Iron	Premature: 200 mcg/kg/d <sup>f</sup> Infant: 50–100 mcg/kg/d <sup>f</sup>	50–100 mcg/kg/d <sup>f</sup>
Manganese	1 mcg/kg/d (max 50 mcg/d <sup>c</sup> )	1 mcg/kg/d (max 50 mcg/d <sup>c</sup> )
Molybdenum	Premature: 1 mcg/kg/d Infant: 0.25 mcg/kg/d (max 5 mcg/d <sup>c</sup> )	0.25 mcg/kg/d (max 5 mcg/d <sup>c</sup> )
Selenium	Premature: 2–3 mcg/kg/d Infant: 1–3 mcg/kg/d (no max stated)	1–3 mcg/kg/d (100 mcg/d max <sup>c,d</sup> )
Zinc	Premature: 450–500 mcg/kg/d Infants <3 mo: 250 mcg/kg/d Infants >3 mo: 50 mcg/kg/d (max 5000 mcg/d)	50 mcg/kg/d (max 5000 mcg/d <sup>c</sup> )

IU, International Unit; max, maximum; PN, parenteral nutrition.

<sup>a</sup>1 mcg/kg RAE (retinol activity equivalent) = 1 mcg/kg retinol.

<sup>b</sup>Authors recommend monitoring plasma copper and ceruloplasmin concentrations in long-term PN patients and patients with burns or cholestasis with appropriate adjustment of doses as needed.

<sup>c</sup>Refers to maximum dose for routine supplementation; however, higher doses may be indicated in patients with established deficiency or increased requirements.

<sup>d</sup>Maximum dose was not specified in above reference but is included in this table as the maximum dose based on the recommended adult dose.

<sup>e</sup>Authors state that chromium contaminates in PN products satisfies requirements; therefore, additional supplementation is unnecessary.

<sup>f</sup>Not currently added to PN in U.S.

generation of metabolic energy. It is currently added to neonatal PN and adult PN in selected cases only.<sup>29</sup> A.S.P.E.N. recommends the routine addition of 2 to 5 mg/kg/d to the PN for neonates<sup>29</sup> if no enteral source is provided.<sup>50,51</sup> Carnitine is currently not provided routinely in either adult or pediatric PN formulas, but there is some evidence that supplementation in these patient populations may be beneficial. A.S.P.E.N. recommends that further investigation is needed in these patient populations.

Choline is a quaternary amine endogenously synthesized from the amino acid methionine and has been listed as a required dietary nutrient since 1998 by the U.S. IOM Food and Nutrition Board. In addition, the FDA requires choline supplementation of infant enteral formulas.<sup>52</sup> It is an essential component of all cell membranes and is necessary for DNA repair due to its role as a methyl donor. It also serves as the precursor for the neurotransmitter acetylcholine. Deficiency states have been reported and include memory deficits, skeletal muscle



**Table 7.** Current Parenteral and Enteral Vitamin and Trace Element Recommendations for Preterm and Term Neonates

Route of Administration	Preterm Neonates		Term Neonates	
	Parenteral <sup>38-40</sup>	Enteral <sup>38,39</sup>	Parenteral <sup>38</sup>	Enteral <sup>1</sup>
<b>Vitamins</b>				
Vitamin A	700–1500 IU/kg/d	700–1500 IU/kg/d	2300 IU/d	1333 IU/d 400 mcg/d
Vitamin D	40–160 IU/kg/d	150–400 IU/kg/d goal 400 IU/d	400 IU/d	400 IU/d
Vitamin E	2.8–3.5 IU/kg/d	6–12 IU/kg/d	7 IU/d	6 IU/d
Vitamin K	10 mcg/kg/d in PN +500 mcg IM at birth	8–10 mcg/kg/d	200 mcg/d +500 mcg IM at birth	2 mcg/d
Thiamin	200–350 mcg/kg/d	180–240 mcg/kg/d	1.2 mg/d	0.2 mg/d
Riboflavin	150–200 mcg/kg/d	250–360 mcg/kg/d	1.4 mg/d	0.3 mg/d
Niacin	4–6.8 mg/kg/d	3.6–4.8 mg/kg/d	17 mg/d	2 mg/d
Vitamin B <sub>6</sub>	150–200 mcg/kg/d	150–210 mcg/kg/d	1000 mcg/d	14 mcg/kg/d
Folate	56 mcg/kg/d	25–50 mcg/kg/d	140 mcg/d	65 mcg/d
Vitamin B <sub>12</sub>	0.3 mcg/kg/d	9.3 mcg/kg/d	1 mcg/d	0.4 mcg/d
Pantothenic acid	1–2 mg/kg/d	1.2–1.7 mg/kg/d	5 mg/d	1.7 mg/d
Biotin	5–8 mcg/kg/d	3.6–6 mcg/kg/d	20 mcg/d	5 mcg/d
Vitamin C	15–25 mg/kg/d	18–24 mg/kg/d	80 mg/d	40 mg
<b>Trace Elements</b>				
Iron	100–200 mcg/kg/d if PN only >2 mo	2000–4000 mcg/kg/d	250–670 mcg/kg/d if PN only >2 mo	2000–4000 mcg/kg/d
Zinc	400 mcg/kg/d	1000–3000 mcg/kg/d	250 mcg/kg/d	2000 mcg/d
Copper <sup>a</sup>	29 mcg/kg/d	120–150 mcg/kg/d	20 mcg/kg/d	200 mcg/d
Selenium	1.5–4.5 mcg/kg/d	1.3–4.5 mcg/kg/d	2 mcg/kg/d	15 mcg/d
Chromium	0.05–0.3 mcg/kg/d	0.1–2.25 mcg/kg/d	0.2 mcg/kg/d	0.2 mcg/d
Molybdenum	0.25 mcg/kg/d	0.3 mcg/kg/d	0.25 mcg/kg/d	2 mcg/d
Manganese	1 mcg/kg/d	0.7–7.5 mcg/kg/d	1 mcg/kg/d	0.3 mcg/d
Iodine <sup>b</sup>	1 mcg/kg/d	10–60 mcg/kg/d	1 mcg/kg/d	110–130 mcg/d

IM, intramuscular; IU, International Unit; PN, parenteral nutrition.

<sup>a</sup>Copper dose may need to be removed or reduced in infants with obstructive jaundice. Check serum copper and ceruloplasmin concentration to determine need for dose change.

<sup>b</sup>Insufficient data at this time to support routine parenteral iodine supplementation in preterm infants.

injury, and possible activation of cellular apoptosis in lymphocytes and hepatocytes. Importantly, choline deficiency may cause or contribute to PN-associated hepatic steatosis; animal models have shown progression to steatohepatitis and even development of hepatocellular carcinoma with long-term choline deficiency. Currently, there is no commercially available parenteral choline product.<sup>30</sup> A.S.P.E.N. recommends that a commercially available parenteral choline product, either as an individual product or incorporated into a multivitamin product, should be developed and routinely added to adult PN formulas at a dose of 550 mg/d. The recommended daily choline neonatal and pediatric PN doses are:

- 0–6 months: 125 mg
- 7–12 months: 150 mg
- 1–3 years: 200 mg
- 4–8 years: 250 mg

- 9–13 years: 375 mg
- >13 years: adult amounts

Additional data will be required to determine whether higher doses (ie, greater than the AI for choline) are optimal.

### *Recommendations for Parenteral TEs*

A.S.P.E.N. has numerous recommendations for changes to the currently available parenteral TE products. This stems from several factors. First, and foremost, while the FDA approved the initial 1979 guidelines for daily parenteral TE doses published by the AMA,<sup>18</sup> the agency's approval has not been updated to reflect the changes advised by recent TE expert conferences (Table 2). These recommendations included greatly reduced daily doses of both copper and manganese based on the reports of manganese toxicity and

**Table 8.** Parenteral Multivitamin Formulations Available in North America

Product (Distributor)	Content per mL	A, IU	D, IU	E, IU	K, mcg	B <sub>1</sub> , mg	B <sub>2</sub> , mg	B <sub>3</sub> , mg	B <sub>5</sub> , mg	B <sub>6</sub> , mg	B <sub>12</sub> , mcg	C, mg	Biotin, mcg	Folic Acid, mcg	How Supplied
<b>Adult</b>															
M.V.I.-12 (Hospira)	10 mL	3300	200 <sup>a</sup>	10 <sup>b</sup>	0	6	3.6	40 <sup>c</sup>	15 <sup>d</sup>	6	5	200	60	600	Unit vial or pharmacy bulk package <sup>e</sup>
M.V.I. Adult (Hospira)	10 mL	3300	200 <sup>a</sup>	10 <sup>b</sup>	150 <sup>f</sup>	6	3.6	40 <sup>c</sup>	15 <sup>d</sup>	6	5	200	60	600	Dual vial, unit vial, or pharmacy bulk package <sup>e</sup>
Infuvite <i>Adult</i> (Baxter)	10 mL	3300	200 <sup>g</sup>	10 <sup>b</sup>	150 <sup>f</sup>	6	3.6	40 <sup>c</sup>	15 <sup>d</sup>	6	5	200	60	600	Pharmacy bulk package <sup>e</sup>
Vitamin B-Complex 100 (Bioniche Pharma)	1 mL	0	0	0	0	100	2	100 <sup>c</sup>	2 <sup>d</sup>	2	0	0	0	0	30-mL multiple-dose vial
<b>Pediatric</b>															
M.V.I. Pediatric (Hospira)	5 mL <sup>h</sup>	2300	400 <sup>a</sup>	7 <sup>b</sup>	200 <sup>f</sup>	1.2	1.4	17 <sup>c</sup>	5 <sup>d</sup>	1	1	80	20	140	Single-dose vial reconstituted to 5 mL
Infuvite <i>PEDIatric</i> (Baxter)	5 mL <sup>i</sup>	2300	400 <sup>g</sup>	7 <sup>b</sup>	200 <sup>f</sup>	1.2	1.4	17 <sup>c</sup>	5 <sup>d</sup>	1	1	80	20	140	Two single-dose vials <sup>i</sup>

IU, International Unit. Information based on manufacturer's labeling information as of February 2010. Manufacturers, products, and product information can frequently change.

<sup>a</sup>Ergocalciferol (D<sub>2</sub>).

<sup>b</sup>dl- $\alpha$ -tocopheryl acetate.

<sup>c</sup>Niacinamide.

<sup>d</sup>15 mg dexpanthenol (d-pantothenyl alcohol).

<sup>e</sup>Dual vial is 2 vials labeled vial 1 (5 mL) and vial 2 (5 mL) with both vials to be used for a single 10-mL dose. Unit vial is a 2-chambered single-dose vial that must be mixed just prior to use and will provide one 10-mL dose. Pharmacy bulk package consists of 2 vials labeled vial 1 (50 mL) and vial 2 (50 mL), and 5 mL of each vial provides 10 mL of a single dose.

<sup>f</sup>Phylloquinone (K<sub>1</sub>).

<sup>g</sup>Cholecalciferol (D<sub>3</sub>).

<sup>h</sup>The 5 mL is the daily dose for infants and children weighing 3 kg or more up to age 11 years, 3.25 mL (65% of daily dose) for infants weighing 1–3 kg, and 1.5 mL (30% of daily dose) for infants weighing less than 1 kg.

<sup>i</sup>Supplied in 2 single-dose vials, vial 2 (1 mL) contains folic acid, biotin, and vitamin B<sub>12</sub>, and vial 1 (4 mL) contains all the other vitamins. The 5 mL is the daily dose for infants and children weighing 3 kg or more up to age 11 years, 65% of daily dose (2.6 mL vial 1 and 0.65 mL vial 2) for infants weighing 1–3 kg, and 30% of daily dose (1.2 mL vial 1 and 0.3 mL vial 2) for infants weighing less than 1 kg.

excessive organ accumulation of both manganese and copper in patients who had received long-term PN.<sup>53-57</sup> Therefore, the current multi-TE products available in the U.S. provide excessive copper and manganese.

TE contamination of PN is also of concern. Beginning in the late 1970s, several reports described contamination of PN formulations with zinc,<sup>58-62</sup> copper,<sup>58,60-63</sup> manganese,<sup>58,62,64,65</sup> chromium,<sup>62,66</sup> and selenium.<sup>60,62,67</sup> Nonnutrient contaminants such as aluminum, arsenic, and strontium were also found.<sup>62,68,69</sup> Aluminum toxicity has been a serious concern, which has been at least partially addressed by the FDA.<sup>70</sup>

Studies analyzing TE contents of PN component products have shown several contaminants in amounts greater than 1 mcg/L, including zinc, copper, manganese, chromium, selenium, boron, aluminum, titanium, barium, cadmium, arsenic, and strontium. TE contamination was found in all PN components tested, even in those that were not intended to contain TEs. The greatest amounts of contamination were found in the amino acids, potassium chloride, calcium gluconate, and

sodium chloride products. Amounts varied between manufacturers and in different lots from the same manufacturer.<sup>62,71</sup>

Pluhator-Murton et al<sup>62</sup> calculated the amount of trace elements in a 2-L PN solution made with the tested components, compared those numbers with the amounts expected to be provided in the same PN solution, and found an extra 1.1 mg Zn, 0.08 mg Cu, 38 mcg Mn, 15 mcg Cr, and 21 mcg Se. The amounts of contaminant Mn and Cr found in that study were approximately 63% of the current recommended daily requirement for Mn and 100% of the daily requirement for Cr.

Buchman et al<sup>71</sup> reported substantial variation in levels of heavy metal contamination between PN formulations that used components from varied manufacturers, as well as differences in levels of contamination between adult, renal, and pediatric formulations. Chromium contamination was substantial in all formulations evaluated but was greatest in a "renal" formulation. Chromium contamination occurred primarily in dextrose, amino acids, and TE components.

**Table 9.** Parenteral Single-Vitamin Products Available in North America

Vitamin (Distributor)	Concentration	How Supplied
<b>Vitamin A</b>		
Aquasol A (Hospira)	50,000 IU/mL	2-mL vials (IM)
<b>Vitamin D<sup>a</sup></b>		
Calcitriol (Calcijex, Abbott)	1 mcg/mL	1-mL vial sodium chloride, EDTA
Paracalcitol (Zemplar, Abbott)	2 mcg/mL	1-mL vial
Paracalcitol (Zemplar, Abbott)	5 mcg/mL	1- and 2-mL vial
Doxercalciferol (Hectorol, Genzyme)	2 mcg/mL	1- and 2-mL vial
<b>Vitamin K</b>		
Phytonadione (K <sub>1</sub> ) (Hospira)	10 mg/mL	1-mL amp
Phytonadione (K <sub>1</sub> ) (Hospira)	2 mg/mL	0.5-mL amp
<b>Vitamin B<sub>1</sub></b>		
Thiamine (various)	100 mg/mL	1- and 2-mL Tubex, 2-mL multidose vials, 1-mL vial
<b>Vitamin B<sub>6</sub></b>		
Pyridoxine (various)	100 mg/mL	1-mL vials
<b>Vitamin B<sub>12</sub></b>		
Cyanocobalamin (various)	100 mg/mL	30-mL multidose vials
Cyanocobalamin (various)	1000 mg/mL	10- and 30-mL multidose vials, 1-mL vial
<b>Vitamin C</b>		
Ascorbic acid (various)	500 mg/mL	50-mL multidose vials, 1-mL amp
Ascorbic acid (various)	1000 mg/mL	2-mL amp
Folic acid (various)	5 mg/mL	10-mL multidose vial

amp, ampule; EDTA, ethylenediaminetetraacetic acid; IM, intramuscular; IU, International Unit. Information based on manufacturer's labeling information as of February 1, 2010. Manufacturers, products, and product information can change frequently. Adapted from Buchman AL, Howard LJ, Guenter P, Nishikawa RA, Compher CW, Tappenden KA. Micronutrients in parenteral nutrition: too little or too much? The past, present, and recommendations for the future. *Gastroenterology*. 2009;137(5)(suppl):S1-S6 with permission from Elsevier.

<sup>a</sup>No single vitamin products in the U.S. contain vitamin D as ergocalciferol (D<sub>2</sub>) or cholecalciferol (D<sub>3</sub>). This table lists analogs/metabolites of vitamin D.

**Table 10.** Parenteral Multi-Trace Element Products Available in North America

Product (Distributor)	Content per mL	Zinc, mg (μmol)	Copper, mg (μmol)	Chromium, mcg (μmol)	Manganese, mg (μmol)	Selenium, <sup>a</sup> mcg (μmol)	How Supplied
<b>Adults</b>							
Multitrace-4 (American Regent)	1 mL	1 (15.3)	0.4 (6.29)	4 (0.08)	0.1 (0.0018)	0 (0)	10-mL MDV
Multitrace-4 Concentrate (American Regent)	1 mL	5 (76.48)	1 (15.73)	10 (0.2)	0.5 (0.0091)	0 (0)	1-mL SDV and 10-mL MDV
4-Trace Elements (Hospira)	5 mL	4 (61.18)	1 (15.73)	10 (0.2)	0.8 (0.0146)	0 (0)	5-mL SDV and 50-mL MDV
Multitrace-5 (American Regent)	1 mL	1 (15.3)	0.4 (6.29)	4 (0.08)	0.1 (0.0018)	20 (0.25)	10-mL MDV
Multitrace-5 Concentrate (American Regent)	1 mL	5 (76.48)	1 (15.73)	10 (0.2)	0.5 (0.0091)	60 (0.76)	1-mL SDV and 10-mL MDV
<b>Neonatal and Pediatrics</b>							
Multitrace-4 Neonatal (American Regent)	1 mL	1.5 (22.94)	0.1 (1.57)	0.85 (0.02)	0.025 (0.0005)	0 (0)	2-mL SDV
Multitrace-4 Pediatric (American Regent)	1 mL	1 (15.3)	0.1 (1.57)	1 (0.02)	0.025 (0.0005)	0 (0)	3-mL SDV
Trace Elements Injection 4, USP—Pediatric (American Regent)	1 mL	0.5 (7.65)	0.1 (1.57)	1 (0.02)	0.03 (0.0006)	0 (0)	10-mL MDV

MDV, multiple-dose vial; SDV, single-dose vial; USP, United States Pharmacopeia. Information based on manufacturer's labeling information as of February 1, 2010. Manufacturers, products, and product information can change frequently.

**Table 11.** Parenteral Individual Trace Element Products Available in North America

Trace Element (Distributor)	Concentration Elemental Form per mL ( $\mu\text{mol}$ )	How Supplied
<b>Copper</b>		
Cupric chloride (Hospira)	0.4 mg/mL (6.29 $\mu\text{mol}/\text{mL}$ )	10-mL vials
Cupric sulfate, pentahydrate (various)	0.4 mg/mL (6.29 $\mu\text{mol}/\text{mL}$ )	10-mL and 30-mL vials
Cupric sulfate (various)	2 mg/mL (31.40 $\mu\text{mol}/\text{mL}$ )	10-mL vials
Chromium as chromic chloride, hexahydrate (various)	4 mcg/mL (0.08 $\mu\text{mol}/\text{mL}$ )	10-mL and 30-mL vials
<b>Iron</b>		
Ferumoxytol (AMAG Pharma)	30 mg/mL (0.53 mmol/mL)	17-mL vials
Iron dextran (various)	50 mg/mL (0.89 mmol/mL)	1- and 2-mL vials
Iron sorbitol (Astra-Canada)	50 mg/mL (0.89 mmol/mL)	2-mL ampule (IM only)
Iron sucrose (American Regent)	20 mg/mL (0.36 mmol/mL)	2.5-mL, 5-mL, and 10-mL vials
Sodium ferric gluconate (Sanofi-Aventis U.S., Watson)	12.5 mg/mL (0.22 mmol/mL)	5-mL ampules
<b>Manganese</b>		
Manganese chloride, tetrahydrate (various)	0.1 mg/mL (0.02 $\mu\text{mol}/\text{mL}$ )	10-mL vials
Manganese sulfate, monohydrate (various)	0.1 mg/mL (0.02 $\mu\text{mol}/\text{mL}$ )	10-mL and 30-mL vials
Molybdenum as ammonium molybdate, tetrahydrate (various)	25 mcg/mL (0.26 $\mu\text{mol}/\text{mL}$ )	10-mL vials
Selenium as selenious acid (various)	40 mcg/mL (0.51 $\mu\text{mol}/\text{mL}$ )	10-mL and 30-mL vials
<b>Zinc</b>		
Zinc sulfate (various)	1 mg/mL (15.30 $\mu\text{mol}/\text{mL}$ )	10-mL and 30-mL vials
Zinc sulfate (various)	5 mg/mL (76.50 $\mu\text{mol}/\text{mL}$ )	5-mL and 10-mL vials
Zinc sulfate (various)	1 mg/mL (15.30 $\mu\text{mol}/\text{mL}$ )	10-mL vials
Zinc chloride (various)		

Information based on manufacturer's labeling information as of February 1, 2010. Manufacturers, products, and product information can change frequently. IM, intramuscular.

**Table 12.** Parenteral Multivitamin Products Available in Europe

Product (Distributor)	Content per mL	A, IU	D, IU	E, IU	K, mcg	B <sub>1</sub> , mg	B <sub>2</sub> , mg	B <sub>3</sub> , mg	B <sub>5</sub> , mg	B <sub>6</sub> , mg	B <sub>12</sub> , mcg	C, mg	Biotin, mcg	Folic Acid, mcg	How Supplied
<b>Adult</b>															
Cernevit (Baxter)	5 mL	3500	220 <sup>a</sup>	11.2	0	3.5	4.1	46	17.3	4.5	6	125	69	414	5-mL powder vial for solution
Vitalipid N Adult (Fresenius Kabi)	10 mL	3300	200 <sup>b</sup>	10	150	0	0	0	0	0	0	0	0	0	10-mL ampule <sup>c</sup>
Solivito N (Fresenius Kabi)	10 mL	0	0	0	0	2.5	3.6	40	15	4	5	100	60	400	10-mL freeze-dried vial <sup>c</sup>
Pabrinex: ampule no. 1 (Archimedes Pharma)	5 mL 10 mL	0	0	0	0	250 500	4 8	0	0	50 100	0	0	0	0	5-mL ampule 10-mL ampule
Pabrinex: ampule no. 2 <sup>d</sup> (Archimedes Pharma)	5 mL 10 mL	0	0	0	0	0	0	160 320	0	0	0	500 1000	0	0	5-mL ampule 10-mL ampule
<b>Pediatric</b>															
Vitalipid N Infant (Fresenius Kabi)	10 mL	2300	400 <sup>b</sup>	7	200	0	0	0	0	0	0	0	0	0	10-mL ampule

IU, International Unit. Information based on manufacturer's labeling information as of February 1, 2010. Manufacturers, products, and product information can change frequently.

<sup>a</sup>Cholecalciferol (D<sub>3</sub>).

<sup>b</sup>Ergocalciferol (D<sub>2</sub>).

<sup>c</sup>Vitalipid N Adult contains only fat-soluble vitamins and Solivito N contains only water-soluble vitamins. Can dissolve Solivito N in the Vitalipid N Adult to provide both fat- and water-soluble vitamins.

<sup>d</sup>Also contains anhydrous glucose: 1 g (5 mL) or 2 g (10 mL).

**Table 13.** Parenteral Multi-Trace Element Products Available in Europe

Product (Distributor)	Content per mL	Zinc, mg (µmol)	Copper, mg (µmol)	Chromium, mcg (µmol)	Manganese, mg (µmol)	Selenium, mcg (µmol)	Molybdenum, mcg (µmol)	Iron, mg (µmol)	Iodide, mg (µmol)	Fluoride, mg (µmol)	Cobalt, mcg (µmol)	How Supplied
<b>Adults</b>												
Additracce (Fresenius Kabi)	10 mL	6.5 (99.4)	1.24 (19.5)	10 (0.2)	0.275 (5.0)	32 (0.41)	19 (0.2)	1.1 (19.7)	0.13 (1)	0.95 (50)	0 (0)	10-mL ampule
Decan (Baxter & Laboratoires Aguettant)	40 mL	10 (153)	0.48 (7.5)	15 (0.3)	0.200 (3.6)	70 (0.89)	25 (0.26)	1 (17.9)0.0015 (0.012)	1.45 (76.3)	1.47 (0.025)	1.47 (0.025)	40-mL ampule
Tracutil (B.Braun)	10 mL	3.3 (50)	0.76 (12)	10 (0.2)	0.55 (10)	24 (0.3)	10 (0.1)	2.0 (35)	0.127 (1)	0.57 (30)	0 (0)	10-mL ampule
<b>Pediatrics and Neonates</b>												
Peditrace (Fresenius Kabi)	1 mL	0.25 (3.82)	0.02 (0.32)	0 (0)	0.001 (0.02)	2 (0.03)	0 (0)	0 (0)	0.001 (0.008)	0.06 (3)	0 (0)	10-mL ampule
Inzolen-Infantibus sine NaK (Kohler)	1 mL	0.097 (1.49)	0.032 (0.5)	8 (0.16)	0.027 (0.5)	0 (0)	0 (0)	0.091 (1.63)	0 (0)	0 (0)	14 (0.24)	10-mL ampule
Oligo-elements Aguettant Pediatricque (Aguettant)	1 mL	0.1 (1.53)	0.03 (0.47)	2 (0.04)	0.01 (0.2)	5 (0.06)	5 (0.05)	0.05 (0.9)	0.005 (0.04)	0.05 (2.63)	1.5 (0.03)	10-mL ampule

Information based on manufacturer's labeling information as of February 1, 2010. Manufacturers, products, and product information can change frequently.

Over the years, the manufacturing processes have evolved so it is unclear as to the amount of TE contamination in the current PN formulas. A.S.P.E.N. recommends that these contamination studies be repeated on the current PN component products. A.S.P.E.N. has multiple recommendations regarding the current multiple TE products as well as individual dosing of some TEs. Therefore, each TE will be discussed separately.

**Zinc.** Zinc is included in the current multiple TE product in the U.S. The data that support the routine addition of 3–4 mg/d in all PN formulations are stronger than in any other TE.<sup>12</sup> Individual parenteral zinc products are also available and can be used to add additional zinc to the PN formula. Patients with enterocutaneous fistulae, diarrhea, and intestinal drainage may require up to 12–17 mg of zinc per liter of lost fluid.<sup>71,72</sup> Patients with severe burns require much larger amounts of zinc per day to compensate for losses through the burnt skin.<sup>73</sup> A.S.P.E.N. recommends no changes to the zinc concentrations in the current parenteral multiple TE or individual zinc products.

**Selenium.** There is strong evidence that selenium should be routinely added to all PN formulas.<sup>11</sup> However, some of the currently available parenteral multiple TE products in the U.S. do not contain selenium. Selenium is available as an individual parenteral product that can be added to PN formulas separately (Tables 10 and 11). However, the recommended daily parenteral intake of selenium has fluctuated considerably (Table 2). The current recommended parenteral intake is 20–60 mcg/d, which seems to be too low, because patients receiving this level of daily intake frequently have low plasma concentrations of selenium.<sup>11</sup> A.S.P.E.N. recommends that selenium be routinely added to PN formulas, either in a multiple TE product or as a separate component. A.S.P.E.N. also recommends that the adult daily parenteral selenium requirement should be increased to 60–100 mcg per day.<sup>11</sup> Patients who are deficient or who are critically ill, septic, or have severe burns may benefit from short-term, very high daily doses administered separate from the PN, but this remains controversial.<sup>74-78</sup>

Selenium is not included in any pediatric or neonatal multiple TE product currently available in the U.S. A.S.P.E.N. recommends that selenium be added to these products. A.S.P.E.N. also recommends that selenium should routinely be provided at a dose of 2 mcg/kg/d in all pediatric and neonatal PN formulas.

**Manganese.** In 2001, Dickerson<sup>53</sup> reviewed 17 reports of 389 patients on PN that developed hypermanganesemia (265 adults and 124 children). Most patients had no clinical symptoms; a small number developed a Parkinson-like syndrome, confusion, irritability, and occasional seizures. Laboratory studies showed increased serum and red blood cell manganese and increased basal ganglia magnetic resonance image (MRI) signal intensities that

regressed after manganese infusion was discontinued; improvement required 6–12 months.

In 2008, Hardy et al<sup>54</sup> reviewed the medical literature after 2001. There were 11 additional reports that included a total of 229 patients who required PN (75 adults and 154 children). Hypermanganesemia occurred particularly in infants with cholestasis, often within 3 weeks of the initiation of PN. Another study in which measurements of manganese content in autopsy tissues were reported from 8 patients who lived 2–21 years on PN showed significant manganese elevation in liver and kidney samples, especially in patients who died of liver or renal failure.<sup>55</sup> While the mechanism of manganese neurotoxic damage is not precisely known, a recent study<sup>56</sup> using cultured rat astrocytes found manganese induced mitochondrial dysfunction and alterations in glutamine/glutamate cycling.

Current adult multiple TE products available in the U.S. provide 500–800 mcg manganese per day and the pediatric/neonatal TE products provide 2–10 mcg/kg/d, and most patients developing hypermanganesemia had received doses within these ranges. Hypermanganesemia is also seen in Europe, where the most widely used products for adults provide 265 mcg/d. A well-designed Japanese dose-finding study showed adult PN patients maintained a stable whole-blood manganese level on a supplement of 55 mcg/d.<sup>79</sup> Less than this caused a fall in red blood cell (RBC) manganese to values lower than control, whereas an increase in RBC manganese and in MRI signal intensity was likely if 110 mcg or more was supplemented,<sup>79</sup> which has also been shown in other studies.<sup>80</sup>

A.S.P.E.N. recommends that the dose of manganese in parenteral multiple TE products be decreased to 55 mcg/d for adults and 1 mcg/kg/d in pediatric and neonatal products with a maximum daily total dose of 55 mcg. Manganese dose should be further decreased or withheld in patients with significant cholestasis or hepatic dysfunction, elevated whole blood manganese levels, or in those with signs and symptoms of manganese toxicity. In addition, A.S.P.E.N. recommends the amount of manganese contamination in a standard adult composite PN formulation be limited to <40 mcg/d. Contamination data for pediatric and neonatal PN formulas are not available and require further research.

**Copper.** Copper toxicity is exemplified by Wilson's disease, an inborn error of copper metabolism leading to high concentrations of copper, particularly in the liver, brain, and kidney, which in turn leads to the development of cirrhosis, neurologic sequelae, and renal impairment.<sup>81</sup> While copper overload in PN patients has not been shown to mimic the clinical aspects of Wilson's disease, very elevated concentrations of hepatic copper, which meet the diagnostic criteria for Wilson's disease (copper >250 mcg/g dry weight), have been reported. Blaszyk et al<sup>57</sup> performed liver biopsies on 28 long-term PN patients with cholestasis, and hepatic copper ranged from 10–2248 mcg/g dry weight, and in 8 of



the 28 PN patients, hepatic copper was >250 mcg/g. The copper doses infused were not described in this paper.

In the previously referenced autopsy tissue study,<sup>55</sup> copper concentrations were measured in heart, muscle, liver, and kidney. Copper was significantly elevated in liver and kidney tissue, especially in patients who died of liver failure. These 8 patients received a commercial multiple TE formulation that met the 1979 recommendations for infusion of 0.5–1.5 mg/d of copper. The subjects had received 1.4 mg/d of copper for a mean of 14 years. Copper balance studies reported by Shike et al<sup>82</sup> indicated this amount was approximately 3 times the typical requirement. By analogy, with cholestatic infants, it is likely that copper accumulates as a result of liver disease, but it is also possible that hepatic copper overload enhances the liver damage.

Currently, the adult parenteral multiple TE products available in the U.S. provide approximately 1 mg/d of copper. A.S.P.E.N. recommends that the dose of copper in adult parenteral multiple TE products be lowered to 0.3–0.5 mg/d and limit the amount of contamination in a composite PN formulation to no more than 0.1 mg/d. Copper doses should be decreased or omitted in patients with significant cholestasis or hepatic dysfunction. Copper requirements are increased in severe burn patients.<sup>73</sup> Because of the absence of contamination data for pediatric and neonatal parenteral TE products, no recommendations for product changes are currently made, but investigation of copper contamination in these products should be required.

**Chromium.** Chromium toxicity varies depending on the chromium valency. Chromium IV, V, and VI are carcinogenic. Chromium in PN formulations, food, and oral supplements is trivalent and considered nontoxic.<sup>1</sup> Analysis of PN formulations showed that chromium was only in the trivalent form.<sup>83</sup> There are several reports in PN patients, both adults and children, of serum and urine chromium concentrations 10–100 times normal values.<sup>84–87</sup> Autopsy tissue data found similar elevations in heart, muscle, liver, and kidney samples.<sup>55</sup> A normal adult diet provides approximately 35 mcg/d of chromium. Recent studies have revised the estimated amount of dietary chromium absorbed from the previous level of 10%–20% down to 0.4%–2.5%.<sup>88</sup> This means the absorbed amount of chromium from a standard adult oral diet is only 0.4–0.9 mcg/d. Therefore, the parenteral requirement is likely to be only one-tenth or less of the previously recommended amounts of 10–15 mcg/d.

According to Pluhator-Murton et al's data,<sup>62</sup> chromium contamination of a 2-L PN composite formula is approximately 15 mcg per day, mainly from the 70% dextrose solution used, and is in addition to the 11 mcg/d intentionally added from a multiple TE product. This amounts to a parenteral chromium dose that is 30–60 times greater than the current estimated requirement. The key question is whether these

high chromium doses are without clinical consequence or are potentially toxic. In adults, there are no reported cases of chromium toxicity in patients on long-term PN, suggesting that these high chromium concentrations are not toxic. This is further supported by a study that found very high serum chromium concentrations and increased urinary chromium excretion related to the implantation of hip prostheses in adult patients with no deterioration in renal function when observed over a 10-year period.<sup>89</sup> Another study randomized uncontrolled patients with diabetes to either a supplement with a combination of chromium picolinate and biotin or placebo for 90 days. The study group experienced a significant decrease in hemoglobin A1c compared with the placebo group, and there was no difference in adverse effects between the 2 groups.<sup>90</sup> There are isolated reports of individuals who developed renal failure due to tubular necrosis following the ingestion of large doses of chromium as chromium picolinate.<sup>91–96</sup> This toxicity did not appear to be due to the picolinate moiety and has been assumed related to chromium. So while increased levels of serum and tissue chromium occur with current PN regimens, the toxicity of these levels at least in adults remains unknown.

Chromium toxicity may be more of a concern in pediatric patients. In 1992, Moukarzel et al<sup>97</sup> found that glomerular filtration rates (GFRs) in PN-dependent children were inversely correlated with their serum chromium concentration, their cumulative parenteral chromium intake, and PN duration. The investigators discontinued parenteral chromium supplementation, and a year later, the children's serum chromium concentrations were lower but still elevated, and their reduced GFR was still below control patients who did not receive PN. The investigators were unable to determine whether chromium contamination had resulted in irreversible renal injury. Buchman et al<sup>71</sup> found renal tubular damage and high concentrations of chromium deposits in the kidneys of rodents after receiving 1 week of PN; however, it was difficult to determine if this was a cause-and-effect relationship.

Current adult multiple TE products available in the U.S. provide 10–15 mcg/d of chromium. Based on oral absorption in healthy individuals,<sup>88</sup> the parenteral requirements may be as low as 0.14–0.87 mcg/d.<sup>10</sup> Because PN components have significant chromium contamination, some physician investigators have stopped adding chromium to PN formulations, but the consequences of such actions have not been evaluated. The requirements for chromium during PN with a high and continuous IV dextrose load are not known, and despite chromium contamination, rare PN-dependent adult patients have been reported to require additional chromium in order to maintain glucose tolerance.<sup>98–101</sup> Until contamination is reduced and the issue of parenteral chromium toxicity is better understood, A.S.P.E.N. recommends that in addition to the current multiple TE products that contain 10–15 mcg/d of chromium, a multiple TE product without added chromium should be made

**Table 14.** Recommendations for Revised Daily Parenteral Dose of Chromium in Neonatal and Pediatric Patients

Age	Male	Female
0–6 mo	0.0006 mcg/kg/d	
7–12 mo	0.012 mcg/kg/d	
1–3 y	0.22 mcg/d	
4–8 y	0.3 mcg/d	
9–13 y	0.5 mcg/d	0.42 mcg/d
14–18 y	0.7 mcg/d	0.48 mcg/d

These recommendations are based on the Adequate Intake (AI) for these age groups and estimated oral absorption of chromium of 2%. Adapted from Moukarzel A. Chromium in parenteral nutrition: too little or too much? *Gastroenterology*. 2009;137(5)(suppl):S18-S28 with permission from Elsevier.

available. Research on chromium requirements during PN and the effects of contamination on requirement for supplementation is urgently needed.

The pediatric and neonatal multiple TE products available in the U.S. provide 0.05–0.2 mcg/d of chromium. Studies of pediatric/neonatal PN patients on this level of supplementation report serum chromium concentrations 4–42 times that of normal.<sup>10,86</sup> Moukarzel<sup>10</sup> recommended that the daily parenteral dose of chromium for neonates and pediatric patients be radically reduced. In view of preliminary studies in newborns on PN that demonstrate chromium nephrotoxicity, and because PN formulations have significant chromium contamination, A.S.P.E.N. recommends that the daily dose of chromium be reduced to the levels recommended by Moukarzel (Table 14) and that a pediatric/neonatal multiple TE product without added chromium should be available for use in this patient population.

**Iron.** Iron is absorbed in the duodenum, and iron malabsorption is rarely the cause of iron deficiency simply due to a short bowel. However, patients with a short bowel often have disease that results in iron loss or have dietary restrictions preventing an adequate intake of iron. In addition, gastric surgery may reduce the availability of dietary iron.

The requirement for iron in males and postmenopausal women who do not have any source of blood loss is about 1 mg/d. It is higher in menstruating women who on average require an additional 0.51 mg/d. However, menstrual losses vary and may necessitate an intake as high as 3.4 mg/d. In patients on PN, iron requirements vary due to diseases causing blood loss or iatrogenic causes such as repeated blood draws. Hence, there is a wide range of requirements in individuals, making a single recommendation for daily parenteral intake difficult.

Multiple TE products in Europe contain iron, but TE products in the U.S. do not contain iron. Stability of total nutrient admixtures containing iron has prevented its addition to trace

element mixtures in the U.S. However, studies using a concentration of 0.5 mg/L have shown stability for 7 days of storage at 4°C and 25°C.<sup>102</sup>

The current options for iron supplementation for adult PN patients in the U.S. are:

1. Patients capable of absorbing oral administered iron who may be supplemented using an oral product
2. Addition of 1–5 mg/d of iron dextran to fat-free PN in patients without deficiency and those not having significant ongoing blood loss
3. Separate infusions of IV iron sucrose in doses of 300 mg per infusion to give a total dose based on the Ganzoni formula<sup>103</sup> so as to meet the deficit followed by daily infusions as above

Which option is used in an individual patient depends on his or her baseline iron stores and ongoing iron losses.

Iron supplementation in pediatric and neonatal PN patients may be important in long-term therapy, but there is insufficient evidence to develop definitive daily recommendations due to potential toxicity. Many ill children and neonates also receive blood transfusions in the hospital, which may be adequate. Children and neonates should be monitored for iron status prior to initiating parenteral therapy using serum iron, transferrin, and ferritin levels.

To permit a routine daily supply of parenteral iron, research is required to examine the stability of iron additives to fat emulsion-containing admixtures.

**Iodide.** Iodide is currently included in the parenteral multiple TE products available in Europe, but it is not included in any of the products available in the U.S. (Tables 10 and 12). The amount of iodide contamination in PN components is unclear but appears adequate to meet basal requirements since thyroid function remains normal in most long-term PN patients.<sup>32</sup> However, one study of 15 pediatric PN patients in Europe<sup>104</sup> found an inverse correlation between duration of PN and urinary iodide concentrations. While 9 (60%) of these patients had iodide deficiency based on urinary iodide concentrations, thyroid function tests remained normal. In the past, the widespread use of povidone-iodine solutions for skin cleansing of catheter sites may have maintained a normal iodide status as studies have shown that iodine skin preparation can result in significant transcutaneous iodine absorption.<sup>105</sup> Since skin cleansing has widely moved to the use of 2% chlorhexidine, the risk of iodide deficiency and the need for parenteral supplementation need to be investigated. Routine supplementation of PN with iodide could be beneficial, but more research is needed for adult, pediatric, and neonatal products.<sup>32</sup>

**Fluoride.** Fluoride is also present in the multiple TE products used in Europe but is not included in any products

available in the U.S. (Tables 10 and 12). The amount of fluoride contamination in PN is variable. Supplementation of PN with fluoride could be beneficial, but more research is needed for adult, pediatric, and neonatal patient populations.<sup>31</sup>

**Molybdenum.** Molybdenum is present in most of the adult and some of the pediatric parenteral multiple TE products in Europe but none of the products in the U.S. Previous studies showed PN was contaminated with molybdenum, but it is unknown what the level of contamination is in current PN formulations. Although molybdenum is not routinely supplemented in PN in the U.S., only 1 case of deficiency in a patient on PN has been reported (see Appendix 10). There are no significant data to warrant recommending routine molybdenum supplementation in PN formulas. Thus, no changes are recommended for adult, pediatric, and neonatal products.

### Counterissues/Problems Definition

The main problem with specifying trace element and vitamin dosages in nutrition products is the individual variability of patient requirements. Nutrient needs vary as a result of prior deficiencies, disease state, surgery, and the presence of sepsis or trauma. Also, micronutrient needs are increased with excessive losses that occur with vomiting, diarrhea, fistulae output, aspirates, wound drainage, and burns. The micronutrient dosages recommended by A.S.P.E.N. are meant to meet basic nutrient needs for the majority of patients, while also acknowledging (or recognizing) that some patients may need greater amounts of certain nutrients, whereas other patients may need to have certain nutrients decreased or omitted.

Although there are a large number of patients receiving PN, the reported incidence of TE toxicities in these patients is very low. One reason may be that PN therapy is usually short term, less than 3–6 months, so the number of long-term PN patients, who are most at risk of low-level, chronic toxicity, is relatively small.<sup>106</sup> Signs and symptoms related to TE toxicities may be missed if the patient is not specifically monitored for these complications. Toxicity may inadvertently be attributed to other factors rather than the accumulation of TE.

Implementation of A.S.P.E.N.'s recommendations for changes in the available parenteral multiple and individual vitamin and TE products will require product submissions to and approval by the FDA. Some of the recommended changes have already been included in preparations that have been safely and effectively used outside of the U.S. for many years. It is recognized that the FDA may require submission of North American-based studies that include safety and efficacy of

the newly recommended products, despite these substances being present in the oral diet. A.S.P.E.N. is concerned that this process may require significant time, financial investment, and other resources. Many companies may be reluctant to make such a commitment on their own, especially for products that have a relatively low profit margin, in the absence of requirements to do so from the FDA. A.S.P.E.N. is also concerned that industry, rather than incurring the expense of product modification, could choose to eliminate products from the marketplace. This could result in devastating effects on the patients these same products are designed to treat. A.S.P.E.N. will encourage the FDA not only to require the recommended modifications but also to actively encourage and assist the pharmaceutical industry in the development and approval of safer and more effective vitamin and TE products. Ultimately, A.S.P.E.N.'s aim is that micronutrient products available in the U.S. and in other countries will meet a uniform standard, allowing manufacturers to experience larger and more financially viable markets.

### Summary/A.S.P.E.N. Recommendations

The routine and appropriate provision of certain vitamins and TEs in PN is essential in improving nutrition status, allowing improvement in the patient's underlying disease process and in preventing complications of deficiency or toxicity.

The current parenteral multiple vitamin products commercially available in the U.S. meet the requirements for most PN patients. However, a separate parenteral cholecalciferol or ergocalciferol product should be available for treatment of patients with vitamin D deficiency who are unresponsive to additional oral vitamin D supplementation or when oral supplementation is impossible.

The current parenteral multiple TE products that are commercially available in the U.S. require significant modification as follows:

Adult parenteral multiple TE products:

- Decrease copper to 0.3–0.5 mg/d
- Decrease manganese to 55 mcg/d
- Product with no chromium (or a maximum of 1 mcg/d)
- Include selenium in all products and increase the dose to 60–100 mcg/d

Pediatric/neonatal parenteral multiple TE products:

- Product with no chromium
- Decrease manganese to 1 mcg/kg/d in neonates
- Add selenium 2 mcg/kg/d in all pediatric/neonatal preparations

The recommendations regarding parenteral carnitine:

- Provide 2–5 mg/kg/d carnitine either as part of a multiple vitamin or multi-TE products or as an individual product in all neonatal PN formulas

The recommendations regarding parenteral choline:

- Provide 550 mg/d of choline routinely to adult PN formulations (requires development of either an individual choline product or addition of choline into either a multiple vitamin or TE product)
- Recommend routine parenteral administration in newborns and pediatric patients with the following dosing:
  - 0–6 months: 125 mg/d
  - 7–12 months: 150 mg/d
  - 1–3 years: 200 mg/d
  - 4–8 years: 250 mg/d
  - 9–13 years: 375 mg/d
  - >13 years: adult amounts

The recommendations for TE contamination in PN formulations:

- Limit copper contamination to <0.1 mg/d total in a typical adult PN formulation
- Limit manganese contamination to <40 mcg/d total in a typical adult PN formulation
- In order to accomplish these recommendations, all PN products should be taken into consideration

The recommendations regarding future research (in order of priority):

- Parenteral chromium requirements in adult, pediatric, and neonatal PN patients (most urgent)
- Need further research and development of appropriate monitoring strategies for trace element and vitamin deficiency and toxicity in PN patients (urgent)
- Studies on TE contamination in the various PN component products, especially manganese contamination in neonatal and pediatric PN formulations
- Feasibility of adding parenteral iron products to PN formulas, to include fat emulsion stability and other potential incompatibilities
- Benefits of carnitine supplementation of PN in adult and pediatric patients
- Benefits of fluoride supplementation of PN in adult, pediatric, and neonatal patients

- Benefits of iodine supplementation of PN in adult, pediatric, and neonatal patients

*A.S.P.E.N. Novel Nutrient Task Force,  
Parenteral Multi-vitamin and Multi-Trace  
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## Appendix 1

### Function, Deficiency, Efficiency, and Toxicity of Vitamins and Trace Elements

Vincent W. Vanek, MD, FACS, FASPEN

	Function/Source/Comments	Deficiency State	Toxicity
Fat-Soluble Vitamins			
Vitamin A	<ul style="list-style-type: none"> <li>Sources: carrots and dark-green leafy vegetables</li> <li>Group of compounds called retinoids</li> <li>Integral component of rhodopsin and iodopsins, light-sensitive proteins in retinal rod and cone cells</li> <li>Essential for vision, growth, cellular differentiation and proliferation, reproduction, and the integrity of the immune system</li> <li>Patients (pts) at risk of deficiency:               <ul style="list-style-type: none"> <li>GI dysfunction—diarrhea or fat malabsorption</li> <li>Chronic alcoholics</li> <li>Impaired vitamin A transport—protein or zinc deficiency</li> </ul> </li> <li>↑ needs or losses—burns, major trauma or surgery, fever, or infection</li> </ul>	<ul style="list-style-type: none"> <li>Night blindness*</li> <li>Follicular hyperkeratosis*</li> <li>Xerosis or xerophthalmia</li> <li>Irreversible corneal lesions</li> <li>Anorexia</li> <li>Immunodepression</li> <li>Metaplasia of respiratory, GI, GU epithelial cells</li> <li>* Early signs of vitamin A deficiency</li> </ul>	<ul style="list-style-type: none"> <li>Acute (&gt;150,000 mcg)               <ul style="list-style-type: none"> <li>Increased intracranial pressure</li> <li>Headache</li> <li>Nausea/vomiting</li> <li>Vertigo</li> <li>Blurred vision</li> <li>Muscular incoordination</li> </ul> </li> <li>Chronic (&gt;30,000 mcg/d)               <ul style="list-style-type: none"> <li>Bone malformations and fractures</li> <li>Dermatitis</li> <li>Alopecia</li> <li>Ataxia</li> <li>Muscle pain</li> <li>Cheilitis</li> <li>Membrane dryness</li> <li>Skin disorders and pruritus</li> <li>Vision disorders</li> <li>Pseudotumor cerebri/HA</li> <li>Hepatocellular necrosis</li> <li>Hyperlipidemia</li> <li>Inhibits vitamin K</li> </ul> </li> <li>Early pregnancy (&gt;7800 mcg/d)—teratogenic with spontaneous abortions, birth defects, and learning disabilities</li> </ul>
Vitamin D	<ul style="list-style-type: none"> <li>Sources (2 forms):               <ul style="list-style-type: none"> <li>Vitamin D<sub>2</sub> (ergocalciferol)—consumed in diet (eggs, butter, and fortified milk and margarine)</li> <li>Vitamin D<sub>3</sub> (cholecalciferol)—synthesized in skin during exposure to solar or artificial ultraviolet light</li> </ul> </li> <li>Requires hydroxylation in the liver to 25-OH-D followed by hydroxylation in the kidneys to its active form of 1,25-(OH)<sub>2</sub>-D</li> <li>Maintains intra- and extracellular calcium and phosphorous levels by enhancing GI absorption and promoting mobilization from bone mineral</li> <li>Also involved with growth and maturation of other cells, including immune and hematopoietic cells</li> <li>Pts at risk for deficiency:</li> </ul>	<ul style="list-style-type: none"> <li>Childhood—rickets that result in deformation of the skeleton</li> <li>Adults—osteomalacia and osteopenia that can result in fractures</li> <li>Hypocalcemia</li> <li>Bone pain and tenderness</li> <li>Hypophosphatemia</li> </ul>	<ul style="list-style-type: none"> <li>Hypercalcemia—anorexia, nausea, vomiting, headache, weakness, fatigue, diarrhea, confusion, psychosis, tremor</li> <li>Hypercalcinuria—renal stones</li> <li>Metastatic calcifications with irreversible renal damage, altered mentation, and cardiovascular damage</li> </ul>

(continued)

## Appendix 1 (continued)

	Function/Source/Comments	Deficiency State	Toxicity
	Elderly or very young with inadequate oral intake of vitamin D Pts with regional enteritis (Crohn's disease), celiac disease, cystic fibrosis, cholestatic liver disease, pancreatic insufficiency, gastric resection, or jejunioileal bypass surgery Pts with liver dysfunction or renal failure Certain drugs—anticonvulsants, cimetidine, isoniazid		
Vitamin E	<ul style="list-style-type: none"> <li>• Sources: vegetable oils (olive, soy, and corn oils, including margarine and shortening), wheat germ, nuts, green leafy vegetables, sunflower and cotton seeds</li> <li>• Group of compounds called tocopherols</li> <li>• Antioxidant and free radical scavenger</li> <li>• Found in cell membranes of all tissues throughout the body and protects the cells from free radical formation from oxidation reactions</li> <li>• Pts at risk for deficiency:               <ul style="list-style-type: none"> <li>• Pts with prolonged steatorrhea, pancreatitis, cystic fibrosis, short bowel syndrome, or cholestasis</li> </ul> </li> <li>• Premature infants and infants with severe malnutrition, liver dysfunction, or abetalipoproteinemia</li> <li>• Pts with mechanical ventilation and on high oxygen concentration</li> </ul> Pts supplemented with $\omega$ -3 fatty acids	<ul style="list-style-type: none"> <li>• Hemolytic anemia (only significant in infants)</li> <li>• Increased platelet aggregation</li> <li>• Axonal neuropathy involving peripheral nerves, posterior column fibers, and gracilis nuclei causing ataxia and weakness</li> <li>• Causes retinal dysfunction, resulting in tunnel vision</li> <li>• Decreased serum creatinine due to excessive urinary losses</li> <li>• Skeletal lesions similar to muscular dystrophy</li> </ul>	<ul style="list-style-type: none"> <li>• Very uncommon even with large doses (3200 International Units/d)</li> <li>• Liver impairment with depressed levels of vitamin K—dependent coagulation factors potentiating bleeding if pt has a coagulopathy or is on oral anticoagulants and can increase incidence of hemorrhagic stroke in these situations</li> <li>• Impaired leukocyte function</li> <li>• Preterm infants may be more susceptible to liver damage</li> </ul>
Vitamin K	<ul style="list-style-type: none"> <li>• Sources (2 forms):               <ul style="list-style-type: none"> <li>• Vitamin K<sub>1</sub> (phyloquinone)—oral intake with green leafy vegetables with smaller amounts in milk, dairy products, meats, eggs, cereal, fruits, and other vegetables</li> <li>• Vitamin K<sub>2</sub> (menaquinone)—synthesized by gut bacterial flora in colon but poorly absorbed</li> </ul> </li> <li>• Functions in the posttranslational <math>\gamma</math>-carboxylation of the clotting factors II (prothrombin), VII, IX, and X as well as proteins C and S, all of which are vital in the clotting cascade and normal blood clotting</li> <li>• Required for the synthesis of other proteins in the plasma, bone, and kidney</li> <li>• Pts at risk for deficiency:</li> </ul>	<ul style="list-style-type: none"> <li>• Coagulopathy with excessive bleeding</li> <li>• Fetal intracranial hemorrhage</li> <li>• Easy bruisability</li> <li>• Mucosal bleeding</li> <li>• Splinter hemorrhages</li> <li>• Melena</li> <li>• Hematuria</li> <li>• Rare in healthy adults</li> <li>• Common in newborns due to immature liver, low vitamin K in breast milk, sterile gut, and poor placental transfer of vitamin K</li> <li>• Fetal skeletal deformities (chondrodysplasia)</li> </ul>	<ul style="list-style-type: none"> <li>• Rare</li> <li>• Rapid IV infusion can cause anaphylactoid reaction with dyspnea, flushing, and cardiovascular collapse</li> <li>• Pregnant woman taking large dose of vitamin K may deliver infants with hemolytic anemia, hyperbilirubinemia, and kernicterus</li> </ul>

(continued)



## Appendix 1 (continued)

	Function/Source/Comments	Deficiency State	Toxicity
	<p>Breast-fed newborns</p> <p>Pts with malabsorption syndromes, cystic fibrosis, tropical sprue, celiac disease, ulcerative colitis, regional enteritis (Crohn's disease), or short bowel syndrome</p> <p>Pts with cholestasis, biliary obstruction, liver disease, or renal failure</p> <p>Pts on certain medications such as large doses of salicylates, broad-spectrum antibiotics, megadoses of vitamin A and E, cholestyramine</p> <p>Pts on long-term PN</p>		
Water-Soluble Vitamins			
Thiamin [also spelled thiamine] (vitamin B <sub>1</sub> )	<ul style="list-style-type: none"> <li>• Sources: enriched and fortified grains, cereals, and bakery products; organ meats (liver, kidney, and heart); lean cuts of pork, legumes; and seeds/nuts</li> <li>• Coenzyme required for oxidative decarboxylation of <math>\alpha</math>-keto acids (eg, pyruvate <math>\rightarrow</math> coenzyme A [CoA] to link glycolysis to Krebs cycle and the conversion of <math>\alpha</math>-ketoglutarate <math>\rightarrow</math> succinyl CoA within the Krebs cycle) and for the activity of transketolase in the pentose phosphate pathway</li> <li>• Inadequate thiamin availability results in inadequate ATP synthesis and abnormal carbohydrate metabolism</li> <li>• High carbohydrate intake increases thiamin requirements</li> <li>• Pts at risk for deficiency: <ul style="list-style-type: none"> <li>• Underdeveloped countries—thiamin-poor diets or diets containing thiamin antagonists</li> <li>• Alcoholics</li> <li>• Refeeding syndrome</li> <li>• PN without thiamine supplementation</li> <li>• Pts with <math>\uparrow</math> needs—fever, infection, trauma, burns, hyperparathyroidism, pregnancy, lactation, strenuous exertion, adolescent growth</li> <li>• Pts with <math>\uparrow</math> losses—dialysis, diuresis, malabsorption, prolonged antacid tx</li> </ul> </li> <li>• Sources: enriched and fortified grains, cereals, and bakery products; meats; poultry, fish; and dairy products</li> <li>• Component of 2 flavin coenzymes</li> <li>• Flavin mononucleotide (FMN)</li> <li>• Flavin adenine dinucleotide (FAD)</li> </ul>	<ul style="list-style-type: none"> <li>• Dry beriberi—causes peripheral neuropathy resulting in paresthesias, anesthesia, and weakness, mostly of the lower extremities</li> <li>• Hypothermia</li> <li>• Wet beriberi—causes cardiovascular symptoms such as cardiomyopathy, edema, tachycardia, dyspnea, hepatomegaly, oliguria, metabolic lactic acidosis</li> <li>• Wernicke-Korsakoff syndrome</li> <li>• Wernicke's disease—ophthalmoplegia, nystagmus, and ataxia</li> <li>• Korsakoff psychosis—short-term memory loss and confabulation but otherwise normal cognition</li> </ul>	<ul style="list-style-type: none"> <li>• Rare</li> <li>• Easily cleared from the kidney so toxicities are rare and have never been reported from oral thiamine alone</li> <li>• No toxicity reported</li> </ul>
Riboflavin (vitamin B <sub>2</sub> )			
	<ul style="list-style-type: none"> <li>• Sources: enriched and fortified grains, cereals, and bakery products; meats; poultry, fish; and dairy products</li> <li>• Component of 2 flavin coenzymes</li> <li>• Flavin mononucleotide (FMN)</li> <li>• Flavin adenine dinucleotide (FAD)</li> </ul>	<ul style="list-style-type: none"> <li>• Oral-buccal lesions such as cheilosis, glossitis, and angular stomatitis</li> <li>• Seborrheic dermatitis</li> </ul>	<ul style="list-style-type: none"> <li>• No toxicity reported</li> </ul>

(continued)

## Appendix 1 (continued)

	Function/Source/Comments	Deficiency State	Toxicity
Niacin (vitamin B <sub>3</sub> )	<p>Catalyzes many oxidative-reduction reactions in the body such as the conversion of tryptophan to niacin and functions in xanthine oxidase, succinic dehydrogenase, and glutathione reductase oxidative enzyme systems</p> <ul style="list-style-type: none"> <li>• Essential for proper functioning of vitamin B<sub>6</sub> and niacin</li> <li>• Pts at risk for deficiency:           <ul style="list-style-type: none"> <li>• Pts with malabsorption (celiac disease, short bowel syndrome, etc), thyroid dysfunction, diabetes, or alcoholism</li> <li>• Pregnancy and lactation</li> <li>• Pts with surgery, trauma, burns, or fractures</li> <li>• Pts on psychotropic drugs, tricyclic antidepressants, or barbiturates</li> <li>• Pts with anorexia nervosa or who avoid dairy products</li> </ul> </li> <li>• Sources: meat and tryptophan-containing foods such as milk and eggs (niacin is unique among vitamins in that it can be formed in the body from dietary tryptophan)</li> <li>• Niacin includes nicotinic acid and nicotinamide</li> <li>• Nicotinamide functions in 2 coenzyme systems, NAD and NADP</li> <li>• These coenzymes are present in all cells and are essential in many metabolic processes, including glycolysis, fatty acid metabolism, and tissue respiration</li> <li>• Pts at risk for deficiency:           <ul style="list-style-type: none"> <li>• Pts with malabsorption, thyroid dysfunction, cancer, burns, or alcoholism</li> </ul> </li> <li>• Pts on isoniazid therapy for tuberculosis</li> <li>• Pts with carcinoid syndrome (tryptophan is metabolized to 5-OH tryptophan and serotonin instead of nicotinic acid)</li> <li>• Hartnup's disease—autosomal recessive congenital disorder that interferes with absorption of tryptophan</li> </ul>	<p>Scrotal and vaginal skin changes</p> <ul style="list-style-type: none"> <li>• Ocular disturbances such as itching, burning, dryness, corneal inflammation, and photophobia</li> <li>• Normochromic, normocytic anemia</li> <li>• Frequently accompanied by vitamin B<sub>6</sub> and niacin deficiency with their associated symptoms</li> </ul>	<ul style="list-style-type: none"> <li>• Nicotinamide has no reported toxicity</li> <li>• Nicotinic acid in high doses (3–9 g/d) can cause:           <ul style="list-style-type: none"> <li>• Flushing</li> <li>• Nausea and vomiting</li> <li>• Liver toxicity</li> <li>• Blurred vision</li> <li>• Impaired glucose tolerance</li> </ul> </li> </ul>
Pantothenic acid (vitamin B <sub>5</sub> )	<ul style="list-style-type: none"> <li>• Sources: meat, whole grain cereals, and legumes</li> <li>• Component of CoA (involved in gluconeogenesis, synthesis of heme and sterols, and release of energy from carbohydrate, fat, and ketogenic amino acids) and acyl carrier protein (necessary for fat synthesis)</li> <li>• Pts at risk for deficiency:           <ul style="list-style-type: none"> <li>• Chronically malnourished</li> <li>• Alcoholics</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Rare and usually in combination with other vitamin B deficiencies</li> <li>• Growth retardation</li> <li>• Infertility</li> <li>• Abortion and neonatal death</li> <li>• Listlessness and fatigue</li> </ul>	<ul style="list-style-type: none"> <li>• Rare</li> <li>• High doses (10–20 g/d) have been reported to cause diarrhea and fluid retention</li> </ul>

(continued)

## Appendix 1 (continued)

	Function/Source/Comments	Deficiency State	Toxicity
Vitamin B <sub>6</sub>	<ul style="list-style-type: none"> <li>• Sources: chicken, fish, kidney, liver, pork, eggs, rice, soy beans, oats, whole wheat, peanuts, and walnuts</li> <li>• Comprises 3 forms: pyridoxine, pyridoxal, and pyridoxamine</li> <li>• Liver, erythrocytes, and other tissues convert these forms into pyridoxal phosphate and pyridoxamine phosphate, which are essential coenzymes in transamination and decarboxylation reactions</li> <li>• These reactions are important in the transformation of certain amino acids and in the metabolism of lipids and nucleic acid, as well as conversion of tryptophan to niacin</li> <li>• These coenzymes are also essential for glycogen phosphorylase</li> <li>• Pts at risk for deficiency:               <ul style="list-style-type: none"> <li>• Usually seen in conjunction with other B vitamin deficiencies</li> <li>• Certain medications inhibit vitamin B<sub>6</sub> metabolism such as isoniazid, cycloserine, penicillamine, ethanol, and theophylline</li> </ul> </li> </ul>	<p>Abnormalities of skin and hair</p> <ul style="list-style-type: none"> <li>• Abdominal pain, vomiting, and diarrhea</li> <li>• Impaired mentation and insomnia</li> <li>• Paresthesias</li> <li>• Poor wound healing</li> <li>• Increased susceptibility to infection</li> <li>• Adrenal cortical failure</li> <li>• Sudden death</li> </ul>	<ul style="list-style-type: none"> <li>• Acute toxicity is rare</li> <li>• However, if taken in high doses for a prolonged period of time (treatment of PMS or certain mental disorders), it can cause ataxia, peripheral neuropathies, and severe sensory neuropathy with photosensitivity</li> </ul>
Vitamin B <sub>12</sub> (cobalamin)	<ul style="list-style-type: none"> <li>• Sources: fish, eggs, and milk</li> <li>• Must be converted to one of its coenzyme forms, methylcobalamin or 5'-deoxyadenosylcobalamin</li> <li>• Adequate absorption depends on:               <ul style="list-style-type: none"> <li>• Dietary intake</li> <li>• Acid-pepsin in stomach to liberate B<sub>12</sub> from food sources</li> <li>• Pancreatic proteases to free B<sub>12</sub> from binding with R factors</li> <li>• Secretion of IF by gastric parietal cells to bind to B<sub>12</sub></li> <li>• Ileal B<sub>12</sub>-IF receptors</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Usually accompanies deficiencies of other B vitamins</li> <li>• Stomatitis, angular cheilosis, and glossitis</li> <li>• Irritability, depression, and confusion</li> <li>• Convulsions</li> <li>• Dermatitis</li> <li>• Normochromic, normocytic, sideroblastic anemia</li> <li>• In infants, various neurologic symptoms and abdominal distress</li> </ul>	<ul style="list-style-type: none"> <li>• No toxicity reported</li> </ul>

(continued)

## Appendix 1 (continued)

	Function/Source/Comments	Deficiency State	Toxicity
	<ul style="list-style-type: none"> <li>• Functions:           <ul style="list-style-type: none"> <li>• Coenzyme that shifts hydrogen atoms from one carbon to another (eg, converts methylmalonyl CoA to succinyl CoA, which is vital in lipid and carbohydrate metabolism)</li> <li>• Coenzymes that transfer methyl groups (eg, convert methyl folate back to tetrahydrofolic acid [THFA], the metabolically active form of folic acid, which has numerous functions, including synthesis of thymidylate and DNA)</li> <li>• Coenzymes also convert homocysteine to methionine, which is needed for myelin formation for nerves</li> <li>• Pts at risk for deficiency:               <ul style="list-style-type: none"> <li>• Total vegetarians</li> <li>• ↓ absorption—pernicious anemia, total gastrectomy, tropical sprue, celiac disease, resection of terminal ileum, gastric bypass surgery, intestinal parasites</li> <li>• ↑ requirements—pregnancy, lactation, infancy, hyperthyroidism, alcoholism, megadoses of vitamin C</li> <li>• Pts on ethanol, neomycin, colchicine, potassium, aminosalicilic acid, metformin, proton pump inhibitors</li> </ul> </li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Unsteadiness</li> <li>• Confusion</li> <li>• Depression</li> <li>• Impaired mentation and memory</li> <li>• Delusion</li> <li>• Psychosis</li> <li>• Visual disturbances</li> <li>• Leukopenia</li> <li>• Thrombocytopenia</li> </ul>	
Folate	<ul style="list-style-type: none"> <li>• Sources: liver, yeast, leafy vegetables, legumes, some fruits (as much as 50% of folate in food destroyed with cooking)</li> <li>• Folate and folacin are generic descriptors for compounds that have nutrition properties and chemical structures similar to those of folic acid (pteroylglutamate, PTE-Glu.)</li> <li>• Folic acid must be converted to its active form, THFA</li> <li>• Functions as coenzymes that transport single carbon fragments from one compound to another in amino acid metabolism and synthesis of purines and pyrimidines, which are essential in DNA</li> <li>• Deficiency leads to impaired cell division and alterations in protein synthesis</li> <li>• Pts at risk for deficiency:           <ul style="list-style-type: none"> <li>• Chronic alcoholics</li> <li>• Malabsorption—celiac disease, inflammatory bowel disease, and short bowel syndrome</li> <li>• ↑ cell division/metabolism—trauma, burns, infections, cancer, chronic hemolytic anemia, hyperthyroidism, pregnancy, lactation, and early infancy</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Megaloblastic anemia</li> <li>• Neural tube defects (anencephaly and spina bifida) in newborns of mothers not taking folate supplement</li> <li>• Glossitis</li> <li>• Diarrhea</li> <li>• Weight loss</li> <li>• Impaired cell-mediated immunity</li> <li>• Dementia</li> </ul>	<ul style="list-style-type: none"> <li>• Folic acid and the anticonvulsant phenytoin inhibit uptake of each other in the GI tract and possibly at the brain cell membrane, so large doses of folic acid (&gt;400 mcg) can precipitate seizures in epileptics on phenytoin</li> </ul>

(continued)

## Appendix 1 (continued)

	Function/Source/Comments	Deficiency State	Toxicity
Vitamin C (ascorbic acid)	<ul style="list-style-type: none"> <li>Sources: fruits (especially citrus fruits) and vegetables with smaller amounts in meat, fish, poultry, eggs, and dairy products</li> <li>Antioxidant and free radical scavenger</li> <li>Necessary for:               <ul style="list-style-type: none"> <li>Collagen synthesis via hydroxylation of proline and lysine</li> <li>Carnitine biosynthesis and neurotransmitter synthesis and metabolism</li> <li>Enhanced intestinal absorption of nonheme iron</li> <li>Hepatic microsomal hydroxylation of cholesterol required for its excretion in bile acids</li> <li>Reduction of toxic transition metals</li> <li>Reductive protection of folic acid and vitamin E</li> <li>Immune-mediated and antibacterial functions of white blood cells</li> </ul> </li> <li>Pts at risk for deficiency:               <ul style="list-style-type: none"> <li>Smokers</li> <li>Pregnancy and lactation</li> <li>Pts with major surgeries, trauma, burns, cancer</li> <li>Pts on PN</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Mild deficiency</li> <li>Anorexia</li> <li>Fatigue</li> <li>Muscle pain</li> <li>Increased susceptibility to stress and infection</li> <li>Severe deficiency</li> <li>Scurvy</li> <li>Weakening of the collagenous structures (bone cartilage, teeth, and connective tissue)</li> <li>Bleeding gums</li> <li>Petechiae and ecchymosis</li> <li>Perifollicular hemorrhage</li> <li>Impaired wound healing</li> <li>Anemia</li> <li>Joint effusions with arthralgia</li> <li>Fatigue</li> <li>Depression</li> </ul>	<ul style="list-style-type: none"> <li>Rare</li> <li>Doses &gt;500 mg/d can cause nausea and diarrhea</li> <li>Withdrawal from high chronic doses should be gradual to avoid "rebound scurvy"</li> <li>Pts with renal failure, kidney stones, or iron overload disease should avoid large doses of vitamin C</li> <li>Large amounts of vitamin C can cause false-positive fecal occult blood and glycosuria testing and may hinder heparin or coumarin anticoagulation therapy</li> </ul>
Biotin	<ul style="list-style-type: none"> <li>Sources: liver, egg yolk, soy flour, cereals, and yeast</li> <li>Sulfur-containing water-soluble vitamin, which can also be synthesized by intestinal bacteria</li> <li>Magnesium and ATP required for conversion of biotin to its active coenzymes</li> <li>Biotin functions as a component of 4 enzymes that transport carboxyl units to various substrates as follows: acetyl CoA carboxylase (required for fatty acid synthesis), pyruvate carboxylase (required for gluconeogenesis), propionyl CoA carboxylase (for propionate metabolism), and 3-methylcrotonyl CoA carboxylase (required for catabolism of branched-chain amino acids)</li> <li>Pts at risk for deficiency:               <ul style="list-style-type: none"> <li>Avidin, a biotin-binding glycoprotein, is found only in raw eggs and consumption of large amounts of raw eggs can cause biotin deficiency</li> <li>Pregnancy and lactation</li> <li>Alcoholics</li> <li>Pts with partial or total gastrectomy or burns</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Dry scaly dermatitis</li> <li>Anorexia</li> <li>Pallor</li> <li>Glossitis</li> <li>Nausea and vomiting</li> <li>Impaired mentation</li> <li>Hyperesthesias</li> <li>Muscle pain</li> <li>Hair loss</li> <li>Elevated serum cholesterol and bile pigments</li> </ul>	<ul style="list-style-type: none"> <li>No toxicity reported</li> </ul>

(continued)

## Appendix 1 (continued)

Trace Elements	Function/Source/Comments	Deficiency State	Toxicity
Chromium	<ul style="list-style-type: none"> <li>• Sources: chromium value of many foods unknown but, yeast, calf's liver, American cheese, and wheat germ have high bioavailability of chromium</li> <li>• Enhances the ability of insulin to bind to insulin receptors on the cell surface and thereby participates in metabolism of carbohydrates, protein, and fat</li> <li>• Pts at risk of deficiency: Burns, trauma, short bowel syndrome PN pts without chromium supplementation</li> </ul>	<ul style="list-style-type: none"> <li>• Very rare and only reported in 3 long-term PN patients</li> <li>• Hyperglycemia and glucosuria refractory to insulin</li> <li>• Peripheral neuropathy</li> <li>• Encephalopathy</li> <li>• Hyperlipidemia</li> </ul>	<ul style="list-style-type: none"> <li>• No toxicity reported from dietary chromium</li> <li>• Toxic levels of airborne chromium</li> <li>• Allergic dermatitis</li> <li>• Skin ulcers</li> <li>• Bronchogenic carcinoma</li> </ul>
Copper	<ul style="list-style-type: none"> <li>• Sources: liver, seafood (especially shellfish), nuts, legumes, and seeds</li> <li>• Incorporated into metalloenzymes that are involved with connective tissue formation; metabolism of iron (ceruloplasmin), cholesterol, and glucose; myelin synthesis; conversion of dopamine to norepinephrine in the brain, serotonin synthesis, melanin pigment formation; and antioxidant participating in the immune system</li> <li>• Pts at risk of deficiency: Low birth weight infants PN pts without copper supplementation Chronic peritoneal dialysis</li> </ul>	<ul style="list-style-type: none"> <li>• Hypochromic, microcytic anemia</li> <li>• Neutropenia</li> <li>• Osteopenia</li> <li>• Depigmentation of skin and hair</li> <li>• Skeletal abnormalities</li> <li>• Neurologic abnormalities</li> </ul>	<ul style="list-style-type: none"> <li>• Acute (rare): nausea, vomiting, diarrhea, epigastric abdominal pain, coma, oliguria, acute renal failure, hepatic necrosis, vascular collapse, and death</li> <li>• Chronic: accumulates in liver (hepatic necrosis and cirrhosis), kidneys (renal failure), brain (neurologic disorders), and corneas</li> <li>• Wilson's disease—hereditary condition of copper toxicity</li> </ul>
Fluoride	<ul style="list-style-type: none"> <li>• Sources: fluorinated water and tea</li> <li>• Assists in enamel formation of teeth and helps avoids caries, especially during maximal tooth formation (first 8 years of life); however, older children and adults continue to benefit from consumption of fluoridated water</li> <li>• Pts at risk of deficiency: Infants and children who drink nonfluoridated water</li> </ul>	<ul style="list-style-type: none"> <li>• Contributes to dental caries</li> </ul>	<ul style="list-style-type: none"> <li>• Acute, high dose (5–10 g)—death</li> <li>• Chronic (years of 20–80 mg/d)—mottling of teeth, calcification of tendons and ligaments, exostoses, and increased brittleness of bones</li> </ul>
Iodine	<ul style="list-style-type: none"> <li>• Sources: seafood, iodized table salt, and certain baked breads and dairy products</li> <li>• Essential nutrient that is incorporated into thyroid hormones, thyroxine (T4) and tri-iodothyronine (T3), which modulate resting energy expenditure and are important in growth and development</li> </ul>	<ul style="list-style-type: none"> <li>• Newborns—spontaneous abortions, stillbirths, congenital abnormalities, hypothyroidism, dwarfism, deafness and severe mental retardation (cretinism), increased perinatal and infant mortality</li> <li>• Adults—thyroid goiter and hypothyroidism, impaired mentation</li> </ul>	<ul style="list-style-type: none"> <li>• Chronic ingestion of large quantities can lead to hypothyroidism with goiter or hyperthyroidism</li> </ul>

(continued)



## Appendix 1 (continued)

	Function/Source/Comments	Deficiency State	Toxicity
Iron	<ul style="list-style-type: none"> <li>• Sources: meat, eggs, vegetables, fortified cereals</li> <li>• Forms of iron in body</li> </ul> <p>Present in hemoglobin (60% of iron in body) Myoglobin (4% of iron in body) Iron-containing enzymes (5%–15% of iron in body) Remaining iron is as storage iron (hemosiderin) in liver, spleen, bone marrow, and circulating iron bound to carrier protein transferrin</p> <ul style="list-style-type: none"> <li>• Ionic forms of iron: Ferric (Fe<sup>3+</sup>) Ferrous (Fe<sup>2+</sup>)</li> <li>• Functions: Involved in transport and storage of oxygen by its incorporation in hemoglobin and myoglobin</li> </ul> <p>Incorporated into nonheme metalloenzymes that are involved in energy release from oxidative phosphorylation and ATP generation; detoxifying drugs, carcinogens, and pesticides; biosynthesis of aldosterone, glucocorticoids, and sex hormones; and synthesis of DNA, unsaturated fatty acids, carnitine, collagen, and neurotransmitters</p> <ul style="list-style-type: none"> <li>• Lab tests—serum iron, serum ferritin, TIBC, transferrin saturation</li> <li>• Pts at risk for deficiency: Growing children Women in childbearing ages Chronic blood loss</li> </ul>	<ul style="list-style-type: none"> <li>• Most common nutrient deficiency in U.S.</li> <li>• Microcytic, hypochromic anemia (causing tachycardia, fatigue, pallor, and altered mental and motor development)</li> <li>• Glossitis</li> <li>• Impaired temperature regulation in the cold</li> <li>• Decreased resistance to infection</li> </ul>	<ul style="list-style-type: none"> <li>• Hemosiderosis or siderosis—excessive total body iron that accumulates in iron stores and RE system, little consequence</li> <li>• Hemochromatosis</li> <li>• Hereditary or acquired (chronic hemosiderosis)</li> <li>• Classic triad</li> <li>• Cirrhosis</li> <li>• Diabetes mellitus</li> <li>• Hyperpigmentation (gray tinge) of the skin</li> <li>• Other</li> <li>• Fatigue</li> <li>• Testicular atrophy and sterility</li> <li>• Arthropathy</li> <li>• Cardiac arrhythmias</li> <li>• Hypothyroidism</li> </ul>
Manganese	<ul style="list-style-type: none"> <li>• Sources: whole grains and cereals and, to a lesser extent, fruits and vegetables</li> <li>• Incorporated into metalloenzymes involved with energy release, fatty acid and cholesterol synthesis, and release of lipids from the liver</li> </ul>	<ul style="list-style-type: none"> <li>• Deficiency states not well documented but some reports of dermatitis and hypocholesterolemia</li> </ul>	<ul style="list-style-type: none"> <li>• Neurotoxicity (primarily associated with oversupply associated with chronic PN)</li> </ul>
Molybdenum	<ul style="list-style-type: none"> <li>• Sources: milk, beans, breads, and cereals</li> <li>• Incorporated into several enzymes, including aldehyde oxidase, xanthine oxidase, and sulfite oxidase</li> <li>• Pts at risk for deficiency: Deficient in copper intake or have dysfunction in copper metabolism</li> </ul>	<ul style="list-style-type: none"> <li>• Deficiency rare but was reported in a long-term PN patient causing amino acid intolerance, irritability, visual field defects, coma; patient also noted to have hypermethioninemia, increased urinary excretion of xanthine and sulfite, and decreased serum uric acid</li> </ul>	<ul style="list-style-type: none"> <li>• Excess of 10–15 g/d can cause gout-like syndrome with elevated serum molybdenum, uric acid, and xanthine oxidase</li> <li>• Even moderate doses of molybdenum can cause increased urinary excretion of copper and possible copper deficiency</li> </ul>

(continued)

## Appendix 1 (continued)

	Function/Source/Comments	Deficiency State	Toxicity
Selenium	<ul style="list-style-type: none"> <li>• Sources: seafood, kidney, liver, and some meats</li> <li>• Incorporated at the active site of glutathione peroxidase, an enzyme that catalyzes the breakdown of hydroperoxides and has metabolic interrelationships with vitamin E, an antioxidant</li> <li>• Participates in enzymatic conversion of thyroxine to its more active metabolite, tri-iodothyronine</li> <li>• Cofactor for protein and DNA synthesis</li> </ul>	<ul style="list-style-type: none"> <li>• Deficiency state not well characterized but in 3 long-term PN patients with low serum selenium levels, muscular discomfort or weakness</li> <li>• Cardiomyopathy has also occurred in PN patients with low selenium levels</li> <li>• Anemia</li> </ul>	<ul style="list-style-type: none"> <li>• Garlic smell to breath (from ↑ production of dimethylselenide in body and release from the lungs)</li> <li>• Nausea and vomiting</li> <li>• Abdominal pain</li> <li>• Loss of hair and nails</li> <li>• Tenderness and loss of fingernails</li> <li>• Diarrhea</li> <li>• Peripheral neuropathy</li> <li>• Fatigue</li> <li>• Irritability and altered mental status</li> </ul>
Zinc	<ul style="list-style-type: none"> <li>• Sources: meat, liver, eggs, and seafood (especially oysters)</li> <li>• Essential nutrient participating in multiple metalloenzyme involving zinc in most central metabolic pathways, including metabolism of protein, fat, and carbohydrates; DNA binding; gene regulation; transcription of DNA to RNA; synthesis of heme, long-chain fatty acids, and prostaglandins; cholesterol transport; stabilization of cell membrane lipids; sexual maturation and reproduction; and immune function</li> <li>• Pts at risk for deficiency: Chronic PN without zinc supplementation Pts with severe diarrhea, inflammatory bowel disease, malabsorptive disorders, pregnancy, starvation, alcoholic cirrhosis, diabetes mellitus</li> </ul>	<ul style="list-style-type: none"> <li>• Alopecia</li> <li>• Skin rash of face, groins, hands, and feet</li> <li>• Growth retardation</li> <li>• Delayed sexual development</li> <li>• Impaired wound healing and immune function</li> <li>• Diarrhea</li> <li>• Blunting of taste and smell</li> </ul>	<ul style="list-style-type: none"> <li>• Acute (&gt;200 mg orally): Epigastric abdominal pain Nausea and vomiting Diarrhea</li> <li>• Chronic (&gt;20 mg/d orally) Decreased serum copper levels (hypocupremia) Microcytosis and neutropenia Reduced HDL cholesterol Impaired immune function</li> </ul>

ATP, adenosine triphosphate; CoA, coenzyme A; GI, gastrointestinal; GU, genitourinary; HA, headache; HDL, high-density lipoprotein; IF, intrinsic factor; IV, intravenous; NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate; PMS, premenstrual syndrome; PN, parenteral nutrition; Pts, patients; RE, reticuloendothelial; THFA, tetrahydrofolic acid; TIBC, total iron binding capacity; tx, treatment.

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## Appendix 2

### Vitamin A and Parenteral Nutrition

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#### Introduction

Vitamin A (retinol), a fat-soluble vitamin, was initially identified in 1928 and coined the “anti-infective” vitamin.<sup>1</sup> Since that time, vitamin A and its active compounds have become identified with many other vital functions, including cellular differentiation, vision, epithelial integrity, immune function, growth, development, and reproduction.<sup>2</sup> The provitamin A active compounds,  $\beta$ -carotene,  $\alpha$ -carotene, and cryptoxanthin, are biologically interdependent based on their structural and/or functional relationships. Of the 500 carotenoids found naturally, only 50 have provitamin A activity. The primary provitamin A active compound after oxidative cleavage of the 15,15' double bond is the trans- $\beta$ -carotene.<sup>3</sup> Vitamin A activity is often expressed as retinol equivalents, 1 mcg all-trans-retinol = 6 mcg all trans- $\beta$ -carotene = 12 mcg other provitamin carotenoids.<sup>2</sup> The Dietary Reference Intakes,<sup>4</sup> published by the Institute of Medicine, more specifically describe retinol activity equivalents (RAEs) where 1 RAE = 1 mcg retinol = 12 mcg  $\beta$ -carotene = 24 mcg  $\alpha$ -carotene = 24 mcg  $\beta$ -cryptoxanthin. Dietary sources of preformed vitamin A are found in a high concentration in liver (3000–15,000 mcg retinol/100 g).<sup>5</sup> Milk and whole eggs are also good food sources with 30–70 mcg retinol/100 mL and 100–300 mcg/100 g, respectively.  $\beta$ -Carotene equivalents are high in carrots (2000–7000 mcg/100 g), green leafy vegetables (2000–3000 mcg/100 g), yellow sweet potatoes (2000–4000 mcg/100 g), and papaya (1000–1500 mcg/100 g).<sup>5</sup> Bioconversion from provitamin A carotenoids is, however, variable and ranges from a conversion efficiency of 3.6–28:1 by weight.<sup>6</sup>

#### Metabolic Effects

Dietary retinyl esters are hydrolyzed to retinol in the intestinal lumen, taken up into the intestinal cell and reesterified into retinyl esters (REs), coupled to chylomicrons, and released into the bloodstream via the thoracic duct.<sup>7</sup> The chylomicron remnants containing RE are taken up by the liver through an apolipoprotein E receptor.<sup>7</sup> Vitamin A is kept in the liver perisinusoidal stellate cells and, when released for cellular events, is bound to retinol-binding protein and coupled to transthyretin to avoid renal clearance.<sup>7</sup> Serum levels do not correlate with liver stores.

Vitamin A's major role in vision is photoreceptor function.<sup>8</sup> Vitamin A in the 11-cis isoform combines with photoreceptor opsin to form rhodopsin.<sup>8</sup> The metabolic effects of vitamin A in mucosa-associated epithelium are related to expression of cytokeratins and terminal differentiation.<sup>7</sup>

## Reliable Assessment for Deficiency and Toxicity

Deficiency signs manifest first as night blindness<sup>9</sup> followed by xerophthalmia<sup>9,10</sup> and blindness. Infectious diseases are often associated with vitamin A deficiency because of altered epithelial keratinization. In addition, T cell immune function may be affected by vitamin A status.<sup>3</sup>

Vitamin A status is traditionally assessed by serum retinol or the concentration of retinol binding protein (RBP).<sup>11</sup> The normal range of serum retinol concentration is 1–3  $\mu\text{mol/L}$  measured by high-performance liquid chromatography (HPLC)<sup>12</sup> with RBP correlates of  $<0.48$  mmol/L associated with severe vitamin A deficiency.<sup>13</sup> In periods of stress, serum retinol is not reliable and the RBP-to-transthyretin ratio is a better marker for deficiency.<sup>14</sup> In addition, when field testing the status of vitamin A, it is easier to use a radioimmunoassay for RBP concentration rather than HPLC technology.<sup>13</sup>

Preformed vitamin A is absorbed at rates of 70%–90%, but if ingestion is excessive or the vitamin A is given by intramuscular or intravenous injection, thereby bypassing gastrointestinal regulation, toxicity can result.<sup>15</sup> In contrast, provitamin carotenoid sources are absorbed at lower rates of 20%–50%.<sup>15</sup> The cleavage of provitamin A carotenoids to retinal is highly regulated, making them unlikely to cause toxicity.

Vitamin A toxicity can present with elevated intracranial pressure (leading to symptoms including vomiting, headaches). Bony abnormalities have also been described with vitamin A toxicity, most likely due to vitamin A antagonism of vitamin D at the receptor level,<sup>16</sup> resulting in bone resorption and decreased bone formation.<sup>17</sup>

Retinyl esters in serum, which are normally  $<0.2$   $\mu\text{mol/L}$  in the fasting state,<sup>18</sup> can be measured using HPLC to detect toxicity.

Serum retinol concentrations have been found to be dependent on age, gender, and season of the year.<sup>19</sup> Older volunteers, especially males, and autumn were associated with higher serum retinol levels in a large trial in France.<sup>19</sup>

## Modifications for Special Clinical Conditions—Adults and Pediatrics (Burns, Cholestasis, HIV, Hematology/Oncology, Renal Failure, Trauma, Sepsis, Intestinal Injury, Cystic Fibrosis)

Vitamin A is a fat-soluble vitamin absorbed from the core of the complex micelle. Deficiency can result from inadequate dietary intake or defective intestinal delivery due to abnormal hepatobiliary function or damaged epithelial integrity. Deficiency can also occur with impaired vitamin A mobilization from the intestine (abetalipoproteinemia) or the liver (protein calorie malnutrition and zinc deficiency lead to reduced RBP formation).

In the hospital, patients with pressure ulcers,<sup>20</sup> wounds, or burns<sup>21</sup> must receive adequate vitamin A for restoration of epithelial surfaces. In fact, topical application of tretinoin and glycolic acid improved mouth healing and subsequent mouth opening in inhalation-burn patients.<sup>21</sup> Detailed monitoring of vitamin A intake and laboratory assessment is, however, critical because toxicity has been documented in patients with  $>25\%$  burns on enteral supplementation.<sup>22</sup> In a case report, 2 patients on prolonged enteral feeding for 272 and 180 days demonstrated elevated liver enzymes and toxic concentrations of vitamin A<sup>22</sup> on an intake of 1–2 L of 102 mcg/100 mL vitamin A per day in their enteral food source.

The mechanism of vitamin A toxicity in the liver is not fully understood but appears to occur when the dose of vitamin A exceeds the available RBP.<sup>23</sup> The fat-storing cells then produce a matrix of laminin and type III collagen that results in hepatic fibrosis<sup>24</sup> and a characteristic picture on biopsy.

Because of the importance of vitamin A to T cell function,<sup>25</sup> immunity can be compromised by vitamin A deficiency. Linear growth has been improved in children  $<18$  months of age with human immunodeficiency virus (HIV) on vitamin A supplementation.<sup>26</sup> However, in a randomized trial in Tanzania, women with HIV disease showed no significant increase in CD4, CD8, or CD3 counts.<sup>27</sup> Care must be taken in interpreting low serum vitamin A levels in patients with protein calorie malnutrition since stores may be adequate, but the liver may not release vitamin A due to a low RBP.<sup>28</sup>

Supplementation of vitamins is often practiced to prevent or attenuate cancer risk. However, in a large ( $N = 8171$  women) study with random and blinded assignment to supplementation,  $\beta$ -carotene supplementation conveyed no protection from cancer incidence or mortality.<sup>29</sup> Patients with renal failure have reduced RBP renal clearance and are at risk for developing vitamin A toxicity. In a retrospective study to determine the status of vitamin A in hematopoietic stem cell transplant patients with acute renal failure, investigators found 17 of 19 patients had abnormally high levels.<sup>30</sup>

When the hepatobiliary cycle is defective and intestinal absorption is impaired, as can be the case in short bowel syndrome (SBS), patients have been found to have lower serum concentrations of vitamin A.<sup>31</sup> Home parenteral nutrition (PN) patients with SBS can become vitamin A deficient without a parenteral vitamin A source and develop night blindness.<sup>32</sup> Since vitamin A is adsorbed onto glass and plastic containers and oxidized to a nonphysiologic epoxide by light exposure, vitamin A deficiency can develop unless the vitamin is added to the PN solutions just prior to infusion.<sup>33</sup> A case report after gastric bypass surgery for obesity has also described night blindness that corrected after vitamin A therapy.<sup>8</sup>

The individual with cystic fibrosis (CF) is at particular risk for vitamin A depletion not only because of fat malabsorption but also due to zinc deficiency.<sup>34</sup> In a recent Cochrane review, however, there was no evidence-based recommendation for vitamin A in a patient with CF.<sup>35</sup> In fact, serum retinol has been

found to be elevated in preadolescent children with CF on an elevated vitamin A intake of  $816 \pm 336$  mcg retinol activity equivalents per day ( $165\% \pm 69\%$  of the recommended dietary allowance).<sup>36</sup>

With all special conditions reviewed, it was apparent that a relatively narrow window exists between deficiency and toxicity; therefore, it is essential that the clinician investigate all supplements and food sources the patient is ingesting to predict adequacy<sup>37</sup> and practice prudent supplementation.

### Modifications for Gender and the Elderly

Knowledge of typical blood concentrations and dietary intakes related to sex and age can be helpful in baseline assessment in the clinical setting. In a large cohort ( $N = 12,741$ ) examined for retinol,  $\alpha$ -tocopherol, and  $\beta$ -carotene serum concentrations, retinol concentrations were higher in older volunteers, especially male participants, in France.<sup>19</sup> Vitamin A supplementation has not been demonstrated to reduce the incidence of infection in the older nursing home patient.<sup>38</sup> In fact, when examining dietary intakes in the United States, women tend to have intakes of vitamin A from food above the estimated average requirement (EAR), and with typical supplementation, they ingest almost 3 times the EAR.<sup>39</sup> Thirty percent of U.S. residents use vitamin supplements regularly.<sup>37</sup> Modifications of the diet should be consistent with these data.

### Considerations in Pregnancy and Lactation

Vitamin A recommendations are higher in pregnancy and lactation to support growth and cell differentiation.<sup>40,41</sup> The Dietary Reference Intakes are dependent on age and range from 750–770 mcg/d RAE for pregnant women 14–18 years and 19–50 years, respectively.<sup>4</sup> Isotretinoin, used for acne, is a known teratogen in pregnancy and should be avoided.<sup>42</sup>

Lactation increases demands for vitamin A, and recommendations are 1200–1300 mcg/d RAE for 14- to 18-year-olds and 19- to 50-year-old women, respectively.<sup>4</sup> Maternal

supplementation does correlate with increased breast milk concentrations and a low likelihood of serum vitamin A level in the infant.<sup>43</sup>

### Considerations in Neonates

For the healthy infant 0–6 months, the advisable intake of vitamin A is 400 mcg/d RAE. From 6 months to 1 year, the vitamin A intake should increase to 500 mcg/d RAE.<sup>4</sup> Preterm infant requirements are higher because of low stores and the need for increased growth and development.<sup>44</sup> Mechanical ventilation or steroid use in the neonatal intensive care unit increases the need for vitamin A.<sup>45</sup> Recommendations for parenteral and enteral nutrition for the preterm infant range from 700–1500 International Units/kg/d.<sup>44,46</sup>

Delivery to the preterm infant on parenteral vitamin A can be compromised by losses in the delivery system.<sup>47,48</sup> This can result in as little as 17%–66% of the expected amount being received. European studies have demonstrated enhanced delivery when the preterm infant is given a vitamin product admixed in intravenous fat emulsion (IVFE).<sup>49</sup> In the U.S., we have yet to have access to these vitamin products. In the U.S., patients receive parenteral fat-soluble vitamin products not approved for admixture in IVFE. Many clinicians will therefore give injections of vitamin A to the extremely preterm infant to reduce the likelihood of chronic lung disease.<sup>50</sup>

### Drug and Nutrient Interactions

Vitamin A supplementation (VAS) may enhance the concurrent delivery of vaccinations.<sup>51</sup> To reduce mortality after 6 months, a study was done to determine if VAS at the time of vaccination had a beneficial effect.<sup>51</sup> The investigators found that the effect of VAS was not helpful in measles-vaccinated girls who did not have up-to-date diphtheria-tetanus-pertussis vaccine but had a benefit in lowering mortality in children with no record of immunizations at study enrollment. Of important note is that VAS did reduce the risk of developing xerophthalmia in all cases.<sup>51</sup>

**Table A2.1.** Recommended Intake Based on Dietary Reference Intake<sup>4</sup>

Life Stage	Infant											
	Infant <sup>a</sup> 0–6 mo	7–12 mo	Child 1–3 y	Child 4–8 y	Male 9–13 y	Male 14+ y	Female 9–13 y	Female 14+ y	Preg 14–18 y	Preg 19+ y	Lact 14–18 y	Lact 19+ y
Vitamin A, mcg/d, RAE <sup>b</sup>	400	500	300	400	600	900	600	700	750	770	1200	1300

Lact, lactating; Preg, pregnant.

<sup>a</sup>Infant refers to the term infant; the preterm infant requirements are estimated to be 750–1500 International Units/kg/d,<sup>52</sup> keeping in mind that 3.3 International Units of vitamin A = 1 RAE.

<sup>b</sup>Retinol activity equivalents (RAEs) consist of 1 RAE = 1 mcg retinol, 12 mcg  $\beta$ -carotene, 24 mcg  $\alpha$ -carotene, or 24 mcg b-cryptoxanthin (DRI).



## Conclusion

Vitamin A and its active compounds are important for vision, skin, growth, development, reproduction, and immune function. Dietary insufficiency, fat malabsorption, and calorie, protein, or zinc deficiency can all predispose the patient to vitamin A deficiency, resulting in poor outcomes in any of the vitamin A-related functions. Toxicity is less common but can occur with intravenous nutrition, liver disorders, or renal dysfunction. The use of synthetic retinoid therapy during pregnancy should be avoided. Serum retinol or the retinol binding protein transthyretin ratio can be used to assess deficiency. Retinyl ester levels can be used to establish toxicity.

## Recommendations

To avoid deficiency or toxicity, a careful approach to dietary intake should take into account the current recommendations for healthy people. Considerations and special monitoring are needed for hospitalized individuals. Recommended intakes of vitamin A (mcg/d RAE) can be seen in Table A2.1.

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## Appendix 3

### Thiamine (Vitamin B<sub>1</sub>) in Enteral and Parenteral Nutrition

Theresa A. Fessler, MS, RD, CNSC

#### Introduction

Thiamine (also spelled thiamin) was the first B vitamin to be discovered and is also known as vitamin B<sub>1</sub> and aneurin. Thiamine pyrophosphate is a coenzyme in the metabolism of carbohydrates and branched-chain amino acids.<sup>1,2</sup> Thiamine is water soluble, stable at acidic pH, and unstable in alkaline solutions and with exposure to ultraviolet (UV) light.<sup>3</sup> The major food sources of thiamine are various whole, enriched, or fortified grain products and pork. Other sources include legumes, poultry, processed meats, and soy-based meat substitutes.<sup>1,3</sup>

#### Metabolism and Functions

Thiamine functions in several phosphorylated forms, chiefly as the coenzyme form thiamine pyrophosphate (TPP), which is sometimes referred to as thiamine diphosphate (TDP). Thiamine is necessary for decarboxylation of  $\alpha$ -keto acids, as well as transketolation reactions of hexose and pentose phosphates.<sup>1,4</sup> Thiamine is absorbed mainly in the jejunum, by carrier-mediated active transport at lower concentrations and by passive diffusion at higher concentrations. Only a small percentage of a high oral dose is absorbed. Absorption declines at a dose above 5 mg.<sup>2</sup> Thiamine is carried in erythrocytes and plasma<sup>2</sup> and is not stored to a significant extent in any tissues but is in more significant amounts in muscle, heart, liver, kidney, and brain.<sup>3</sup> Urinary excretion is increased when serum levels elevate and decreased when serum levels are low, with maximum excretion 2 hours after oral intake. The biological half-life of thiamine has been determined to be 9–18 days, and the adult body is thought to contain approximately 30 mg.<sup>1</sup>

#### Thiamine Deficiency and Toxicity

The thiamine deficiency disease has long been known as “beriberi.” Thiamine deficiency symptoms include anorexia, weight loss, mental abnormalities, muscle weakness, and enlarged heart. Muscle wasting is seen in “dry” beriberi, and “wet” beriberi is characterized by the presence of edema due to congestive heart failure.<sup>1</sup> Prolonged mild thiamine deficiency can lead to peripheral nerve damage.<sup>5</sup>

Thiamine deficiency as it occurs in modern industrialized countries is better known as an acute neurologic disorder called Wernicke's encephalopathy (WE). Symptoms of WE include ophthalmoplegia, ataxia, and confusion.<sup>5</sup> Without prompt treatment, WE progresses to irreversible brain damage known as Korsakoff's psychosis and can also result in coma or death. Korsakoff's syndrome is characterized by chronic severe loss of working memory or amnesia of recent events, with memory deficits of events up to months prior.<sup>5</sup> WE has been historically found in chronic alcoholic patients but has also been reported in patients who were given parenteral nutrition (PN) without multivitamins. Reasons for not using multiple vitamins in PN in these cases were attributed to iatrogenic error, shortage of multivitamin product, and, in Japan, cost issues resulting from a national health insurance policy change.<sup>4,6</sup>

WE has been reported in other malnourished patients such as those who have undergone gastrointestinal surgery and in patients with hyperemesis gravidarum, small bowel obstruction, anorexia nervosa, gastrointestinal disorders, and various cancers. In some cancers, thiamine is used by rapidly growing tumors, and some chemotherapeutic drugs can interfere with thiamine function.<sup>5,7</sup> Since thiamine is lost in dialysate, poorly nourished renal patients on dialysis are at risk for thiamine deficiency. Patients with magnesium deficiency due to chronic diuretic use are also at risk, as magnesium is a cofactor in transketolase reactions and in conversion of thiamine to thiamine pyrophosphate.<sup>5</sup>

Because intestinal absorption is limited, the recommended treatment for WE is intravenous (IV) or intramuscular (IM) administration of thiamine.<sup>5</sup> In a recent study, 100 mg of IV thiamine for 3 days normalized neurologic symptoms of WE in 6 of 7 patients who received PN without multivitamins,<sup>4</sup> but higher doses are advised. Patients with suspected or diagnosed WE should receive 500 mg of IV thiamine hydrochloride 3 times per day for 2–3 days and, if favorable response occurs, followed with 250 mg thiamine per day, given IV or IM, for 3–5 days.<sup>5</sup> Prophylactic treatment with 250 mg of IM thiamine per day for 3–5 days has been recently recommended for malnourished patients at risk for WE.<sup>5</sup> Those who are deficient in thiamine are most likely deficient in several other vitamins, and thus treatment with IV multivitamin mixtures is prudent. In the United Kingdom, for example, a high-potency B-complex formulation (Pabrinex) has been used in the treatment of WE.<sup>8</sup>

Erythrocyte transketolase activity and erythrocyte TPP are 2 tests that have been used to measure thiamine status. Erythrocyte transketolase activity is low in thiamine-depleted individuals and increases after the addition of TPP to lysed erythrocytes, but the test has limitations in that it has not correlated well with thiamine intake in several studies, and there are likely genetic and other individual differences that affect enzyme activity.<sup>1</sup> Erythrocyte TPP declines at a similar rate as in other tissues in a thiamine-deficient state. Measurement of erythrocyte TPP itself has been found to be a more consistent and specific indicator, with normal range of 70–90 nmol/L.<sup>1</sup> A whole-blood TPP test is also available, with

the normal range listed as 74–222 nmol/L<sup>9</sup> or 80–150 nmol/L.<sup>10</sup> Magnetic resonance imaging is currently the most useful method to confirm WE.<sup>5</sup>

Data are lacking on adverse effects of excessive oral thiamine intake, and thus a tolerable upper intake level (UL) has not been determined.<sup>2</sup> Parenteral thiamine is considered safe, yet there is a low risk of serious allergic reaction. Thus, it is recommended that parenteral thiamine be diluted in 100 mL of normal saline or 5% dextrose solution and infused over a period of 30 minutes and that treatment be done in a facility equipped to treat anaphylactic reaction.<sup>5</sup>

## Requirements for Healthy Individuals

The recommended requirements for thiamine have been determined by the Institute of Medicine of the National Academy of Sciences and published in 1998.<sup>1</sup> The Recommended Dietary Allowance (RDA) for thiamine for adults is 1.1 mg (females) to 1.2 mg (males) per day and 1.4 mg per day for pregnancy and lactation. Criteria used for establishing adult thiamine requirements included the amount needed to maintain erythrocyte transketolase activity, urinary thiamine excretion, and other information. The requirements for children and teenagers were established by extrapolation methods using adult data. The RDA for children is 0.5 mg/d for ages 1–3 years, 0.6 mg/d for ages 4–8 years, 0.9 mg/d for ages 9–13 years, and 1–1.2 mg/d for ages 14–18 years. The Adequate Intake (AI) of thiamine for infants was determined by using information on infants fed breast milk from well-nourished mothers. The AI is 0.2 mg/d for infants aged 0–6 months and 0.3 mg/d for infants aged 6–12 months.<sup>1,2</sup>

## Requirement Modifications in Specific Conditions

The RDA for thiamine is 1.4 mg/d for pregnancy and lactation. Because of its function in carbohydrate metabolism, thiamine needs are likely related to energy utilization and body size. Thiamine needs are higher for patients on dialysis, those with malabsorption, or during pregnancy or lactation with more than 1 infant.<sup>1</sup>

## Thiamine Content in Current PN and Enteral Nutrition Regimens

Aside from the need for parenteral thiamine and B-complex supplements for use in deficiency states, there are no data to suggest that new products are needed for PN regimens, except, of course, not to exclude thiamine. Current adult parenteral multivitamin products in the U.S. contain 6 mg of thiamine hydrochloride per daily dose.<sup>11–13</sup> Other products, available in Europe, contain 3.1 and 3.51 mg thiamine per dose.<sup>14,15</sup> Pediatric parenteral multivitamin solutions in the U.S. provide 1.2 mg thiamine per daily dose.<sup>13,16</sup> All of these products meet or exceed the RDA or AI levels.

Enteral nutrition (EN) formulas in the U.S. provide adequate thiamine to meet or exceed RDA or AI levels, if sufficient amounts of formula are ingested to meet energy needs. Standard adult EN formulas contain 1.6–4 mg thiamine per 1500–2000 kcal. Standard pediatric enteral formulas contain 1.7–2.5 mg thiamine per 1000 kcal.<sup>17,18</sup> Standard formulas for term infants contain 0.06–0.1 mg thiamine per 100 kcal.<sup>19,20</sup> Formula for premature infants contains 0.175–0.25 mg thiamine per 100 kcal.<sup>20,21</sup>

One recent study confirmed that current PN and EN regimens provide adequate thiamine for premature infants.<sup>22</sup> A recent Japanese study confirms a significant decline in blood levels of thiamine in children receiving PN without thiamine.<sup>23</sup>

## Recommendations

- Thiamine is of critical importance during enteral and parenteral feeding, especially in malnourished patients.
- Multivitamins, specifically thiamine, should never be omitted in PN regimens.
- Standard adult and pediatric multivitamins for IV infusion provide greater than the established RDA or AI dose of thiamine.
- Standard EN formulas generally provide greater than or equal to the RDA dose of thiamine when providing full energy needs.
- Supplemental parenteral thiamine or B-complex product, in addition to that provided in standard EN or PN, should be provided for patients who are symptomatic or at high risk for thiamine deficiency and those at risk for refeeding syndrome in general.
- Supplemental parenteral thiamine and/or B-complex vitamins, in addition to that provided in standard EN or PN, should be administered to patients at risk or symptomatic for WE.

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## Appendix 4

### Requirements and Metabolism of Riboflavin (Vitamin B<sub>2</sub>) and Niacin (Vitamin B<sub>3</sub>) in Parenteral Nutrition

Khursheed N. Jeejeebhoy, MBBS, PhD, FRCPC

#### Introduction

The need for any vitamin can be expressed in 3 different ways. The traditional way was called Recommended Daily Allowance (RDA), which is established and periodically revised by the Food and Nutrition Board. For the labeling of foods, the Reference Daily Intake (RDI) was established by the Food and Drug Administration (FDA). It was based initially on the highest 1968 RDA for each nutrient, to ensure that needs were met for all age groups. The Dietary Reference Intakes (DRI) are the most recent set of dietary recommendations established by the Food and Nutrition Board of the Institute of Medicine, 1997–2001. They replace previous RDAs and may be the basis for eventually updating the RDIs. These definitions need to be kept in mind when the intake of patients on parenteral nutrition (PN) is being considered. The currently available parenteral multivitamin mixture available in North America provides riboflavin 3.6 mg/d and niacin as niacinamide 40 mg/d. The pediatric formulation provides 0.56 mg of riboflavin per day.

#### Riboflavin (B<sub>2</sub>)

##### *Metabolic Effect*

Riboflavin is a component of mono and dinucleotides complexed with adenine as flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). These compounds combine with proteins to form enzymes called flavoproteins. These enzymes are concerned with dehydrogenation and oxidation reactions involving pyruvate, acetyl-CoA, and amino acids. In the process, the flavin becomes reduced by accepting hydrogen. The reduced form is reoxidized and again available to accept hydrogen. It also acts as part of the electron transfer chain.

Reliable assessment of deficiency and toxicity. There are 3 methods to assess riboflavin status.

1. Urinary excretion. The urine riboflavin should be at least 80 mcg/g creatinine. In deficiency, it falls below 27 mcg/g creatinine. However, catabolic states increase riboflavin excretion as do drugs such as antibiotics and phenothiazines, making urinary excretion less reliable.
2. Erythrocyte riboflavin levels can be measured and used to detect deficiency and should be at least 10 mcg/dL red cells.
3. The most reliable method assessing riboflavin status is by the glutathione reductase activity in red blood

cells before and after the addition of FAD. The increase in activity by this addition is an index of deficiency. Less than 20% (ratio <1.2) is acceptable, 1.2–1.4 is subnormal, and >1.4 is a deficient state.

#### *Riboflavin Toxicity Has Not Been Described*

Clinical effects of deficiency. In a deficiency state, there may be sore throat, stomatitis, glossitis, and seborrheic dermatitis of the face, trunk, and scrotum. In addition, photophobia and vascularization of the cornea have been observed. Marrow aplasia and a normocytic normochromic anemia may occur.

#### *Normal Requirements*

The oral intake should be 0.6 mg/1000 kcal. Hence, in an average adult, intake should be 1.2–1.6 mg/d. For patients receiving PN, the American Medical Association (AMA)<sup>1</sup> recommends 3.6 mg/d in adults. In other studies, 1.8–10 mg has been used and shown to be adequate biochemically.<sup>2,3</sup> In patients on home PN, infusion of the current formulation given daily maintained biochemical stability but when given 3 times a week caused deficiency.<sup>4</sup>

#### *Modifications for Cirrhosis, Cancer, Renal Failure, Trauma, Sepsis, and Burns*

In critically ill patients, the addition of 10 mg of riboflavin per day maintained normal levels when measured on average 16 days after start of PN.<sup>3</sup> On the other hand, in cancer patients, biochemical deficiency was noted despite 7.2 mg/d of riboflavin.<sup>5</sup>

#### *Modification for Gender and the Elderly*

There is no effect of age on riboflavin requirements, but the DRI for women is about 0.2 mg lower than it is for men.

#### *Relevance to Pregnancy, Lactation, and Pediatric Populations*

During pregnancy and lactation, an additional 0.3–0.5 mg/d should be given, making the total intake 1.5–2.1 mg/d. In infants, 2 mL of the pediatric formulation, giving 0.56 mg/d, maintained riboflavin balance.<sup>6</sup>

#### Niacin

##### *Metabolic Effects*

Niacin in the form of nicotinamide is a component of 2 nucleotides. These nucleotides are nicotinamide adenine mononucleotide (NAD) and di-nicotinamide adenine dinucleotide (NADP) nucleotides. They combine with various carrier proteins to form enzymes concerned with electron transfer reactions related to energy metabolism.



### Reliable Assessment of Deficiency and Toxicity

Blood levels of niacin are not a reliable index of niacin status. <sup>1</sup>N-methylnicotinamide and its 2-pyridone derivative are measured in the urine to assess niacin status. The excretion of <0.8 mg <sup>1</sup>N-methylnicotinamide per 24 hours is a sign of deficiency. Another way of assessing status is the ratio of <sup>1</sup>N-methylnicotinamide and its 2-pyridone derivative. A ratio of <1.0 is a sign of deficiency.

### Clinical Effects of Deficiency

Clinical niacin deficiency is called pellagra and is due to both a poor intake of niacin and to a deficiency or reduced conversion of tryptophan to niacin. Clinical deficiency is the result of a complex disorder involving not only a lack of niacin and tryptophan but also an excessive leucine intake, which inhibits the conversion of tryptophan to niacin. There must also be concurrent deficiencies of riboflavin, thiamine, and pyridoxine, which are needed for this conversion. Pellagra presents as a wasting disease with dermatitis of the exposed areas due to photosensitivity. Fatigue, insomnia, and apathy are followed by confusion, hallucinations, disorientation, and finally psychosis. Widespread mucosal inflammation causes glossitis, stomatitis, vaginitis, and diarrhea.

### Requirements

Tryptophan is converted to niacin in the body, and therefore it is necessary to define niacin intake as niacin equivalents (NEs). Sixty milligrams of tryptophan is equivalent to 1 mg niacin. This conversion requires the presence of thiamine, riboflavin, and pyridoxine.

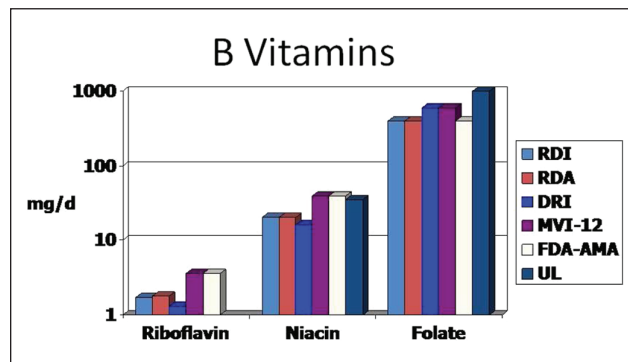
The recommended oral intake is 6.6 mg of NE per 1000 kcal. Thus, about 13–18 mg/d should be taken by adults. For PN, the AMA recommends 40 mg/d in adults.<sup>1</sup> In home PN patients, 100 mg twice weekly avoids deficiency.<sup>7</sup> However, daily infusion of the current formulation is required to maintain normal levels of niacin.<sup>4</sup>

### Modifications for Cirrhosis, Cancer, Renal Failure, Trauma, Sepsis, and Burns

Cancer patients receiving PN had biochemical deficiency of niacin despite receiving 40 mg/d. In the same study, niacin status was measured in only 1 patient receiving 80 mg/d and was normal.<sup>5</sup>

### Modification for Gender and the Elderly

There is no modification for age. The DRI for women is set at about 1–2 mg/d lower than it is in men.



**Figure A4.1.** Comparison of parenteral intake with Recommended Daily Allowance (RDA), Reference Daily Intake (RDI), and Dietary Reference Intakes (DRI).

### Relevance to Pregnancy, Lactation, and Pediatric Populations

During pregnancy and lactation, an additional 2 and 5 NE/d is respectively recommended. For those aged 0–1 year, adequate intake is 2–4 mg/d; age 1–8 years, 5–6 mg/d; age 9–13 years, 9–12 mg; and 14 mg and above, it is in the adult range.

### Comparison of Intravenous Intake With the RDA, RDI, and DRI

The parenteral intake based on available formulations easily meets the requirements based on RDA, RDI, and DRI (Figure A4.1).

### Conclusions

There are no good controlled studies to evaluate the exact need of riboflavin and niacin in PN. However, the available data suggest that the current formulation will meet requirements in stable patients. In critically ill patients, riboflavin intake of 10 mg, which is 3 times the amount in the usual dose of the current formulation, will maintain biochemical stability. In patients with cancer, it appears that much larger doses of riboflavin and niacin may be required to maintain normal biochemistry. In these patients, further studies need to be done.

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## Appendix 5

### Pantothenic Acid

Peggy Borum, PhD

#### Introduction

Pantothenic acid is a water-soluble B vitamin that functions as a component of coenzyme A.<sup>1</sup>

#### Metabolic Function

Since coenzyme A is involved in many aspects of metabolism, including fatty acid metabolism, pantothenic acid is important in most areas of metabolism.<sup>1</sup> Clinical and basic science research publications are somewhat limited compared with many other micronutrients. However, recently developed analytical methods have been used to expand our understanding of the metabolic roles of pantothenic acid. Peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ) is associated with increased fatty acid catabolism and is commonly targeted for the treatment of hyperlipidemia. PPAR $\alpha$  activation with fibrate medication in healthy human volunteers was associated with greater than a 5-fold decrease in urinary pantothenic acid excretion, suggesting that it may prove useful as an indicator of PPAR $\alpha$ -induced fatty acid  $\beta$ -oxidation in humans.<sup>2</sup> In male rats, pantothenic acid supplementation stimulates the ability of adrenal cells to secrete corticosterone and progesterone and induces adrenal hyperresponsiveness to ACTH stimulation.<sup>3</sup> New clinical uses of pantothenic acid are also being investigated. Although more data from randomized controlled studies are needed, there are results suggesting that pantothenic acid combined with vitamin C contributes to the healing and treatment of surgical wounds.<sup>4</sup>

#### Reliable Assessment Methods of Deficiency and Toxicity

Pantothenic acid deficiency is very rarely observed in humans. Signs and symptoms of deficiency may include irritability and restlessness, fatigue, apathy, malaise, sleep disturbances,

nausea, vomiting, abdominal cramps, hypoglycemia, increased sensitivity to insulin, and neurological symptoms such as numbness, paresthesias, muscle cramps, and staggering gait.<sup>1</sup>

#### Requirement in Parenteral Nutrition

A Recommended Dietary Allowance (RDA) has not been set due to insufficient available scientific evidence. Daily Adequate Intake (AI) of pantothenic acid levels has been established by the Food and Nutrition Board of the U.S. Institute of Medicine based on pantothenic acid sufficient to replace urinary excretion. No adverse effects have been associated with high intakes of pantothenic acid.<sup>1</sup> Parenteral nutrition (PN) pantothenic acid recommendations are derived from the deliberations of expert panels.<sup>5,6</sup> Pantothenic acid is stable in a 3-L plastic bag of PN while stored in darkness at 2–8°C for 96 hours or during 24 hours of simulated infusion initiated immediately after mixing.<sup>7</sup>

#### Modifications Due to Gender, Age, Pregnancy, and Lactation

Several different groups of patients, including children, have been maintained on PN with commercial intravenous multivitamin products with no evidence of pantothenic acid deficiency or toxicity.<sup>8,9</sup> Elevated blood concentrations of pantothenic acid in patients receiving PN are usually associated with the presence of renal disease.<sup>10</sup>

#### Recommendations

##### Pantothenic Acid

Population	Recommendation	Reference
Oral nutrition: adults	AI = 5 mg/d	1
Oral nutrition: pregnant females	AI = 6 mg/d	1
Oral nutrition: breastfeeding females	AI = 7 mg/d	1
Oral nutrition: children, 0–6 mo	AI = 1.7 mg/d	1
Oral nutrition: children, 7–12 mo	AI = 1.8 mg/d	1
Oral nutrition: children, 1–3 y	AI = 2 mg/d	1
Oral nutrition: children, 4–8 y	AI = 3 mg/d	1
Oral nutrition: children, 9–13 y	AI = 4 mg/d	1
Oral nutrition: children, 14–18 y	AI = 5 mg/d	1
PN: adults	15 mg/d	5
PN: term infants and children	5 mg/d	6
PN: preterm infants and children	2.5 mg/kg/d	6

AI, Adequate Intake; PN, parenteral nutrition.



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## Appendix 6

### Vitamin B<sub>6</sub> (Pyridoxine)

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### Introduction

Vitamin B<sub>6</sub> consists of several related compounds, including pyridoxal (PL), pyridoxine, and pyridoxamine and their respective 5'-phosphates. In parenteral nutrition (PN) formulations, pyridoxine is supplied as pyridoxine hydrochloride because this compound is more stable than other forms of the vitamin.<sup>1</sup> It is phosphorylated to its active form, pyridoxal-5'-phosphate (PLP), by the liver, the site of primary metabolism.<sup>2,3</sup> In a study of normal volunteers infused with vitamin B<sub>6</sub>, plasma steady-state concentration was reached within 30 minutes, and the serum half-life was only a few minutes<sup>4</sup>; only 6.7% of the administered

dose was detected unmetabolized in the urine. If active metabolites were included, the urine amount was somewhat greater.

### Metabolic Effects

Pyridoxine hydrochloride is an inactive compound and is metabolized in the liver to the active moieties PLP, the primary form bound to serum albumin in plasma, and pyridoxamine-5'-phosphate (PMP).<sup>2,3</sup> PLP undergoes oxidation in the liver to 4-pyridoxic acid, which is excreted.<sup>5</sup>

PLP functions as a coenzyme for aminotransferases that catalyze the formation of  $\alpha$ -keto acids from their respective amino acids. PLP is also important in the hepatic transsulfuration pathway (via the PLP-dependent enzymes  $\beta$ -synthase and cystathionine  $\gamma$ -lyase), as well as in decarboxylation and dehydration reactions. Carnitine biosynthesis requires PLP-dependent 3-hydroxytrimethyl-lysine aldolase. PLP plays an active role in both glycogenolysis and gluconeogenesis and is the coenzyme for glycogen phosphorylase. Vitamin B<sub>6</sub> may also play a role in lipid metabolism and in the maintenance of normal immune function, although these roles remain somewhat speculative. PLP-dependent  $\delta$ -aminolevulinic synthase is important for heme biosynthesis.

As with other B vitamins, exposure of vitamin B<sub>6</sub> to sunlight leads to destruction,<sup>6</sup> although this has not been shown in all studies.<sup>7</sup>

### Reliable Assessment for Deficiency and Toxicity

Vitamin B<sub>6</sub> deficiency has been associated with seborrheic dermatitis,<sup>8</sup> microcytic anemia,<sup>9</sup> a peripheral neuropathy, epilepsy, abnormal electroencephalograms,<sup>10,11</sup> depression, and confusion.<sup>12</sup> A glove and stocking sensory neuropathy has also been reported in B<sub>6</sub> toxicity with ingestion of large doses (1–6 g/d for 2–40 months) of pyridoxine.<sup>13,14</sup> The Food and Nutrition Board set a tolerable upper limit of 100 mg/d<sup>14</sup> in adults. Toxicity has not been reported from parenteral administration of currently recommended doses.

High-performance liquid chromatography (HPLC) is the primary method for determination of vitamin B<sub>6</sub> in both plasma and tissues.<sup>15</sup> The plasma concentration of PLP reflects the hepatic concentration.<sup>16,17</sup> PLP <20 nmol/L is associated with vitamin B<sub>6</sub> deficiency,<sup>14,18</sup> although at this level, some individuals will exhibit no signs of deficiency.<sup>19,20</sup> As with choline,<sup>21</sup> plasma PLP is very high in the fetus and slowly decreases to normal adult concentrations over the first year of life.<sup>22</sup> The concentration of PLP at which deficiency occurs in the neonate is unknown. Erythrocyte PLP reflects plasma PLP except in individuals who have received very high doses.<sup>23</sup> Plasma PL and PLP are more affected by critical illness than red or white cell concentrations, suggesting that intracellular concentrations are a better measure of status in such patients.<sup>24</sup> Whole-blood vitamin B<sub>6</sub> concentrations (normal >40 nmol/L) fluctuate with the menstrual cycle.<sup>25</sup>

Significant fluctuation has also been observed with measurements of the activation of erythrocyte aspartate and alanine aminotransferase enzyme activities on incubation with PLP (normal <1.25 to <1.8, respectively),<sup>26</sup> thereby limiting their usefulness. Urinary 4-pyridoxic acid excretion (normal >3  $\mu\text{mol/d}$ ) or urinary total vitamin B<sub>6</sub> (normal >0.5  $\mu\text{mol/d}$ ) reflects recent intake rather than a deficiency or toxicity state.<sup>14</sup> An increase in plasma homocysteine following a methionine load has also been used to indicate vitamin B<sub>6</sub> deficiency (normal: <1.25–1.8).<sup>27</sup> However, high plasma homocysteine concentration may be related to other factors, such as choline deficiency, in the PN patient.<sup>28</sup> Erythrocyte glutamic oxaloacetic transaminase activity also reflects pyridoxine status.<sup>29</sup>

With regard to PN, serum PLP concentration was decreased in 3 of 30 patients who required nightly PN and were awaiting intestinal transplantation, although no identifiable symptoms were present.<sup>30</sup> A low level was not reported when the blood samples were obtained following the discontinuation of the nightly PN. Pyridoxine hydrochloride, 2.4 mg/d, was insufficient to maintain normal serum PLP in a group of adult South African patients who required prolonged PN,<sup>31</sup> although Howard et al<sup>32</sup> found that urinary 4-pyridoxic acid excretion remained normal at this dose. Three milligrams of daily intravenous pyridoxine hydrochloride was sufficient to maintain normal pyridoxine status in a group of Japanese adult patients requiring PN,<sup>33</sup> and a study of long-term home PN-requiring patients indicated this dose was sufficient to maintain normal plasma concentrations.<sup>34</sup>

Whole-blood pyridoxine concentrations were elevated in some patients who received 4 mg daily,<sup>35</sup> although at this dose, Inculet et al<sup>36</sup> found that urinary excretion remained normal but became substantially elevated when the dose was doubled. Urinary excretion probably reflects the infused dose. Hariz et al<sup>37</sup> also found that 4.5 mg/d of pyridoxine maintained somewhat elevated vitamin B<sub>6</sub> concentration in the blood of children who received home PN after a week of therapy, although neither the form of vitamin B<sub>6</sub> nor urinary excretion was reported. It is to be noted that Shils et al<sup>34</sup> found that the amount of pyridoxine contained in an intravenous multivitamin formulation was nearly double that indicated on the label.

Based on the above results, the Food and Drug Administration (FDA) recommendation to increase vitamin B<sub>6</sub> supply to 6 mg/d during PN seems to lack experimental support.<sup>38</sup> However, such an intake will not be harmful and will ensure an adequate vitamin B<sub>6</sub> intake in those patients who are already depleted or who have a high amino acid intake.

### Modification for Cirrhosis, Renal Failure, Trauma, Sepsis, and Burns

Renal insufficiency has been associated with decreased vitamin B<sub>6</sub> status as indicated by decreased plasma PLP, elevated urinary pyridoxic acid (PA), and elevated post-methionine load homocysteine concentration.<sup>39,40</sup>

### Modification for Gender and the Elderly

The Dietary Reference Intake (DRI) was reduced in 1998 from that recommended in 1989 to an estimated average requirement of 1.1 mg/d and a DRI of 1.3 mg/d for both male and female adults, with slightly higher intakes recommended for the elderly (1.7 mg/d for men >51 years and 1.5 mg/d for women >51 years).<sup>14</sup>

### Relevance to Pregnancy, Lactation, and the Pediatric Population

A study in 6 preterm infants who received 63% of their energy requirements via PN indicated that a pyridoxine dose of 394  $\pm$  243 mcg/100 kcal/d (equivalent to current recommendations) maintains normal serum pyridoxal concentrations in blood samples obtained during PN infusion.<sup>41</sup>

The American Medical Association–Nutrition Advisory Group (AMA-NAG) recommendations indicated that children <10 kg should receive 10% of the general pediatric dose per kilogram.<sup>42</sup> At a later meeting sponsored by the FDA, experts noted that term infants and children up to age 11 years could all receive the same vitamin dose, which is somewhat more than the RDA for 0–12 months and slightly less than the Recommended Daily Allowance (RDA) for older children.<sup>42</sup> Using the AMA-NAG recommendations, Moore et al<sup>43</sup> reported that term infants and children maintained normal plasma glutamic oxaloacetic transaminase activities.

Elevated serum pyridoxic acid concentrations have been described with doses of 300–700 mcg/d.<sup>44</sup> For infants, the adequate oral intake (AI) was based on the amount of vitamin B<sub>6</sub> in human milk. This dose was extrapolated, based on expected weight for older infants (7–12 months).<sup>14</sup> For older children, estimated average requirements (EARs) and RDAs are extrapolated based on adult data. The current RDA is 1.9 mg/d for pregnancy and 2 mg/d for lactation.<sup>14</sup>

### Drug and Nutrient Interactions

PL kinase, which catalyzes the phosphorylation of vitamin B<sub>6</sub>, requires zinc as a cofactor. Niacin, folate, and carnitine require vitamin B<sub>6</sub> for their biosynthesis and metabolism.

Vitamin B<sub>6</sub> is antagonized by hydralazine, gentamicin, isoniazid, levodopa and other medications, and ethanol.<sup>27</sup> Isoniazid and hydralazine cause increased excretion of pyridoxine in urine. Vitamin B<sub>6</sub> requirement in such individuals is therefore probably higher than the recommendations for a healthy population, but data are not available to identify the requirement more precisely.

### Conclusions and Clinical Recommendations

The current recommended dose of 6 mg daily for adults and extrapolated pediatric dosing appears adequate and appropriate.

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## Appendix 7

### Vitamin B<sub>12</sub>

Lyn Howard, MD, FRCP

#### Introduction

Vitamin B<sub>12</sub> or cobalamin is essential for normal blood formation and normal neurologic function.<sup>1</sup>

In the United States, the median adult B<sub>12</sub> intake from food is 5 mcg/d for men and 3.5 mcg/d for women. Since B<sub>12</sub> occurs only in animal products, strict vegetarians (vegans) may develop B<sub>12</sub> deficiency unless they take a supplement.

Absorption of dietary B<sub>12</sub> is a complicated process. It depends on gastric acid and pepsin to release food-bound B<sub>12</sub>. The released B<sub>12</sub> binds to R proteins secreted by the salivary glands and gastric mucosa. In the alkaline pH of the duodenum, pancreatic proteases digest the R proteins, and liberated B<sub>12</sub> binds to intrinsic factor (IF). IF is a glycoprotein secreted by the gastric parietal cells. The B<sub>12</sub>-IF complex travels down the small intestine and attaches to specific receptors in the distal ileum. The B<sub>12</sub>-IF is internalized into the ileal enterocyte; B<sub>12</sub> is then broken off and enters the circulation bound to transcobalamin (TC) carrier proteins I, II, or III. Most circulating B<sub>12</sub> (>80%) is attached to TC I, which seems to be physiologically inert; 10%–15% of circulating B<sub>12</sub> is attached to TC II. Tissues have TC II receptors, allowing them to capture B<sub>12</sub> as needed.<sup>2</sup> The liver takes up 50% of dietary B<sub>12</sub> and provides the main storage site. The average B<sub>12</sub> hepatic content is 1.0 pg/g of tissue. The total body B12 content is 1–3 mg.

**Table A7.1.** Factors Impairing Vitamin B<sub>12</sub> Absorption

- Gastric resection, atrophic gastritis, or pernicious anemia: ↓ gastric acid, proteases, and intrinsic factor
- Chronic pancreatitis, cystic fibrosis: ↓ pancreatic proteases
- Bacterial overgrowth or small intestinal parasites: consume B<sub>12</sub>-IF complex
- Ileal resection or ileitis: eliminate or ↓ B<sub>12</sub>-IF receptors
- Genetic absence of TC II: ↓ tissue distribution

IF, intrinsic factor; TC, transcobalamin.

A number of factors listed in Table A7.1 can disrupt B<sub>12</sub> absorption. Very large doses of sublingual or oral crystalline B<sub>12</sub> (500–1000 mcg/d) are ±1% absorbed by mass action even if IF is absent. The sublingual and oral routes seem equally effective and may be preferred to a monthly intramuscular injection.<sup>3–6</sup> Patients with tobacco amblyopia or patients with B<sub>12</sub> deficiency who smoke have increased urinary thiocyanate losses and should receive a new form of B<sub>12</sub>, hydroxocobalamin, which is a potent cyanide antagonist. This compound is currently available only in a parenteral form. Cyanocobalamin, the traditional salt, is used in oral, sublingual, and parenteral multivitamin formulations and risks worsening tobacco/B<sub>12</sub> ophthalmic symptoms.<sup>7</sup>

Vitamin B<sub>12</sub> has an enterohepatic cycle. Each day, about 1.4 μg B<sub>12</sub> is secreted into the bile, and approximately half of this is recaptured if IF is present. If IF is absent or the distal ileum has been resected, clinical B<sub>12</sub> deficiency can develop in a few months. In comparison, B<sub>12</sub> deficiency in vegans develops over many years. In normal circumstances, B<sub>12</sub> is excreted chiefly in the stool. Fecal B<sub>12</sub> reflects unabsorbed B<sub>12</sub> from food or bile, desquamated intestinal cells, and B<sub>12</sub> synthesized by colonic bacteria. After a parenteral injection of B<sub>12</sub>, if the circulating vitamin exceeds TC binding capacity, the excess is secreted in the urine. Vitamin B<sub>12</sub> toxicity has not been described.

#### Metabolic Function

Vitamin B<sub>12</sub> is the cofactor for 2 enzymes. With methionine synthetase, B<sub>12</sub> transfers a methyl group from circulating methyltetrahydrofolate to homocysteine, forming tetrahydrofolate and methionine. Tetrahydrofolate is required for deoxyribonucleic acid (DNA) synthesis. With L-methylmalonyl-CoA mutase, adenosyl B<sub>12</sub> isomerizes L-methylmalonyl-CoA to succinyl CoA.

The hematologic effect of B<sub>12</sub> deficiency is identical to folate deficiency since both vitamins are involved in methyl transfer, a step toward DNA synthesis. The defect is most apparent in rapidly dividing cells and in the bone marrow, gut lining, and cervix mucosa. In the bone marrow, red cell precursors are large with primitive nuclei and are called megaloblasts. The peripheral blood shows anemia with macrocytosis of red blood cells, neutropenia with hypersegmented polymorphs, and thrombocytopenia. Deficient



patients are pale, fatigued, and short of breath. They may complain of a sore tongue, loss of appetite, flatulence, and constipation due to abnormal functioning of the macrocytic bowel. No gynecologic symptoms have been described. The hematologic and bowel symptoms improve after a few weeks of B<sub>12</sub> therapy.

The neurologic effects of B<sub>12</sub> deficiency develop more slowly and reflect a lack of adenosyl B<sub>12</sub>. Twenty-five percent of patients with the neurologic syndrome have no hematologic manifestations. The clinical picture may include a peripheral sensory neuropathy with tingling, numbness, and reduced vibration and position sense, especially in the legs; motor weakness with gait disturbances; and central deficits such as loss of concentration and memory, leading to premature dementia. Occasionally, there are visual changes, impotency, and loss of bowel and bladder control. Lindenbaum et al<sup>8</sup> and later Beck<sup>9</sup> described neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia and macrocytosis. This suggests all neuropsychiatric patients should be screened for B<sub>12</sub> deficiency. Neurological deficits come on slowly, and full reversibility with B<sub>12</sub> treatment is less certain.

### Reliable Assessment Methods

Evaluation of B<sub>12</sub> starts with relatively nonspecific hematologic tests such as hemoglobin concentration, hematocrit, red cell count, and mean red cell volume. Serum or plasma B<sub>12</sub> levels are the most common specific test ordered, but they develop late after tissue levels are already depleted. Plasma or serum values can be normal despite tissue deficiency because of recent intake. In parenteral patients receiving daily B<sub>12</sub> infusions, serum B<sub>12</sub> levels are hard to interpret. The lower limit of serum B<sub>12</sub> for adults is 120–180 pmol/L or 170–250 pg/mL. Normal serum values are 300–900 pg/mL. The value varies with the laboratory method used.

Measurement of serum methylmalonic acid (MMA) is currently the most sensitive and specific test of B<sub>12</sub> depletion. It measures adenosyl-B<sub>12</sub> function. If patients with established B<sub>12</sub> deficiency are supplemented inadequately, MMA rises in 95%, but serum B<sub>12</sub> is low (<200 pg/mL) in only 69%. False MMA positives are seen in severe renal failure or major volume depletion. MMA specificity is confirmed when the high value subsides with B<sub>12</sub> supplementation.

Elevated homocysteine and increased urinary excretion of formiminoglutamic acid after histidine loading (FIGLU test) are seen in both B<sub>12</sub> and folic acid deficiency and reflect the methyl group transfer function of these 2 vitamins. As a result, these tests are not as specific as MMA for pinpointing B<sub>12</sub> depletion.

### Vitamin B<sub>12</sub> Requirements in Parenteral Nutrition

Adult parenteral multivitamin products provide 5 mcg/d of crystalline cyanocobalamin. This is similar to the oral B<sub>12</sub>

**Table A7.2.** Reasons to Continue 5 mcg/d of Vitamin B<sub>12</sub> as the Adult Parenteral Multivitamin Dose

- Although this dose results in serum B<sub>12</sub> levels at upper limits of normal, there is no evidence for a B<sub>12</sub> toxicity syndrome.
- High serum levels may reflect daily parenteral B<sub>12</sub> infusion rather than tissue levels that are probably normal.
- Parenteral B<sub>12</sub> is delivered into the systemic circulation rather than the portal system, and thus first-pass uptake of 50% by the liver and binding to appropriate transcobalamin (TC) carrier proteins are likely to be less efficient. In addition, 25% of systemic blood “first passes” the kidneys. Immediate loss of significant amounts of B<sub>12</sub> in the urine is probable.
- B<sub>12</sub> secreted into the bile may not be recaptured because of loss of ileal receptors.
- Smokers have increased urinary B<sub>12</sub> losses as thiocyanate.

Recommended Daily Allowance (RDA), which, however, is only 50% absorbed.<sup>10</sup> Serum B<sub>12</sub> tends to be elevated in patients receiving chronic parenteral nutrition (PN), usually in the 700- to 900-pg/mL range.<sup>10</sup> This might suggest that parenteral 5 mcg/d is excessive, but there are several good reasons, summarized in Table A7.2, to continue this generous dose.

Elkhatib et al<sup>11</sup> speculated that high serum B<sub>12</sub> in long-term PN patients might be a marker for intestinal failure–associated liver disease. They studied 13 patients with short bowel syndrome (<200 cm residual small bowel) and complete terminal ileum resection who had been on PN for 6.1 ± 3 years. All patients had at least 1 liver biopsy for presumed intestinal failure–associated liver disease. The biopsies were evaluated and scored for the degree of steatosis, inflammation, and fibrosis. There was no correlation between serum B<sub>12</sub> concentration and liver pathology, nor was there any correlation with hepatic chemistries taken just prior to the liver biopsy. Thus, in these circumstances, the high serum B<sub>12</sub> was not a marker of intestinal failure–associated liver disease.

*Gender.* Women have higher serum B<sub>12</sub> values and higher transcobalamin levels compared with men.<sup>12</sup> However, this does not appear to indicate a higher requirement for B<sub>12</sub> in women.

*Age.* Tables 4–7 in the main section show recommended B<sub>12</sub> intakes enterally and parenterally for neonates, infants, children, adolescents, and adults. The liver of well-nourished babies contains only 25–30 mcg B<sub>12</sub>. Breast milk from vegan mothers tends to be low (0.23 mcg/d), and these infants may develop increased urinary MMA concentrations at 2–14 months,<sup>13</sup> indicating B<sub>12</sub> deficiency. The pediatric parenteral dose is generous and will certainly build pediatric liver stores rapidly. There are no known adverse consequences of providing this generous amount of B<sub>12</sub>.

*Pregnancy.* Serum B<sub>12</sub> concentrations decline in early pregnancy, and by the sixth month, they are about half the nonpregnancy concentration. This may reflect the mother’s expanded intravascular volume. In the third trimester, transcobalamin II increases to about a third more than in the



nonpregnant women. The RDA for pregnancy is 2.6 mcg B<sub>12</sub> per day. Again, this is more than covered by the usual parenteral dose of 5 mcg B<sub>12</sub> per day.

**Lactation.** Healthy B<sub>12</sub>-replete mothers secrete approximately 0.33 mcg B<sub>12</sub> per day in breast milk. This amount decreases to 0.25 mcg B<sub>12</sub> per day after 6 months. The RDA for lactation is 2.8 mcg B<sub>12</sub> per day. This again is more than met in women supported by PN (5 mcg B<sub>12</sub> per day).

Recommendations for B<sub>12</sub> in Parenteral NutritionThe current dose of 5 mcg/d for adults generously meets requirements. When patients with short bowel syndrome are gradually weaned off PN, B<sub>12</sub> adequacy needs to be checked at interval since most of these patients have lost their ileum and therefore B<sub>12</sub>-IF receptors. Alternatively, supplements can be started from the onset of weaning. If the patient smokes, hydroxocobalamin, rather than cyanocobalamin, is the compound of choice. Commercial sublingual, oral, and multivitamin preparations currently use hydroxocobalamin, and it would be desirable if this can be changed.

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## Appendix 8

### Folate and Parenteral Nutrition

Lyn Howard, MD, FRCP

#### Introduction

Folate functions as a coenzyme in single-carbon transfer reactions and exists in many chemical forms. It has a critical role in pyrimidine, purine, and amino acid metabolism.

Food folate (pteroyl polyglutamate) consists of a p-aminobenzoic acid molecule linked at one end to a pteridine ring and at the other to 2–7 glutamate molecules. This glutamate side chain is highly polar, and folate is not absorbed by the small intestine until most of the side chain is removed by folate conjugases, which are secreted by small bowel enterocytes. Once the polyglutamate is converted to the monoglutamate, folate is actively transported into the enterocyte by a saturable pH-dependent process. The bioavailability of food folate (polyglutamate) is about 50%. All folate supplements are in the monoglutamate form, which is 100% bioavailable.<sup>1</sup> In 1998, the United States made fortification of cereal grains with folate monoglutamate mandatory to ensure an intake of at least 400 mcg/d. This was done to reduce the incidence of neural tube birth defects (NTD) in the in utero infants.<sup>1</sup> This fortification appears to have decreased NTD by 50%.<sup>1</sup>

Total body folate is approximately 22 mg in healthy adults, and half of this is stored in the liver.<sup>2</sup> Folate circulates primarily as methyltetrahydrofolate (methyl-THF) bound to protein carriers. It is transported into cells by a specific receptor. In the cell, folate is attached to membrane carriers or folate binding protein-mediated systems.<sup>3</sup> These transport systems are not saturated under physiologic conditions, so folate influx into tissues can be expected when supplements are given and plasma folate rises. In the cell, folate is stored as the polyglutamate form.

Folate catabolism starts with cleavage of the intracellular polyglutamate to monoglutamate, which is then acetylated and excreted in the urine. Folate is also excreted into the bile, but much of this is reabsorbed. Fecal folate losses reflect unabsorbed food folate, folate excreted into the bile, and folate synthesized by the intestinal microflora.<sup>4</sup> There are no data on gut losses in extreme short bowel patients maintained on long-term home parenteral nutrition (PN).

## Metabolic Function

The main function of folate compounds is to transfer 1-carbon moieties, such as methyl and formyl groups, to organic compounds. These 1-carbon moieties are chiefly obtained from serine, which in turn is converted to glycine. The most critical 1-carbon transfers of folate are (1) the conversion of homocysteine to methionine, (2) the addition of C<sub>2</sub> and C<sub>8</sub> in purine synthesis, and (3) the methylation of deoxyuridylic acid to form thymidylic acid in pyrimidine synthesis. This last reaction is unique in that dihydrofolate (DHF) is formed rather than tetrahydrofolate (THF). DHF must be reduced by dihydrofolate reductase before it can reenter the donor pool. A number of drugs, such as methotrexate, pyrimethamine, and trimethoprim, can inhibit dihydrofolate reductase, inducing folate deficiency. Table A8.1 summarizes the many causes of folate deficiency. The clinical presentation reflects the defect in purine and pyrimidine metabolism, especially in rapidly dividing cells in the bone marrow and in intestinal and cervical epithelia. Cytoplasmic development is normal, but impaired deoxyribonucleic acid (DNA) synthesis and delayed cell division result in large cells with primitive nuclei. In the bone marrow, these are most striking in the red cell series and termed *megaloblasts*. These cells eventually lose their nuclei and move into the circulation as macrocytes. Other hematopoietic cells are also affected. Polymorphs develop increased nuclear segmentations, and platelets are reduced in number. Folate-deficient patients are pale, fatigued, and short of breath. They may also have a sore tongue, angular cheilosis, loss of appetite, flatulence, and constipation related to their macrocytic bowel. All these symptoms subside after a few weeks of folate therapy. This clinical picture is identical to the hematologic effects of vitamin B<sub>12</sub> deficiency. This reflects the fact that folate and B<sub>12</sub> are both involved in the conversion of methyl-THF to THF, which then receives 2 carbon moieties to form N<sub>5,10</sub>-methylene THF (the active form for purine and pyrimidine synthesis).

Folate toxicity has not been described.

## Reliable Assessment Methods

Erythrocyte folate is the best test for long-term folate deficiency, and it correlates fairly well with folate concentrations in other tissues such as the liver.<sup>5</sup> Deficiency is present when erythrocyte folate is below 140 ng/mL.

Serum folate less than 4 ng/mL indicates a negative folate balance, but it does not distinguish between a transient reduction in folate intake and chronic folate deficiency. The normal serum concentration is 6–20 ng/mL.

Plasma homocysteine rises with folate deficiency, but different laboratories use different upper limits. Greater than 14 μmol/L is perhaps the most commonly used value. Elevated plasma homocysteine is also seen in vitamin B<sub>12</sub> deficiency.

## Appendix A8.1. Factors Leading to Folic Acid Deficiency

1. Inadequate intake	Common in alcoholics
2. Increased requirement	Pregnancy Infancy Malignancy Increased hematopoiesis Hemodialysis
3. Malabsorption	Tropical sprue Celiac disease Drugs; phenytoin, barbiturates
4. Impaired metabolism	Inhibitors of dihydrofolate reductase; methotrexate, trimethoprim pentamidine Alcohol Rare enzyme deficiencies; dihydrofolate reductase

Vitamin B<sub>6</sub> status, age, gender, and renal insufficiency also affect plasma homocysteine levels.

Urinary folate is not a sensitive index of folate status.

## Folate Requirements in PN

In the early years of PN, a number of patients died with an acute megaloblastic crisis occurring within a few weeks of starting the therapy.<sup>6</sup> Wardrop et al<sup>7</sup> suggested the mechanism could be alcohol toxicity. At that time, parenteral fat was not available, so all needed calories were given as dextrose, with its attendant hyperglycemic problems, or as a dextrose-alcohol mixture. The toxic effect of alcohol on hematopoiesis was well known.<sup>8</sup> Later investigators described this syndrome in PN patients not receiving any alcohol.<sup>9</sup> They found, however, an association with high levels of glycine and methionine. Folate supplementation prevented this syndrome. A later speculation pointed to the common practice of using mostly glycine to provide nonessential amino acid nitrogen. Glycine is a highly soluble amino acid. It was suggested that excessive glycine may block the serine-glycine conversion, which provides the 1-carbon moieties that convert THF to N<sup>5,10</sup>-methylene THF, the active form in purine and pyrimidine synthesis. In those early years, folate was not always added to short-term PN. After supplemental folate was shown to avoid this megaloblastic syndrome, 200 mcg/d was added. This has now been increased to 400 mcg/d of folate monoglutamate to cover patients with longstanding malnutrition and depleted folate stores. Most PN patients have high normal serum folate levels.<sup>1</sup>

## Age

Tables 4–7 in the main section show recommended folate intakes enterally and parenterally in neonates, children, adolescents, and adults. The amount is expressed as mcg/kg/d for small infants (<3.0 kg), but thereafter it is a standard pediatric

dose in mcg/d. The parenteral dose is 30% higher than the enteral dose until adulthood, when it is the same, 400 mcg/d.

### Pregnancy

The U.S. 1998 mandate for folate fortification of cereal followed the publication of several studies showing that periconceptional folate supplementation reduced the risk of a second NTD in mothers who have had this complication by as much as 35%–40%.<sup>10,11</sup> A randomized study in Hungary evaluated the effect of a multivitamin providing 800 mcg/d of folic acid or placebo in 4753 women planning a pregnancy but with no prior history of NTD.<sup>12</sup> The study was prematurely terminated after there were 6 cases of NTD in the controls and none in the group receiving vitamin supplementation. The effect of supplemental folate alone was not assessed. Currently, the evidence for a protective effect of folate supplements or fortified food or both is much stronger than that for natural food folate. Preliminary data indicate a 50% reduction in NTDs since cereal fortification was required.<sup>1</sup> Current parenteral multivitamin products provide 400 mcg/d. There is no specific pregnancy product. It seems wise to recommend increasing folate acid in the adult formula so as provide for women who become pregnant and are dependent on PN. There are no known adverse consequences of this increased amount in nonpregnant adults.

### Recommendation for Folic Acid in PN

The current dose of 600 mcg/d for adults appears to generously meet requirements even for females who are pregnant or lactating. If the patient has short bowel syndrome and is being weaned off PN, monitoring erythrocyte folate and starting oral supplements are appropriate. Most short bowel patients retain their duodenum and some of their jejunum, and these are the chief sites for folate absorption, and thus oral supplementation can be effective.

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## Appendix 9

### Biotin

Peggy Borum, PhD

### Introduction

Biotin is a water-soluble B vitamin that functions as a coenzyme in bicarbonate-dependent carboxylation reactions.<sup>1</sup>

### Metabolic Function

Biotin metabolism does not appear to be the same in all tissues of the body. Biotin deficiency in rats results in a decrease of pyruvate carboxylase and of propionyl-CoA carboxylase of about 90% in adipose tissue, jejunum, and spleen but only a 40% decrease in heart, indicating that the effect of biotin deficiency differs among organs.<sup>2</sup> Biotin plays an important role in the metabolism of glucose, amino acids, and fatty acids as it functions as a coenzyme for 4 carboxylases. It is known that biotin plays a role in immune function, cell proliferation, and fetal development. New evidence suggest that biotin also plays an important role in regulating expression of genes encoding cytokines and their receptors, oncogenes, genes involved in glucose metabolism, and genes that play a role in cellular biotin homeostasis. Data suggest that biotinyl-AMP functions in the activation of soluble guanylate cyclase, biotin deficiency increases nuclear translocation of NF- $\kappa$ B, and biotin functions in remodeling of chromatin by biotinylation of histones.<sup>3,4</sup> Biotin is covalently attached to specific lysine residues in histones in a reversible process that depends on the exogenous biotin supply.<sup>5</sup> In addition to biotin serving as a coenzyme for pyruvate carboxylase, biotin also influences both the synthesis and degradation of pyruvate carboxylase.<sup>6</sup> In mice, biotin deficiency may upregulate tumor necrosis factor (TNF)- $\alpha$  production, and biotin excess may downregulate TNF- $\alpha$  production, leading to the suggestion that biotin status influences inflammatory diseases.<sup>7</sup>

## Reliable Assessment Methods of Deficiency and Toxicity

Biotin deficiency has been documented in individuals consuming raw egg whites over long periods and in patients receiving parenteral nutrition (PN) that does not contain biotin. There is not a good laboratory test for detecting biotin deficiency, so the condition is usually identified by its symptoms. Biotin deficiency may result in dermatitis (red scaly rash around eyes, nose, and mouth), conjunctivitis, alopecia, and central nervous system abnormalities such as depression, lethargy, hallucinations, and paresthesia of the extremities. Biotin deficiency in infants may result in hypotonia, lethargy, developmental delays, and withdrawn behavior.<sup>1</sup>

## Requirement in PN

A Recommended Dietary Allowance (RDA) has not been set due to insufficient available scientific evidence. Daily Adequate Intake (AI) of biotin levels has been established by the Food and Nutrition Board of the U.S. Institute of Medicine based on extrapolation from the amount of biotin in human milk. People with a genetic biotinidase deficiency and people on hemodialysis or peritoneal dialysis treatment may have an increased requirement for biotin. No adverse effects of excess biotin have been reported in humans or animals. No toxicity has been observed in patients receiving up to 200 mg orally and up to 20 mg parenterally to treat biotin-responsive inborn errors of metabolism and acquired biotin deficiency. Due to insufficient data on adverse effects, the upper tolerable intake limit (UL) could not be determined.<sup>1</sup> PN biotin recommendations are derived from the deliberations of expert panels.<sup>8,9</sup>

Biotin is stable in a 3-L plastic bag while stored in darkness at 2–8°C for 96 hours or during 24 hours of simulated infusion initiated immediately after mixing.<sup>10</sup> There have been several reports of biotin deficiency in patients on PN with varying prevalence rates. In 49 patients receiving home PN, 3 had symptoms of biotin deficiency, including dry eyes and angular cheilitis or hair loss.<sup>11</sup> In another study, patients on biotin-free PN for 1 month had clinical symptoms consistent with biotin deficiency, reduced plasma biotin concentrations, and decreased propionyl CoA carboxylase activity. After 4 months of biotin-supplemented PN, both plasma biotin concentrations and propionyl CoA carboxylase activity increased to near-normal levels.<sup>12</sup> Almost half of 13 children on home PN for 1.5 months to 7 year and 17 hospitalized infants and children receiving PN had initially low levels of plasma biotin. Biotin rose sharply during the first month of supplementation with 60 mcg/d of parenteral biotin but returned to the normal range.<sup>13</sup> However, in another study of 102 children receiving all or part of their nutrition needs from home PN, only 1 case of biotin deficiency was recognized.<sup>14</sup> Plasma biotin concentrations of term infants and children on biotin-supplemented PN were maintained at reference levels, but the biotin levels of preterm infants increased

significantly to more than 2 standard deviations above reference levels.<sup>15</sup> When adult patients on long-term PN have plasma biotin concentrations above the normal range, the patients usually have some form of renal dysfunction.<sup>16</sup>

After studying 3 patients with clinical symptoms of biotin deficiency on biotin-free PN and using large doses of biotin therapy (100 µg/d in all patients; an initial larger dose of 1 mg/d for 1 week plus 10 mg/d for 7 weeks in 1 patient), some investigators “speculate that the biotin supplement currently recommended for pediatric patients (20 micrograms/day) may not be adequate therapy for biotin deficiency and might not even be adequate to maintain normal biotin status during TPN [total parenteral nutrition].”<sup>17</sup>

## Modifications Due to Gender, Age, Pregnancy, and Lactation

Individuals eating an oral diet may be at greater risk for biotin deficiency than previously recognized. Women who smoke appear to have accelerated biotin metabolism, which results in marginal biotin deficiency.<sup>18</sup> In a recent study, 18 of 22 pregnant women had laboratory characteristics of marginal biotin deficiency that responded to biotin supplementation.<sup>19</sup> Biotin status of pregnant women affects the developing fetus. Culture of human embryonic palatal mesenchymal (HEPM) cells in the biotin-deficient and biotin-physiological (control) media for 5 weeks showed a decrease in biotin after 1 week and decreased proliferation of HEPM cells in the biotin-deficient state after 2 weeks of culture (41.3% of the control). Nuclei of biotin-deficient cells also had decreased numbers of biotinylated histones compared with control cells. Suppressed proliferation of mesenchymal cells “may delay or inhibit the growth of palatal processes in embryos and thus it may partially contribute to the mechanisms for cleft palate induction.”<sup>20</sup>

## Recommendations

Population	Biotin	
	Recommendation	Reference
Oral nutrition: adults	AI = 30 mcg/d	1
Oral nutrition: pregnant females	AI = 30 mcg/d	1
Oral nutrition: breastfeeding females	AI = 35 mcg/d	1
Oral nutrition: children, 0–6 mo	AI = 5 mcg/d	1
Oral nutrition: children, 7–12 mo	AI = 6 mcg/d	1
Oral nutrition: children, 1–3 y	AI = 8 mcg/d	1
Oral nutrition: children, 4–8 y	AI = 12 mcg/d	1
Oral nutrition: children, 9–13 y	AI = 20 mcg/d	1
Oral nutrition: children, 14–18 y	AI = 25 mcg/d	1
PN: adults	60 mcg/d	8
PN: term infants and children	20 mcg/d	9
PN: preterm infants and children	8 mcg/kg/d	9

AI, Adequate Intake; PN, parenteral nutrition.



## Appendix 9 References

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## Appendix 10

### Molybdenum in Parenteral Nutrition

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#### Introduction

Molybdenum functions as a cofactor for a limited number of enzymes in humans. The Institute of Medicine's Food and Nutrition Board has developed Adequate Intakes (AIs) for infants (2–3 mcg/d) and Recommended Dietary Allowances (RDAs) for children and adults (17–50 mcg/d) (Table A10.1). The average dietary intake of molybdenum by adult men and women is 109 and 76 mcg/d, respectively. The tolerable upper intake level (UL) is 2 mg/d based on impaired reproduction and growth in animals.<sup>1</sup>

In the United States, parenteral molybdenum is available as a single-entity trace element injection (Table 11 in the main paper). The United States Pharmacopeia (USP) includes molybdenum as a substrate in its "Trace Elements Injection" monograph,<sup>3</sup> but no such multiple trace element injection product containing molybdenum is available in the United States.

#### Metabolic Function

Molybdenum has been shown to act as a cofactor for a limited number of enzymes: sulfite oxidase, xanthine oxidase, and aldehyde oxidase. These enzymes are involved in the catabolism of sulfur amino acids and heterocyclic compounds, including purines and pyridines. A clear molybdenum deficiency syndrome has not been achieved in animals, despite major reduction in the activity of these enzymes. Rather, molybdenum deficiency is based on a genetic defect that prevents sulfite oxidase synthesis.<sup>1</sup>

#### Reliable Assessment Methods

Plasma and serum molybdenum concentrations are very low in humans and are difficult to measure. As a consequence, there are few reports on plasma or serum molybdenum concentrations. Plasma concentrations do not reflect molybdenum status and cannot be used as an indicator of estimating requirements.<sup>1</sup>



**Table A10.1.** Dietary Reference Intake: Molybdenum<sup>2</sup>

Life Stage Group	RDA/AI*, mcg/d
<b>Infants</b>	
0–6 mo	2*
7–2 mo	3*
<b>Children</b>	
1–3 y	17
4–8 y	22
<b>Males</b>	
9–13 y	34
14–18 y	43
19–30 y	45
31–50 y	45
50–70 y	45
>70 y	45
<b>Females</b>	
9–13 y	34
14–18 y	43
19–30 y	45
31–50 y	45
50–70 y	45
>70 y	45
<b>Pregnancy</b>	
≤18 y	50
19–30 y	50
31–50 y	50
<b>Lactation</b>	
≤18 y	50
19–30 y	50
31–50 y	50

Recommended Dietary Allowances (RDAs) in bold type; Adequate Intakes (AIs) in ordinary type followed by an asterisk (\*).

The primary route of molybdenum excretion is the urine. Urinary molybdenum reflects dietary intake, increasing as dietary intake increases. Although related to dietary intake, urinary molybdenum alone does not reflect status.

Several biochemical changes have been observed in special situations. In molybdenum cofactor deficiency, urinary sulfate was low and urinary sulfite was present. Serum uric acid concentrations were low, urinary xanthine and hypoxanthine increased, and plasma methionine was increased. However, these observations have not been associated with molybdenum intakes in normal, healthy people and cannot be used as indicators for estimating molybdenum requirements.

### Requirements in Parenteral Nutrition

The published, estimated daily molybdenum parenteral nutrition (PN) requirements from various professional groups are listed in Table A10.2. Most professional groups indicate the need for molybdenum in long-term (eg, home PN) patients.

Abumrad et al<sup>9</sup> in 1981 reported a case of a 24-year-old man suffering from intolerance to amino acids, mainly l-methionine, while on prolonged PN (18 months). The patient displayed tachycardia, tachypnea, central scotomas, night blindness, and irritability, leading to coma. The symptoms disappeared with discontinuation of the administered l-amino acid solutions. Biochemical abnormalities included high plasma methionine and low serum uric acid levels associated with increased urinary excretion of sulfite, thiosulfate, hypoxanthine, and xanthine with decreased urinary excretion of uric acid. Treatment with ammonium molybdate (300 mcg/d) improved the clinical condition, reversed the sulfur handling defect, and normalized uric acid production. This is the only

**Table A10.2.** Published Parenteral Nutrition Requirements for Molybdenum

Group	Adult	Pediatric
AGA 2001 <sup>4</sup>	[Not discussed]	[Not discussed]
A.S.P.E.N. 2002 <sup>5</sup>	“Not routinely added”	“Although not a conventional addition, molybdenum supplementation may be appropriate in long term TPN therapy.”
ESPGHAN/ESPEN 2005 <sup>6</sup>	Not applicable	“An intravenous molybdenum supply of 1 mg/kg per day (0.01 mmol/kg per day) seems adequate and is recommended for the LBW infant. GOR D” “For infants and children an intravenous molybdenum supply of 0.25 mg/kg per day (up to a maximum of 5.0 mg/day) is recommended. GOR D” <sup>a</sup>
ESPEN 2009 <sup>7</sup>	“0.2–0.26 micromole/day” <sup>b</sup> [19–25 mcg/d] <sup>c</sup>	Not applicable
Critical Care Nutrition 2009 <sup>8</sup>	[Not discussed]	[Not discussed]

AGA, American Gastroenterological Association; A.S.P.E.N., American Society for Parenteral and Enteral Nutrition; ESPEN, European Society for Clinical Nutrition and Metabolism; ESPGHAN, European Society of Paediatric Gastroenterology, Hepatology and Nutrition; GOR D, grade of recommendation—grade D.

<sup>a</sup>Directly quoted from publication. Doses appear to be incorrect (increased) by a factor of 1000.

<sup>b</sup>Parenteral intake provided by proprietary sources for home parenteral nutrition use in Europe.

<sup>c</sup>Calculated mcg values from micromole amounts per day.

published case of PN-induced molybdenum deficiency in man. The National Academy of Sciences/Institute of Medicine<sup>1</sup> notes that molybdenum deficiency has not been observed in healthy people, and the only case that might be considered a dietary deficiency is that of Abumrad et al.

While there are no reports of molybdenum deficiency in infants, low birth weight (LBW) infants might be at risk because they are born before adequate stores can be acquired, have rapid growth requiring increased intakes, and frequently receive PN. Friel and coworkers<sup>10</sup> performed a molybdenum balance study in 16 LBW infants on PN. They speculate that an intravenous intake of 1 mcg/kg/d would be adequate for the LBW infant.

The amount of molybdenum provided daily as part of the background contamination of current PN formulations in the U.S. is uncertain. In Sweden (1977), the amount of assayed molybdenum provided in a PN balance study was a mean of 9.9 mcg/d (range, 8.6–11 mcg/d).<sup>11</sup> In Australia (1981), the amount of assayed molybdenum in PN products (used to compound PN formulations) ranged from <5 to 15 mcg/L. The total amount of molybdenum infused daily was 10 mcg/d or less.<sup>12</sup> In the U.S. (1989), the amount of daily molybdenum in a model PN formulation was calculated (from individual assays of PN products) to be 244 mcg/d.<sup>2</sup> No more recent publications of PN molybdenum contamination amounts are available.

## Recommendations for Molybdenum in PN

1. Only 1 case of molybdenum deficiency in PN (none in the diet) has been reported.
2. The amount of molybdenum provided as a contaminant in current U.S. PN products is uncertain.
3. The commercial U.S. availability of a single-entity molybdenum injection should be retained.
4. Plasma and urine molybdenum levels do not indicate nutrient status or requirements.
5. Practitioners should be alert for a constellation of signs and biochemical abnormalities described in the Abumrad et al<sup>9</sup> case as potential indicators for molybdenum PN supplementation.
6. Further research is needed to assess the level of molybdenum contamination of U.S. PN products.

## Appendix 10 References

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