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A Call to Action to Bring Safer Parenteral Micronutrient Products to the U.S. Market

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Abstract

The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) started an intensive review of commercially available parenteral vitamin and trace element (TE) products in 2009. The chief findings were that adult multi-TE products currently available in the United States (U.S.) provide potentially toxic amounts of manganese, copper, and chromium, and neonatal/pediatric multi-TE products provide potentially toxic amounts of manganese and chromium. The multivitamin products appeared safe and effective; however, a separate parenteral vitamin D product is needed for those patients on standard therapy who continue to be vitamin D depleted and are unresponsive to oral supplements. The review process also extended to parenteral choline and carnitine. Although choline and carnitine are not technically vitamins or trace elements, choline is an essential nutrient in all age groups, and carnitine is an essential nutrient in infants, according to the Food and Nutrition Board of the Institute of Medicine. A parenteral choline product needs to be developed and available. Efforts are currently under way to engage the U.S. Food and Drug Administration (FDA) and the parenteral nutrient industry so A.S.P.E.N.'s recommendations can become a commercial reality. (*Nutr Clin Pract*. 2015;30:559-569)

Keywords

minerals; trace elements; parenteral nutrition; parenteral nutrition solutions; micronutrients; vitamins

Background

Parenteral nutrition (PN) became an established hospital therapy in the 1960s and extended to long-term support with home parenteral nutrition (HPN) in the early 1970s. In these early years, commercially available parenteral multivitamins were far from complete, and commercial parenteral multi-trace element (TE) products did not exist. Some hospital pharmacies were making their own single TE solutions. During this era, many papers were published describing micronutrient deficiency syndromes, especially in long-term PN patients.[1-8]

In 1972, this problem was recognized by several nutrition experts, including Phillip White, who chaired the Nutrition Advisory Group of the American Medical Association (NAG-AMA). An urgent symposium was organized in the Nashville, Tennessee, airport.[9] Invited participants were representatives of the Food and Drug Administration (FDA), physicians and pharmacists supervising large PN programs, and scientists working in the PN industry. In the area of micronutrients, the FDA expressed concern about "polypharmacy" but eventually agreed to the concept of multivitamin and multi-TE products because they promised to be safer than adding a multitude of single micronutrients to PN bags. The FDA requested proposals for these parenteral multivitamin and multi-TE products as soon as possible. NAG-AMA spearheaded this task. A multivitamin formula providing 8 water-soluble vitamins and 4 fat-soluble vitamins was sent to the FDA in 1975. The amounts recommended were based on the research and clinical observations underpinning the oral recommended dietary allowances (RDAs). The parenteral water-soluble vitamin requirements were double the RDA for a specific age group to cover greater utilization associated with illness and an increased excretory loss due to systemic rather than portal delivery. The parenteral fat-soluble vitamin requirements were initially set at about one-third to two-thirds of the 1968 RDA,[10,11] taking into account their reduced enteral absorption and potential toxicity. By 1979, a commercial adult multivitamin product was on the market. This product did not contain vitamin K because in a significant number of adult patients with short bowel syndrome, the pathology was gut infarction and the patients were receiving chronic anticoagulant therapy for a proven or suspected clotting disorder. The commercial pediatric multivitamin, which did include vitamin K, became available in 1981. Over time these NAG-AMA vitamin recommendations seemed appropriate as determined by blood levels[10] and functional tests[12] in stable adults receiving long-term HPN.

In 1985, NAG-AMA and the FDA cosponsored a second conference on parenteral vitamins following reports of inadequate water-soluble vitamin restitution in very depleted patients.[13-16] The recommended doses of ascorbic acid, thiamine, pyridoxine, and folate were increased, and inclusion of a modest dose of vitamin K was recommended for adult multivitamin products. It took 15 years for these changes to be incorporated into a new commercial product.[17] It was unclear why these changes took so long to become available.

In 1977, NAG-AMA convened a panel of experts to devise a parenteral multi-TE formula. There was no RDA source of research for this task and little was known about gut absorption of TEs. Manganese and copper were known to be excreted in bile. The TE content of breast milk was reviewed since it indicated infant growth requirements, which might simulate healing in older subjects. In 1978, the panel recommended to the FDA daily parenteral doses of zinc, manganese, copper, and chromium thought to be appropriate for adults and children.[18] In 1979, selenium was added following the discovery of the link between Keshan disease in China and selenium deficiency.[19]

In the mid-1980s, reports began to appear indicating patients receiving PN were going from TE deficiencies to TE toxicities. While the toxic effects of the doses of manganese in the multi-TE products available in the U.S. have been firmly established,[20-22] the toxic effects of the doses of copper and chromium are less clear (Table 1). In long-term PN patients, multiple studies have shown elevated levels of copper in the liver and often the elevation is in the range seen with Wilson disease.[24,32] However, it is unclear what the clinical significance is of these elevated copper levels in the liver. Shike et al[31] demonstrated that most patients achieved copper balance with 0.3 mg/d, although 0.4–0.5 mg/d was needed if gastrointestinal losses were high. The recommended parenteral daily dose of copper in adults was decreased from 0.5–1.5 mg to 0.3–0.5 mg in 1984,[41] but the current adult multi-TE products available in the U.S. still provide 1–1.2 mg/d, which is double the recommended dose.

A syndrome of glucose intolerance, similar to the presentation of chromium insufficiency,[6,7] has been described in one adult who had elevated chromium levels.[36] This patient's condition did in fact improve on chromium supplementation. This incongruous observation raises questions about the form of the high chromium in a PN patient's serum[33,34] and tissues.[24] Chromium has several valencies, some of which are carcinogenic, but so far, the PN patients' excessive chromium has been found to be in the noncarcinogenic trivalent form.[34] These high serum chromium levels in chronic PN patients have not been shown to be toxic in adults; however, in children and infants, these elevated serum levels of chromium have been associated with reduced glomerular filtration rate (GFR) suggesting nephrotoxicity.[33,34] One study of 15 children (ages 1–18 years) receiving long-term PN (median 9.5 years, range 1–14 years) showed that 1 year after removing chromium supplementation, their reduced GFR did not significantly change, suggesting residual, and perhaps permanent, damage or that the chromium was not the cause of the decreased GFR.[33] Even if toxicity from the multi-TE products available in the U.S. cannot be conclusively proven, there is no debate that the doses of manganese, copper, and chromium in the adult multi-TE products and manganese and chromium in the neonatal/pediatric multi-TE products result in high serum and tissue levels and need to be reduced.

Despite these serious concerns about the commercial parenteral multi-TE products, the FDA has not issued any recommendations for reformulation of these products. As a

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Table 1. Summary of Actual or Potential Toxicities Associated With the Parenteral Multi-Trace Element Products Available in the United States.

Element	Relevant References and Findings
Manganese (Mn)	Huang et al[23]—excess Mn associated with Parkinson's disease. Fell et al[20]—11 of 57 children on long-term home parenteral nutrition (HPN) had elevated serum Mn and cholestasis with 1 also having a movement disorder. Four of the 11 patients died. Six of these children had MRI of the brain and all showed increased signal intensity in basal ganglia. Howard et al[24]—autopsies on 8 HPN patients showed greatly increased hepatic Mn levels. Takagi et al[25]—whole blood Mn maintained by 55 mcg/d, compared with the 300 to 800 mcg/d provided by the commercially available adult multi-TE products. Fitzgerald et al[26]—15 of 20 patients on parenteral nutrition (PN) containing 500 mcg Mn per day for 36 or more days had elevated red blood cell Mn levels. Wardle et al[27]—whole blood Mn concentration was increased in 26 of 30 patients receiving long-term PN. Takagi et al[28]—whole blood Mn concentration is strongly correlated to MRI intensity in the globus pallidus of the brain. Dickerson[29] and Hardy et al[30]—reviews summarizing many case reports and observational studies of Mn toxicity associated with use of PN that included the commercially available multi-TE products.
Copper (Cu)	Shike et al[31]—balance study in 28 PN patients showed that most patients achieved balance with 0.3 mg/d but 0.4–0.5 mg/d was needed if gastrointestinal losses were high, which is much lower than the 1–1.2 mg/d in the commercially available adult multi-TE products. Plasma Cu did not correlate with Cu balance. Blaszyk et al[32]—89% of in vivo liver biopsies from 28 long-term HPN patients had increased hepatic Cu levels and 29% met criteria for Wilson disease. Howard et al[24]—autopsy tissue from 8 long-term HPN patients showed elevated Cu levels in the liver in 7 patients and 4 patients met the criteria for Wilson disease.
Chromium (Cr)	Moukarzel et al[33,34]—serum Cr 4–40 times higher than normal in adults, children, and infants on long-term PN and associated with decreased glomerular filtration rate in children and infants. Howard et al[24]—autopsy liver, kidney, and heart Cr levels markedly increased. Pluhator-Murton et al[35]—showed Cr major contaminant of PN components. Verhage et al[36]—case report of neurological symptoms suggesting Cr deficiency despite elevated Cr levels in one patient. Ito et al[37]—Cr contamination found in parenteral amino acid solutions, phosphate salts, and lipids. Leung and Galbraith[38]—significantly elevated serum Cr in patients on short-term PN. Cr contamination found mostly in trivalent form and mostly in the amino acid solutions. Mouser et al[39]—elevated serum and urine Cr levels in infants and children receiving long-term PN. Bougle et al[40]—elevated serum and urine Cr in children receiving PN >4 weeks, with significant contamination found in amino acid solution and an electrolyte additive.

MRI, magnetic resonance imaging; PN, parenteral nutrition; TE, trace element.

consequence, adult patients receiving PN, especially those receiving long-term HPN, continue to receive excessive doses of manganese, copper, and chromium, and neonatal and pediatric PN patients continue to receive excessive doses of manganese and chromium.

The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) has taken the leading role in this reformulation task because the Society's central professional focus is safe and effective nutrition support. However, many other disciplines that also rely on safe PN have supported and participated in this effort.

Steps to Implementing the A.S.P.E.N. Micronutrient Recommendations

What does it take to initiate an FDA-mandated change in a commercial product? The steps are as follows:

Step 1: Obtain detailed, up-to-date review of parenteral vitamin, TE, choline, and carnitine nutrient requirements for patients dependent on PN with evidence for deficiency or toxicity with currently available commercial products, recommendations for changes in current products, and delineation of future research priorities.

Step 2: Demonstrate consensus for these recommended micronutrient changes in current products among medical disciplines prescribing PN.

Step 3: Discuss with the micronutrient industry the feasibility of producing safer and more complete parenteral micronutrient products.

Step 4: Present to the FDA the toxicities and inadequacies of the standard micronutrient products available in the U.S.

An update on the progress of each of these steps is described below.

Table 2. Summary of A.S.P.E.N. Recommendations From the Position Paper.[41]

Parenteral multivitamin products:

Meets requirements for most parenteral nutrition (PN) patients. Separate parenteral vitamin D required for patients who on standard therapy continue to be vitamin D depleted and are unresponsive to oral vitamin D supplements.

Parenteral multi-trace element (TE) products:

Adults:

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

Pediatric/neonatal:

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

Parenteral carnitine products:

- No change in the product but should provide 2–5 mg/kg/d to all neonates

Parenteral choline product:

- None currently available; requires commercial development with doses shown below

Adults:

- 550 mg/d

Pediatric/neonatal:

- 0–6 mo: 125 mg/d
- 7–12 mo: 150 mg/d
- 1–3 y: 200 mg/d
- 4–8 y: 250 mg/d
- 9–13 y: 375 mg/d
- >13 y: 550 mg/d

Recommendations for TE contamination in all PN components combined:

- Limit manganese contamination to <40 mcg/d in final PN volume
- Limit copper contamination to <0.1 mg/d in final PN volume

Step 1: Obtain Detailed Review of Vitamins, TE, Choline, and Carnitine Required for Safe and Effective PN With Recommended Changes to Products

This step occurred in 2 stages. First, an A.S.P.E.N. Research Workshop was conducted and the proceedings were published in 2009,[42] and second, an A.S.P.E.N. position paper was published in 2012.[41]

The Research Workshop received financial support from A.S.P.E.N., the National Institutes of Health–National Institute of Diabetes and Digestive and Kidney Diseases (NIH-NIDDK), and the other organizational parties, including the American Gastroenterological Association; European Society for Clinical Nutrition and Metabolism; North American Society for Pediatric Gastroenterology, Hepatology and Nutrition; and the Oley Foundation, which supports persons who live on home parenteral and enteral nutrition. In addition, educational grants were received from the major PN companies. Fourteen nutrients were selected for presentation because they involved new developments or major controversy.[42] Two of these nutrients, choline and carnitine, were not technically vitamins or TEs, but the Food and Nutrition Board of the Institute of Medicine has determined that choline is an essential nutrient in all age groups and carnitine is an essential nutrient in infants.[43,44]

In 2009, following the Research Workshop, A.S.P.E.N. created the Parenteral Vitamin and TE Working Group (WG), which included several of the participants from the Research Workshop. The WG reviewed the published presentations from the Research Workshop and conducted a literature search on the vitamins and TEs not presented during the workshop. This information, along with current vitamin, TE, choline, and carnitine requirements for different age groups, and a compilation of parenteral vitamin and TE products available in the U.S. and outside of the U.S. were published in the A.S.P.E.N. Position Paper in 2012.[41] This paper concluded with A.S.P.E.N.'s recommended changes in commercial parenteral multivitamin, multi-TE, choline, and carnitine products (Table 2) and A.S.P.E.N.'s research recommendations (Table 3). It should be noted that the parenteral chromium requirement was the research topic with the highest priority. After publication of the position paper, some typographical errors were identified (Appendix 1); however, none of these errors significantly affected A.S.P.E.N.'s recommendations.

Table 3. A.S.P.E.N.'s Future Research Recommendations in Order of Priority.[41]

1. Parenteral chromium requirements in adult, pediatric, and neonatal parenteral nutrition (PN) patients
2. Research and development of appropriate monitoring strategies for trace element (TE) and vitamin deficiency and toxicity in PN patients
3. Studies on TE contamination of PN products need to be updated, particularly manganese and chromium contamination of neonatal and pediatric formulas
4. Feasibility of adding parenteral iron to PN formulas to include fat emulsion stability and other potential incompatibilities
5. Benefits of carnitine supplements of PN in adult and pediatric patients
6. Benefits of fluoride supplementation of PN in all age groups
7. Benefit of iodide supplementation of PN in all age groups

Even though vitamin D is included in all of the parenteral multivitamin products, vitamin D deficiency unresponsive to oral supplementation has been reported in long-term HPN patients,[45-48] which is why A.S.P.E.N. recommended that a separate parenteral vitamin D product needs to be available.[41] Also, a parenteral choline product needs to be available because it is considered an essential nutrient in all age groups and is not currently being provided to HPN patients unable to tolerate any oral intake.[41,44]

A.S.P.E.N.'s recommendations for changes in the neonatal, pediatric, and adult multi-TE products available in the U.S. are compared with the content of these products (Tables 4, 5, and 6). The neonatal and pediatric multi-TE products have to be compared on per kg/d dosing based on the fixed concentrations within the product. Since there are significant differences between published recommended TE requirements in neonatal and pediatric patients (Table 7), the WG feels that a more in-depth and comprehensive review of the medical literature by neonatal and pediatric experts is warranted.

Step 2: Develop National Consensus on the Parenteral Micronutrient Changes Advocated by A.S.P.E.N.

The A.S.P.E.N. Research Workshop[42] was attended by representatives from the FDA, NIH-NIDDK, and the organizational partners. The audience also included scientists from the major parenteral nutrient industry and clinicians managing large PN programs. The workshop received international attention because parenteral vitamin, TE, choline, and carnitine requirements are an issue in all countries using PN, especially long-term HPN. The published 2009 workshop proceedings[42] were sent to all attendees. The A.S.P.E.N. Position Paper[41] was distributed to the FDA, the parenteral nutrient companies, and clinical organizations with members who frequently prescribe, formulate, or supervise PN patients. Table 8 lists those organizations that endorsed or supported the A.S.P.E.N. Position Paper. There appears to be a global consensus on the issue regarding the excessive doses of manganese, copper, and chromium in the previously available multi-TE products, as well as the need for availability of parenteral vitamin D and choline products.

Step 3: Discuss the Feasibility of Producing Safer and More Complete Parenteral Micronutrient Products With the Parenteral Micronutrient Industry

In response to the A.S.P.E.N. Position Paper sent to the parenteral nutrient companies, several companies have requested further information and discussions with the WG regarding the recommended changes to the multi-TE products, as well as the development of separate parenteral vitamin D and choline products. Since publication of the position paper, 2 new adult multi-TE products have become available in Europe that meet the A.S.P.E.N.-recommended changes for manganese, copper, and chromium (Table 9). However, most European multi-TE products contain several TEs that are not in the standard products available in the U.S., notably iron, molybdenum, iodide, and fluoride. European PN specialists have used this expanded formula for many years and have not experienced adverse effects. In the U.S., permanent adoption of an expanded formula requires additional stability studies, particularly in iron and lipid mixtures. Studies are also needed to evaluate if some of these TEs are already present as contaminants.

There are ongoing discussions between A.S.P.E.N. and some of the parenteral micronutrient companies regarding reformulation of current products available in the U.S. or future products. Several companies are interested in developing a safer parenteral multi-TE product that meets A.S.P.E.N.'s recommendations. While this is A.S.P.E.N.'s immediate goal, a long-term goal is to consider a more expanded formula if research shows it to be safe and appropriate. A universal multi-TE product is a rational concept; furthermore, such expansion would provide a larger market with wider commercial interest and hopefully greater stability of product availability.

Step 4: Present the Toxicity and Inadequacies of the Standard Micronutrient Products Available in the U.S. to the FDA

From the start of this effort in 2009, the FDA has been included in A.S.P.E.N.'s review process of parenteral vitamin, TE, choline, and carnitine requirements and products. In the past several years, there have been serious shortages in the U.S. of

Table 4. Comparison of Adult Multi-Trace Element Products Available in the U.S. and A.S.P.E.N.-Recommended Changes.[41]

	MULTI-TE PRODUCTS AVAILABLE IN U.S.				TEMPORARY U.S. IMPORTATION*
Trace Elements	Multitrace-4/-5® (MTE4/5) (3 mL daily dose)	Multitrace-4/-5 (MTE4/5) Concentrate® (1 mL daily dose)	4-Trace Elements® (5 mL daily dose)	A.S.P.E.N. Recommendations	Addamel N® (10 mL daily dose)
Zinc (Zn)	3 mg	5 mg	4 mg	No changes (3–5 mg)**	6.5 mg
Copper (Cu)	1.2 mg	1 mg	1mg	Decrease to 0.3–0.5 mg	1.3 mg
Manganese (Mn)	0.3 mg	0.5 mg	0.8 mg	Decrease to maximum of 0.055 mg	0.27 mg
Chromium (Cr)	12 mcg	10 mcg	10 mcg	10 mcg sufficient for most patients but need product without Cr for patients prone to Cr toxicity	10 mcg
Selenium (Se)	0 mcg (MTE4) 60 mcg (MTE5)	0 mcg (MTE4) 60 mcg (MTE5)	0 mcg	60–100 mcg (dose higher than 60 mcg preferred)	32 mcg
Iron (Fe)	—	—	—	Routine supplementation of PN could be beneficial, but more research is needed especially with lipid containing PN	1.1 mg
Molybdenum (Mo)	—	—	—	Insufficient data to recommend routine administration	19 mcg
Iodide (I)	—	—	—	Routine supplementation of PN could be beneficial, but more research is needed	130 mcg
Fluoride (F)	—	—	—	Routine supplementation of PN could be beneficial, but more research is needed	950 mcg
Vial size	10-mL multi-dose vials	1-mL single and 10-mL multi-dose vials	5-mL single and 50-mL multi-dose vials	—	10-mL single dose
Manufacturer	American Regent (Shirley, NY)	American Regent (Shirley, NY)	Hospira (Lake Forest, IL)	—	Fresenius Kabi(Lake Zurich, IL)

A.S.P.E.N., American Society for Parenteral and Enteral Nutrition; FDA, U.S. Food and Drug Administration; PN, parenteral nutrition; TE, trace elements; U.S., United States.
*5/29/2013 FDA granted temporary importation due to a shortage of multi-TE products.
**A.S.P.E.N. recommendations in the original position paper were for no changes in the standard products available in the U.S., which as shown in this table was 3–5 mg/day.

many PN components, and this has been especially true for parenteral multi-TE products. In 2013, A.S.P.E.N. worked with the FDA to select European multi-TE adult (Addamel N) and pediatric (Peditrace) products that were approved by the FDA in May 2013 for temporary importation to help with these shortages. Unfortunately, the newer European multi-TE products shown in Table 9 were not yet available at that time. The adult imported product, Addamel N, does not meet A.S.P.E.N.'s recommendations (Table 4). The neonatal/pediatric imported product, Peditrace, meets the A.S.P.E.N. recommendations regarding decreased amounts of manganese and chromium and addition of the recommended dose of selenium; however, it also contains iodide and fluoride (Tables 5 and 6). The WG continues to discuss with the FDA the implementation of the A.S.P.E.N.–recommended changes so that safer PN component products become available for our patients.

Summary

The efforts of the A.S.P.E.N. Parenteral Vitamin and TE WG and others have resulted in the development of new multi-TE products in Europe, and hopefully these products and other

Table 5. Comparison of Pediatric/Neonatal Multi-Trace Element Products Available in the U.S. and the A.S.P.E.N.–Recommended Changes.[41]

	MULTI-TE PRODUCTS AVAILABLE IN U.S. (Manufacturer Dosing Recommendations)				TEMPORARY U.S. IMPORTATION*
Trace Elements	Multitrace-4 Neonatal® (per 1 mL)	Multitrace-4 Pediatric® (per 1 mL)	Trace Elements Injection 4, USP-Pediatric® (per 1 mL)	A.S.P.E.N. Recommendations	Peditrace® (per 1 mL)
Zinc (Zn)	1.5 mg (0.1 mg/kg/d, 0.3 mg/kg/d premature infants <3 kg)	1 mg (0.1 mg/kg/d)	0.5 mg (0.1 mg/kg/d)	No changes (0.3 mg/kg/d premature infants <3 kg and 0.1 mg/kg/d for infants/children >3 kg)**	0.25 mg (0.25 mg/kg/d ≤15 kg 3.75 mg/d >15 kg)***
Copper (Cu)	0.1 mg (0.02 mg/kg/d)	0.1 mg (0.02 mg/kg/d)	0.1 mg (0.02 mg/kg/d)	0.02 mg/kg/d	0.02 mg (0.02 mg/kg/d ≤15 kg 0.3 mg/d >15 kg)***
Manganese (Mn)	25 mcg (2–10 mcg/kg/d)	25 mcg (2–10 mcg/kg/d)	30 mcg (2–10 mcg/kg/d)	Decrease to 1 mcg/kg/d in neonates with maximal daily dose in pediatrics to 55 mcg/day	1 mcg (1 mcg/kg/d ≤15 kg 15 mcg/d >15 kg)***
Chromium (Cr)	0.85 mcg (0.14–0.20 mcg/kg/d)	1 mcg (0.14–0.20 mcg/kg/d)	1 mcg (0.14–0.20 mcg/kg/d)	Reduce dose to values shown in Table 6 and have product available without Cr for patients at increased risk of toxicity	0 mcg
Selenium (Se)	0 mcg	0 mcg	0 mcg	Add with dose of 2 mcg/kg/d	2 mcg (2 mcg/kg/d ≤15 kg 30 mcg/d >15 kg)***
Iron (Fe)	—	—	—	Routine supplementation of PN could be beneficial, but more research is needed especially with lipid-containing PN	—
Molybdenum (Mo)	—	—	—	Insufficient data to recommend routine administration	—
Iodide (I)	—	—	—	Routine supplementation of PN could be beneficial, but more research is needed	1 mcg (1 mcg/kg/d ≤15 kg 15 mcg/d >15 kg)***
Fluoride (F)	—	—	—	Routine supplementation of PN could be beneficial, but more research is needed	57 mcg (57 mcg/kg/d ≤15 kg 855 mcg/d >15 kg)***
Vial size	2-mL vials	3-mL vials	10-mL multi-dose vials	—	10-mL vials
Manufacturer	American Regent (Shirley, NY)	American Regent (Shirley, NY)	American Regent (Shirley, NY)	—	Fresenius Kabi (Lake Zurich, IL)

A.S.P.E.N., American Society for Parenteral and Enteral Nutrition; FDA, U.S. Food and Drug Administration; PN, parenteral nutrition; TE, trace element; U.S., United States.
*5/29/2013 FDA granted temporary importation due to a shortage of multi-TE products.
**A.S.P.E.N. did not recommend any changes to the multi-TE products available in the U.S., and as shown in this table, the available products recommend 0.3 mg/kg/d for premature infants <3 kg and 0.1 mg/kg/d for infants and children ≥3 kg.
***Manufacturer dosing recommendations are 1 mL Peditrace/kg/d for infants and children with weight up to 15 kg and 15 mL daily for children >15 kg.

Table 6. A.S.P.E.N.–Recommended Changes in Chromium Doses for Neonatal and Pediatric Patients.[41]

Age	Male	Female
0–6 months	0.0006 mcg/kg/day	
7–12 months	0.012 mcg/kg/day	
1–3 years	0.22 mcg/day	
4–8 years	0.30 mcg/day	
9–13 years	0.5 mcg/day	0.42 mcg/day
14–18 years	0.7 mcg/day	0.48 mcg/day

A.S.P.E.N., American Society for Parenteral and Enteral Nutrition. Adapted from Moukarzel A, Chromium in parenteral nutrition: too little or too much? *Gastroenterology*, 2009;137(5)(suppl):S18–S28, with permission from Elsevier.

Table 7. Comparison of Different Recommendations for Trace Element Requirements in Pediatric/Neonatal Patients.

Trace Elements	ASCN (Greene) 1988[49]	ESPGHAN (Koletzko) 2005[50]	A.S.P.E.N. Recommendations 2012[41]	Domellof 2014[51]
Zinc (Zn)	• Pre-term: 0.4 mg/kg/d • Term infant to <3 mo: 0.25 mg/kg/d • Infant >3 mo: 0.1 mg/kg/d • Child: 0.05 mg/kg/d	• Pre-term: 0.45–0.50 mg/kg/d • Term infant to <3 mo: 0.25 mg/kg/d • Infant >3 mo: 0.1 mg/kg/d • Child: 0.05 mg/kg/d	No changes (0.3 mg/kg/d premature infants <3 kg and 0.1 mg/kg/d for infants/children >3 kg)*	Pre-term: 0.4 mg/kg/d**
Copper (Cu)	0.02 mg/kg/d	0.02 mg/kg/d	0.02 mg/kg/d	Pre-term: 0.04 mg/kg/d**
Manganese (Mn)	1 mcg/kg/d	1 mcg/kg/d in neonates with maximal daily dose in pediatrics to 55 mcg/day	1 mcg/kg/d in neonates with maximal daily dose in pediatrics to 55 mcg/day	Pre-term: 1 mcg/kg/d**
Chromium (Cr)	0.20 mcg/kg/d	0 mcg/kg/d (contamination providers sufficient amount)	Reduce dose to values shown in Table 6 and have product available without chromium for patients at increased risk of toxicity	Pre-term: 0.05–0.3 mcg/kg/d**
Selenium (Se)	2 mcg/kg/d	LBW infants: 2–3 mcg/kg/d	2 mcg/kg/d	Pre-term: 5–7 mcg/kg/d**
Iron (Fe)	Lack of compatibility data	<3 weeks: PN, no Fe >3 weeks: PN should supplement Fe with: • Pre-term: 200 mcg/kg/d • Infants/Child: 50–100 mcg/kg/d	Routine supplementation of PN could be beneficial, but more research is needed especially with lipid containing PN	Pre-term: 0–0.25 mg/kg/d**
Molybdenum (Mo)	0.25 mcg/kg/d	• LBW infant: 1 mcg/kg/d • Infants/child: 0.25 mcg/kg/d (max 5 mcg/d)	Insufficient data to recommend routine administration	Pre-term: 0.25 mcg/kg/d**
Iodide (I)	1 mcg/kg/d	1 mcg/kg/d	Routine supplementation of PN could be beneficial, but more research is needed	Pre-term: 10 mcg/kg/d**
Fluoride (F)	No firm recommendations. Infants on PN >3–6 mo, consider F 500 mcg/d	Not mentioned so no recommendations	Routine supplementation of PN could be beneficial, but more research is needed	Not mentioned so no recommendations

ASCN, American Society for Clinical Nutrition; A.S.P.E.N., American Society for Parenteral and Enteral Nutrition; ESPGHAN, European Society of Paediatric Gastroenterology, Hepatology and Nutrition; LBW, low birth weight; PN, parenteral nutrition.
*A.S.P.E.N. did not recommend any changes to the multi-TE products available in the United States, and as shown in Table 5, these products recommend 0.3 mg/kg/d for premature infants <3 kg, and 0.1 mg/kg/d for infants and children >3 kg.
**Author notes that these are "approximate values" and the iodide recommendation assumes no use of iodide-containing antiseptics.

Table 8. Endorsements or Support of the "A.S.P.E.N. Position Paper: Recommendations for Changes in Commercially Available Parenteral Multi-Vitamin and Multi-Trace Element Products."[41]

Organizations	Response
Society of Critical Care Medicine (SCCM)	Endorsed
American Society of Health-System Pharmacists (ASHP)	Endorsed
American Academy of Pediatrics (AAP)	Endorsed
American Society for Nutrition (ASN)	Offered organizational support
Academy of Nutrition and Dietetics Dietitians in Nutrition Support Dietetic Practice Group (AND/DNSDPG)	Adopted position paper
The European Society for Clinical Nutrition and Metabolism (ESPEN)	Partial endorsement*

*Endorsed the amounts recommended for provision of vitamins, the trace elements zinc, copper, selenium, and manganese, and the need for more research on the provision of iron, chromium, iodide, and fluoride; but could not endorse the recommendations that there is insufficient evidence to provide iron, chromium, molybdenum, iodide, and fluoride in the multi-trace element (TE) products as currently all of these trace elements are included in the multi-TE products available in Europe.

Table 9. Comparison of New Adult Multi-TE Products in Europe (not FDA Approved) and A.S.P.E.N. Recommendations for Multi-TE Products.[41]

		New Unapproved Products	
Trace Elements	A.S.P.E.N. Recommendations (daily dose)	Addaven® (10 mL daily dose)	Nutryelt® (10 mL daily dose)
Zinc (Zn)	No changes (3–5 mg)*	5 mg	10 mg
Copper (Cu)	Decrease to 0.3–0.5 mg	0.4 mg	0.3 mg
Manganese (Mn)	Decrease to maximum of 0.055 mg	0.055 mg	0.055 mg
Chromium (Cr)	10 mcg sufficient for most patients but need product without Cr for patients prone to Cr toxicity	10 mcg	10 mcg
Selenium (Se)	60–100 mcg (dose higher than 60 mcg preferred)	80 mcg	70 mcg
Iron (Fe)	Routine supplementation of PN could be beneficial, but more research is needed especially with lipid containing PN	1.1 mg	1 mg
Molybdenum (Mo)	Insufficient data to recommend routine administration	19 mcg	20 mcg
Iodide (I)	Routine supplementation of PN could be beneficial, but more research is needed	130 mcg	130 mcg
Fluoride (F)	Routine supplementation of PN could be beneficial, but more research is needed	950 mcg	950 mcg
Vial size	—	10-mL single dose	10-mL single dose
Manufacturer	—	Fresenius Kabi (Lake Zurich, IL)	Laboratoire Aguettant (Saint-Fons, France)

A.S.P.E.N., American Society for Parenteral and Enteral Nutrition; FDA, United States Food and Drug Administration; PN, parenteral nutrition; TE, trace element.
*A.S.P.E.N. recommendations in the original position paper were for no changes in the products currently available in the United States that contained 3–5 mg zinc/day (see Table 4).

reformulated or new products that meet the A.S.P.E.N. recommendations will be submitted for FDA approval soon. A.S.P.E.N. will continue to work with the FDA and industry regarding the development of safer parenteral nutrient products.

Appendix 1: Errors in the Original Position Paper

The original position paper[1] had several typographical errors discovered after publication that are listed below. However, none of these errors significantly affected A.S.P.E.N.'s recommendations.

1. Table 7 titled "Current Parenteral and Enteral Vitamin and Trace Element Recommendations for Preterm and Term Neonates": the cell for vitamin B_{12} under the "Preterm Neonates: Enteral" column incorrectly listed a value of 9.3 mcg/kg/d. The correct value is 0.3 mcg/kg/d. The correct table appears in a published Corrigendum.[2]
2. Table 4 titled "Current Recommended Adult Daily Oral and Parenteral Micronutrient Requirements": error in the table footnotes. Footnotes (b) and (c) should be combined into one footnote (ie, (b) [see

below], and pertains to Vitamin A; footnote (c) pertains to Vitamin D and should have read as shown below):

[b]1 mcg RAE (retinol activity equivalent) = 1 mcg retinol = 12 mcg β-carotene = 24 mcg α-carotene or β-cryptoxanthin. 1 IU of retinol = 0.3 mcg retinol or 0.3 mcg RAE.
[c]1 mcg cholecalciferol = 40 IU vitamin D

3. Table 7 titled "Current Parenteral and Enteral Vitamin and Trace Element Recommendations for Preterm and Term Neonates": parenteral iron requirement for pre-term neonates was listed as 100–200 mcg/kg/d and for term neonates 250–670 mcg/kg/d, and do not need to give until after 2 months on PN. After further review of the reference used for this table,[3] the parenteral iron requirement for term neonates should be about 100 mcg/kg/d but should not be necessary before age 3 months, and the requirement for pre-term neonates is about double that, 200 mcg/kg/d, and should not be started before 2 months of age or weight has reached 2000 g.
4. Table 7 titled "Current Parenteral and Enteral Vitamin and Trace Element Recommendations for Preterm and Term Neonates": parenteral copper requirement for pre-term neonates was listed as 29 mcg/kg/d due to a typo and instead should be 20 mcg/kg/d.[3]
5. Inconsistencies in discussion and presentation of parenteral chromium requirements and dosing in neonates and pediatric patients: on page 454 of the position paper,[1] there was a sentence that stated the neonatal and pediatric multi-trace element (TE) products available in the United States provided 0.05–0.2 mcg/d. This was not an accurate statement as the daily dose provided by the product depended on the concentration of the TE in the product and how much of the product was given based on the per kg dosing recommendations for the product. Tables 6 and 7 of the original position paper,[1] showed the recommended daily parenteral dose of chromium at that time to be 0.05–0.3 mcg/kg/d for pre-term neonates, 0.2 mcg/kg/d for term neonates, 0.2 mcg/kg/d (to maximum of 5 mcg/d) for infants, and 0.2 mcg/kg/d (to maximum of 5 mcg/d) for children. A.S.P.E.N.'s recommendation in the position paper[1] was to decrease the chromium doses to the levels proposed by Moukarzel during his presentation at the 2009 A.S.P.E.N. Micronutrient Research Workshop,[4] which is shown in Table 6 of the current paper.
6. Error in description of the Pluhator-Murton study[5]: on page 453, it was stated "According to Pluhator-Murton et al's data,[62] 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." In reviewing the Pluhator-Murton study,[5] the expected amount of chromium in the 2-L parenteral nutrition (PN) solution was 11 mcg and the calculated amount was 26 mcg, resulting in contamination accounting for 15 mcg of chromium. This chromium contamination came from multiple, different PN components including dextrose, amino acids, potassium chloride, calcium gluconate, and the multi-TE products. However, it was unclear of the exact contribution of each of these components toward the chromium contamination. Lastly, the 26 mcg/day of chromium that this 2-L PN would have provided was about 2½ times the daily recommended dose of 10 mcg/day, not 30–60 times.

Appendix References

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