

## Review Article

# Australasian Society for Parenteral and Enteral Nutrition guidelines for supplementation of trace elements during parenteral nutrition

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**Background:** This work represents the first part of a progressive review of AuSPEN's 1999 Guidelines for Provision of Micronutrient Supplementation in Adult Patients receiving Parenteral Nutrition, in recognition of the developments in the literature on this topic since that time. **Methods:** A systematic literature review was undertaken and recommendations were made based on the available evidence and with consideration to specific elements of the Australian and New Zealand practice environment. The strength of evidence underpinning each recommendation was assessed. External reviewers provided feedback on the guidelines using the AGREE II tool. **Results:** Reduced doses of manganese, copper, chromium and molybdenum, and an increased dose of selenium are recommended when compared with the 1999 guidelines. Currently the composition of available multi-trace element formulations is recognised as an obstacle to aligning these guidelines with practice. A paucity of available literature and limitations with currently available methods of monitoring trace element status are acknowledged. The currently unknown clinical impact of changes to trace element contamination of parenteral solutions with contemporary practices highlights need for research and clinical vigilance in this area of nutrition support practice. **Conclusions:** Trace elements are essential and should be provided daily to patients receiving parenteral nutrition. Monitoring is generally only required in longer term parenteral nutrition, however should be determined on an individual basis. Industry is encouraged to modify existing multi-trace element solutions available in Australia and New Zealand to reflect changes in the literature outlined in these guidelines. Areas requiring research are highlighted.

**Key Words:** trace elements, guidelines, parenteral nutrition, manganese, selenium

## INTRODUCTION

Trace elements (TEs) are present in minute amounts in body tissues and are essential for optimum human growth, health and development.<sup>1</sup> Generally a varied diet will provide adequate TEs, notwithstanding geographical variations in availability. While enteral feeding products and oral supplements include sufficient TEs to ensure nutritional completeness, parenteral nutrition (PN) solutions do not due to chemical stability considerations. TEs need to be added to PN admixtures separately closer to the time of administration using commercially available multi-TE solutions or through compounding individual TE combinations to meet individual clinical requirements.

In 1999 AuSPEN published "Guidelines for Intravenous Trace Elements and Vitamins".<sup>2</sup> The current work represents a review of these guidelines with reference to

the newer information in this field in the ensuing years.

### Scope of guidelines

The guidelines are designed for Australian and New Zealand (NZ) clinicians prescribing and monitoring PN to patients >15 years old. They are intended to provide guidance for the prescription of maintenance doses of TEs for patients receiving PN in accordance with the

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available evidence. Monitoring and clinical judgment are required for tailoring TE prescriptions for PN patients with acute or co-morbid conditions that may predispose them to greater TE losses and/or higher TE requirements.

A secondary purpose of this guideline is to provide a base from which to advocate to industry to modify the currently available multi-TE preparations to reflect the best available evidence and ensure patient safety. This is an important and necessary step required to enable safe and evidence based PN practice in Australia and NZ.

These guidelines do not attempt to address enteral TE requirements or to provide a comprehensive review of the biological roles, dietary sources or deficiency and toxicity states of each TE.

### Definitions

“Short term” PN is considered to be that of <20 days duration (i.e. acute intestinal failure). “Longer term” PN is that required for an extended duration (>20 days, such as those with or transitioning into chronic intestinal failure<sup>3</sup>) and this may be provided during an acute and/or prolonged hospital admission. Home PN (HPN) patients are defined as those requiring “longer term” PN, who are generally medically stable and who would usually receive PN in a community setting.

The term Total Parenteral Nutrition (TPN) is intentionally avoided in these guidelines, in recognition that many patients receiving PN will continue some level of oral intake however the adequacy due to limitations on amount tolerated or secondary to altered anatomy necessitate the need for PN to maintain their nutritional status.

### METHODS

A multidisciplinary group of AuSPEN members with recognised experience in PN provision and/or guidelines development was convened in 2013 to review the 1999 guidelines document. A stepwise review was undertaken (in recognition of the need to provide timely guidance regarding TE recommendations given the changing evidence base underpinning the practice of longer term PN patients): the review of vitamin provision in adults and micronutrient supplementation in paediatrics will follow.

In accordance with the AGREE II tool for guideline development and review,<sup>4</sup> and AuSPEN’s guidelines for guideline development,<sup>5</sup> focused clinical questions pertaining to the provision of TEs in PN support were formulated. The references underpinning the 2012 ASPEN Position Paper on Micronutrient provision were used as the basis for answering the clinical questions posed.<sup>6</sup> Further literature searches covering 2009 to 2013 were conducted for each clinical question. Search terms including the TE and key words from each clinical question were utilised in electronic search engines (Pubmed, CINAHL), using MeSH terms and Boolean search strategies.

The available information was interpreted with reference to the known environmental factors that may impact the baseline TE status of the Australian and NZ population<sup>7,8</sup> and recommendations appropriate to local clinical practice were made.

The strength of evidence underpinning each recommendation was evaluated using the “NHMRC Levels of Evidence and Grades for Recommendations for Develop-

ers of Guidelines”.<sup>9</sup> The level of evidence of each study was assessed as I (highest) to IV (lowest). The body of evidence for each clinical question was assessed and received a grade A (highest), B, C or D (lowest) depending on the strength of evidence available and its applicability to the Australian and NZ context.

The draft guideline was piloted and reviewed using a non-structured approach within the guidelines review committee. Internationally recognised experts in the field of micronutrients (Mette Berger and Alan Shenkin) were sought for their critical appraisal of and input into the guidelines through feedback and application of the AGREE II tool.<sup>4</sup> Multidisciplinary Australian and NZ clinicians with experience in PN provision also provided peer review using the AGREE II framework.<sup>4</sup> Feedback was incorporated into a further revision of the guidelines. The final guideline was approved by members of the guideline development group and AuSPEN Council. A planned review of the guideline is scheduled in 5 years’ time (2019).

### RECOMMENDATIONS

The clinical question underpinning the recommendations for each TE is ‘How should TE requirements be prescribed and monitored for patients on short term and longer term PN (including HPN) to ensure adequate intake to meet individual patient needs and minimise metabolic complications?’ A summary of the recommendations is summarised in Table 1.

#### Zinc (Zn)

A wide range of Zn requirements have been described owing to significant variation in gastrointestinal (GI) or cutaneous losses in various clinical situations. In stable PN patients, 45-60 µmol (2.9-3.9 mg)/day Zn supplementation has been recommended.<sup>6,10-12</sup> In PN patients without diarrhoea, 38 µmol (1.7 mg)/day has been proposed as a minimum safe level.<sup>11</sup> Patients with significant GI losses, such as those with short bowel syndrome (SBS) or high output enterocutaneous fistulae, may require increased Zn provision of up to 183 µmol (12 mg)/d per litre of GI fluid loss.<sup>13</sup> Patients with poor wound healing or major burns<sup>6,10</sup> have elevated Zn requirements and have been shown to tolerate short term Zn supplementation up to 550 µmol (36 mg)/day without toxicity.<sup>14</sup> The possibility of significant Zn losses in HPN patients via perspiration in humid parts of Australia and in the summer months should be considered. Zn toxicity is rare and has only been documented in cases of large dosage errors in amounts >765 µmol (>50 mg)/day.<sup>15</sup> Deficiency is rare and only seen in patients with prolonged Zn deprivation.<sup>14</sup> The currently available TE PN additives in Australia and NZ deliver Zn in a range from 46-100 µmol (3.0-6.5 mg)/day when given at the recommended dose. AuSPEN recommends routine Zn supplementation of 50-100 µmol (3.2-6.5 mg)/day in short and longer term and HPN recipients, but recognizes the broad variation in requirements within the PN population.

Plasma Zn levels are influenced by acute phase response (APR) and therefore decrease in trauma, infection and stress.<sup>11,14</sup> As such serum Zn levels should be interpreted in context of C-reactive protein (CRP) levels.

**Table 1.** Summary of trace element recommendations for PN

	What is the safe and adequate daily supplementation for short term PN?	What is the safe daily and adequate supplementation for longer term PN, incl HPN?	Are there any conditions in which higher supplementation should be considered?	Are there any conditions in which reduced supplementation should be considered?	Considerations for TE monitoring	Standard assay
Zinc (Zn)	50-100 $\mu\text{mol}$ (3.2-6.5 mg)	50-100 $\mu\text{mol}$ (3.2-6.5 mg)	Significant GI losses (diarrhoea, SBS), high output fistulae etc); major (>20% TBSA) burns	No	Plasma Zn levels will be influenced by the presence of APR, and therefore will decrease during trauma, infection and inflammation. There is insufficient evidence to recommend monitoring in longer term and HPN patients, however monitoring frequency will need to be determined based on volume of extra-renal losses (ie diarrhoea, fistula output, burns exudates, etc)	Serum Zn CRP <sup>†</sup>
Copper (Cu)	5-8 $\mu\text{mol}$ (317-508 $\mu\text{g}$ )	5-8 $\mu\text{mol}$ (317-508 $\mu\text{g}$ )	History of gastric bypass surgery; increased GI losses, >20% TBSA burns, CRRT	PN related cholestasis	Serum Cu and ceruloplasmin levels are commonly measured but these are not a reliable marker of Cu deficiency in the presence of an APR. Monitoring should be based on individual clinical indications – no recommendations for routine monitoring.	Serum Cu Ceruloplasmin CRP <sup>†</sup>
Selenium (Se)	0.75-1.25 $\mu\text{mol}$ (60-100 $\mu\text{g}$ ) <i>NHMRC Grade C</i>	0.75-1.25 $\mu\text{mol}$ (60-100 $\mu\text{g}$ ) <i>NHMRC Grade C</i>	Critical illness; >20% TBSA Burns, CRRT	No	Serum Se; RBC GPx as a functional measure of Se status; erythrocyte Se concentration. <i>NHMRC Grade C</i>	RBC GPx Serum Se CRP <sup>†</sup> RBC Se

## Adult (&gt;15 years)

These recommendations represent *maintenance* doses for otherwise stable patients receiving PN. Those with elevated needs during acute illness or those with comorbidities or other clinical considerations that require higher replacement doses need to be assessed and prescribed TEs appropriate for their individual clinical situation.

<sup>†</sup>In TEs that are affected by APR changes, a CRP level should be assayed concurrently with TE levels to provide a measure of context in which to interpret the TE levels obtained (ie if an APR is impacting on the TE levels assayed).

APR: acute phase response; CRP: C-reactive protein; CRRT: continuous renal replacement therapy; FBC: full blood count; GI: gastrointestinal; GPx: glutathione peroxidase; HPN: home parenteral nutrition; PN: parenteral nutrition; RBC: red blood cell; SBS: short bowel syndrome; TBSA: total body surface area.

n/a: not applicable

**Table 1.** Summary of trace element recommendations for PN (cont.)

	What is the safe and adequate daily supplementation for short term PN?	What is the safe daily and adequate supplementation for longer term PN, incl HPN?	Are there any conditions in which higher supplementation should be considered?	Are there any conditions in which reduced supplementation should be considered?	Considerations for TE monitoring	Standard assay
Manganese (Mn)	1 µmol (55 µg)	1 µmol (55 µg) <i>NHMRC Grade C</i>	No	Demonstrated hypermanganesaemia	Serum or Blood Mn levels; Monitoring three to six monthly in HPN patients; Monitoring is unnecessary in short term PN.	RBC Mn Serum Mn CRP <sup>†</sup>
Iron (Fe)	20 µmol (1.1 mg) may not be necessary	20 µmol (1.1 mg)	Conditions predisposing to Fe deficiency: ie Crohn's Disease, menstrual losses, SBS, those with repeated blood loss via blood tests.	Haemochromatosis	FBC; ferritin; transferrin No recommendations re frequency in monitoring – as clinically indicated <i>NHMRC Grade B</i>	FBC Ferritin Transferrin  In the critically ill only: hepcidin
Chromium (Cr)	0.2-0.3 µmol (10-15 µg) may not be necessary	0.2-0.3 µmol (10-15 µg)	Pregnant PN recipients	Renal impairment	No reliable marker of Cr status.	n/a
Molybdenum (Mo)	0.2 µmol (19 µg) probably not necessary	0.2 µmol (19 µg)	No	No	No reliable marker of Mo status. Monitoring generally not required/recommended	n/a
Iodine (I)	1 µmol (130 µg)	1 µmol (130 µg)	No	No	Thyroid size, serial thyroid function tests (TSH, free T4) as clinically indicated. Monitoring at baseline and as clinical indicated thereafter.	TSH T4

**Adult (>15 years)**

These recommendations represent *maintenance* doses for otherwise stable patients receiving PN. Those with elevated needs during acute illness or those with comorbidities or other clinical considerations that require higher replacement doses need to be assessed and prescribed TEs appropriate for their individual clinical situation.

<sup>†</sup>In TEs that are affected by APR changes, a CRP level should be assayed concurrently with TE levels to provide a measure of context in which to interpret the TE levels obtained (ie if an APR is impacting on the TE levels assayed).

APR: acute phase response; CRP: C-reactive protein; CRRT: continuous renal replacement therapy; FBC: full blood count; GI: gastrointestinal; GPx: glutathione peroxidase; HPN: home parenteral nutrition; PN: parenteral nutrition; RBC: red blood cell; SBS: short bowel syndrome; TBSA: total body surface area.

n/a: not applicable

There is insufficient evidence regarding the frequency of monitoring Zn in PN patients. Each patient should have individual clinical symptoms and co-morbid physiological state (i.e. GI losses, hypercatabolism).<sup>11</sup>

### **Copper (Cu)**

Cu deficiency is rare, although has been described in prolonged PN provision in the absence of Cu supplementation,<sup>16</sup> those with a history of gastric resectional or bypass surgery,<sup>17,18</sup> exudative stages of major burns,<sup>19,20</sup> and critically ill patients with prolonged continuous dialysis.<sup>21,22</sup> Patients with significant gastrointestinal losses including diarrhoea may require 6.3-7.8  $\mu\text{mol}$  (400-495  $\mu\text{g}$ )/day to replace losses.<sup>6,14,23</sup> Cu toxicity is rare in humans<sup>23</sup> however excess Cu, which is concentrated in brain, kidney and liver, may cause harmful effects in longer term PN patients in the presence of PN associated cholestasis. In these patients the dose may be reduced to 2.4  $\mu\text{mol}$  (150  $\mu\text{g}$ )/day.<sup>6,14,23</sup> The currently available TE PN additives in Australia and NZ deliver Cu in a range from 6-20  $\mu\text{mol}$  (0.4-1.3 mg)/day when given at the recommended dose. AuSPEN recommends Cu supplementation of 5-8  $\mu\text{mol}$  (317-508  $\mu\text{g}$ )/day, which represents a reduction from the 1999 AuSPEN recommendations.

Serum Cu and ceruloplasmin levels are often elevated in APR, pregnancy, liver disease, malignancy and post myocardial infarction, therefore cannot be considered as a reliable marker of Cu deficiency in these circumstances.<sup>6,14,23,24</sup> CRP levels should be measured concurrently with Cu levels in order to provide a context for interpreting the presence of APR. Low plasma levels, on the other hand, can be considered a reliable measure of deficiency, although have been shown to be low only in very severe deficiency.<sup>24</sup>

It is recommended that requirements be reassessed periodically and adjustments made based on individual clinical requirements.<sup>23</sup>

### **Selenium (Se)**

Prior to 1990 low levels of Se in soils in NZ and in parts of Australia resulted in dietary intakes and Se status lower than in many other countries. This has since improved but Se status remains lower than in many other countries.<sup>8,25</sup> The importance of this in relation to provision of Se in PN remains unclear.

Se intake of 1  $\mu\text{mol}$  (80  $\mu\text{g}$ )/day is thought to be adequate to maintain tissue concentrations in most HPN patients.<sup>26</sup> Short term PN requirements are less certain but many patients will have increased requirements if they have ongoing or concurrent disease or are post-surgical because of increased metabolic and antioxidant needs.<sup>27</sup> Patients who are critically ill, septic, receiving continuous dialysis and/or have major burns may benefit from higher doses of Se as PN supplementation alone or in combination with other antioxidants,<sup>19</sup> though dose recommendations remain unclear.<sup>28,29</sup>

The currently available TE PN additives in Australia and NZ deliver Se in a range from 0.4-0.5  $\mu\text{mol}$  (32-40  $\mu\text{g}$ )/day when given at the recommended dose. These doses are almost certainly too low and AuSPEN supports an increased intake to 0.75-1.25  $\mu\text{mol}$  (60-100  $\mu\text{g}$ )/day for short and longer term patients (including HPN).<sup>6</sup>

(NHMRC Grade C)

Serum Se levels are recognised to fall by (20-30)% with acute illness and should be interpreted in context of a simultaneous CRP level. Red blood cell (RBC) Glutathione Peroxidase (GPx) is recognised as a functional measure of Se status, but it should be noted that RBC GPx activity can be maintained for up to 6 months in patients receiving Se deficient PN.<sup>30</sup> A promising new development suggests the use of RBC Se concentration as a marker of Se status that is unaffected by the APR.<sup>31</sup> (NHMRC Grade C). Local laboratory availability of tests and expertise should be considered. There is insufficient evidence to recommend frequency of monitoring but once a year may be sufficient for most HPN patients.<sup>6</sup>

### **Manganese (Mn)**

While there is a paucity of evidence to guide supplementation in short or longer term PN patients, for HPN patients it appears that Mn toxicity is a greater concern than Mn deficiency.<sup>32</sup> Small cohort studies report variable Mn toxicity in NZ<sup>32</sup> and Australia<sup>33</sup> but data is lacking of any wide-ranging systematic toxicity in HPN patients in Australia and NZ.

Case reports of Mn toxicity in patients on HPN (representing about 500 adult patients) suggest most patients suffered no clinical symptoms, while a small number developed neurological signs including confusion, irritability and Parkinson Disease-like symptoms.<sup>34,35</sup> Elevated whole blood Mn has been shown to correlate with Magnetic Resonance Imaging (MRI) signal intensity in part of the brain (globus pallidus), both of which decrease after cessation of parenteral Mn supplementation.<sup>36</sup>

Normal Mn levels have been demonstrated to be maintained with supplementation of 1  $\mu\text{mol}$  (55  $\mu\text{g}$ )/day<sup>37</sup> while moderate MRI intensity for Mn in the globus pallidus was seen when supplemented with 2  $\mu\text{mol}$  (110  $\mu\text{g}$ )/day.<sup>37</sup> This small study suggested that higher supplementation may lead to increased Mn deposition. Conversely no supplementation in this group caused a fall in RBC Mn but the clinical consequences of this remain uncertain. The currently available TE PN additives in Australia and NZ deliver Mn in a range from 1.4-5.8  $\mu\text{mol}$  (80-270  $\mu\text{g}$ )/day when given at the recommended dose. AuSPEN supports the supplementation of 1  $\mu\text{mol}$  (55  $\mu\text{g}$ )/day of Mn and is of moderate strength evidence. (NHMRC Grade C).

Mn is historically recognised as a contaminant of PN solutions, but there is limited evidence regarding the formulations used in Australia and NZ, particularly with contemporary PN compounding practices. There is an urgent requirement for local contamination studies to be reported in a clinically meaningful way together with a labelling requirement for allowable Mn contamination.

Whole blood Mn is the preferred test for Mn levels as it elevates and normalises again within three months of provision and discontinuation of supplementary Mn, and also correlates with MRI measurements of any brain deposition.<sup>37</sup>

Monitoring Mn levels in short term and longer term PN patients is unlikely to be necessary. Three to six monthly monitoring of Mn in HPN patients may be prudent if high dose Mn supplementation within a TE formulation is used.

Patients who have stable levels and who receive 1 µmol (55 µg)/day may only need yearly monitoring.

### **Iron (Fe)**

Short term PN patients may have sufficient Fe stores to overcome lack of provision of Fe or be given blood products as a therapeutic measure if there are significant blood losses. Longer term and HPN patients require Fe supplementation, especially in SBS or Crohn's disease where additional iron losses may occur.<sup>38</sup> Menstrual losses and repeated blood tests may represent additional losses. Additional requirements in second and third trimesters must be considered in pregnant women who are PN dependent.<sup>38</sup> Clinicians caring for HPN patients should aim to minimise blood tests required for monitoring. The comorbidity of haemochromatosis may constitute a contraindication to Fe administration in PN. Fe overload as a consequence of PN has rarely been reported with longer term PN but nonetheless Fe status needs regular monitoring.<sup>39</sup>

Fe containing TE additives in Australia and NZ provide 20 µg or 1-1.1 mg/dose, and in the absence of toxicity reports over the past decade associated with this dose AuSPEN continues to recommend this as a safe level of supplementation.

Low Fe stores may be indicated by low serum ferritin and a decrease in Fe binding capacity. Ferritin, however, is an APR protein that will increase during illness even in the presence of Fe deficiency anaemia,<sup>38,40</sup> a concurrent CRP level may assist with interpretation. Early Fe deficiency may be indicated by decreased serum transferrin saturation, while Fe deficiency anaemia is indicated by low haemoglobin and haematocrit, and reduced mean corpuscular haemoglobin and volume.<sup>8</sup> (NHMRC Grade B). In critically ill patients hepcidin represents a newly identified means of distinguishing true Fe deficiency from the effects of inflammation.<sup>41</sup>

### **Chromium (Cr)**

Cr is absorbed in the small bowel<sup>42</sup> and patients with some functional small bowel receiving PN may receive adequate Cr from their oral diet and/or Cr contamination through their PN solutions. While older evidence suggests Cr contamination of PN solutions may provide enough to meet current recommendations,<sup>6,43,44</sup> no Australian and/or NZ data is presently available, nor data from international sources with similar studies investigating contamination with changes to PN packaging. The omission of Cr from longer term PN and HPN provision has not been assessed.<sup>6</sup>

While concerns are cited that high serum Cr levels detected in short, longer term and HPN patients may result in toxicity and/or kidney damage,<sup>6,43,44</sup> it should be noted there have been no reports of Cr toxicity in adult patients associated with elevated serum levels either from PN or chromium-containing hip implants.<sup>6,45</sup> Case reports describe Cr deficiency in patients receiving longer term PN provision with inadequate or no Cr provision after 6 months and 2 years of PN commencement.<sup>46-49</sup> Cr depletion during pregnancy has been described,<sup>42</sup> and therefore may need to be considered in the event of providing PN during pregnancy.<sup>42</sup> The currently available TE PN addi-

tives in Australia and NZ deliver Cr in a range from 10-12 µmol (~0.2 µg)/day when given at the recommended dose. AuSPEN recommends that Cr should be routinely supplemented in patients receiving short, longer term and HPN at levels of 0.2 to 0.3 µmol (10-15 µg)/day. This represents a reduction in the upper recommendation from the 1999 AuSPEN Micronutrient guidelines.

Due to the absence of reliable methods for assessing Cr status, Cr levels are not routinely monitored in Australia and NZ.<sup>42</sup> The only reliable method to diagnose a Cr deficiency is by demonstrating resolution in insulin resistance or abnormal glucose clearance that resolves with Cr supplementation, and reappears if supplementation is discontinued.<sup>42</sup>

### **Molybdenum (Mo)**

In the likelihood of reasonable premorbid Mo status in the Australian region,<sup>7</sup> those receiving short term PN may not require Mo supplementation due to adequate body stores. Similarly those receiving supplemental PN in the presence of a functional stomach and proximal small bowel with continuing on an oral/enteral intake may absorb adequate amounts of Mo to avoid the need for parenteral supplementation.

Australia and NZ routinely supplement Mo in their multi-TE solutions although Mo is thought to be a contaminant of PN solutions. However the last locally published investigation into Mo contamination occurred over 30 years ago, and the levels obtained at this time (<5-15 µg/d [ $<0.5$ -16 µmol/d]) cannot be generalised to the present time due to changes in packaging in the ensuing years.<sup>50</sup> Given the absence of reported toxicity or deficiency concerns with the currently provided levels in the presently available multi-trace element solutions, AuSPEN supports maintaining the current level of supplementation in the Australia and NZ PN practice (0.2 µmol (19 µg)/day).

Mo is not routinely monitored due to the limitations of biochemical markers of Mo status.<sup>51</sup> In the absence of routine laboratory data, clinicians should be aware of the cluster of symptoms and biochemistry presented in the only case reporting Mo deficiency.<sup>52</sup> These included generalised oedema, lethargy, disorientation and coma in the presence of elevated plasma methionine levels, low serum uric acid and low urinary uric acid excretion.<sup>52</sup>

### **Iodine (I)**

Patients receiving PN in Australia and NZ may be at higher risk of low baseline I levels due to the region's relatively low soil I levels, particularly if fortified foods such as bread and salt have not been routinely consumed.<sup>53</sup>

In patients with adequate baseline stores, thyroid stores of I may be sufficient to meet metabolic requirements for short term PN provision or for <3 months.<sup>54,55</sup> As I is absorbed in the duodenum and is highly bioavailable<sup>54</sup> patients on PN with a functioning duodenum and maintaining some oral intake may not require additional I supplementation. Patients with intestinal failure or SBS have been shown to maintain their I status and thyroid function while consuming a normal diet and receiving HPN without I supplementation.<sup>56</sup> Additional I supplementation

may be required for pregnant women receiving PN in view the increased requirements for foetal neurocognitive development as well as the maintenance of maternal stores (8). Administration of amioderone or iodinated contrasts are the only likely sources of coincidental I provision in patients receiving PN in Australia and NZ since chlorhexidine antiseptics have replaced povidone-iodine antiseptics in routine practice.<sup>54</sup> The currently available TE PN additives in Australia and NZ deliver I in a range from 1-1.1  $\mu\text{mol}$  (130-140  $\mu\text{g}$ )/day when given at the recommended dose. AuSPEN recommends a daily maintenance dose of 1.0  $\mu\text{mol}$  (130  $\mu\text{g}$ ) I per day for adult patients on short, longer term and HPN.

Monitoring of I status through monitoring of thyroid size and thyroid function tests (thyroid stimulating hormone (TSH), free T4) should be conducted at baseline and routinely thereafter as clinically indicated.<sup>54</sup> Thyroid function tests – TSH, T3 and T4 – are the most commonly used biochemical tests in Australia and NZ to monitor I status in patients receiving PN, however it should be noted these are not reliable measures as they do not consistently fall below normal ranges in the presence of I deficiency.<sup>54</sup> Furthermore, the interpretation of levels of T3, T4 and TSH may be further affected in acutely unwell patients who experience “euthyroid sick syndrome”.<sup>54</sup>

#### **Limitations of these guidelines**

While every effort has been made to ensure the present guidelines represent the best evidence available, having been collated through a robust and systematic process, some limitations exist. First, there is a paucity of research in the area of TE provision in PN. The majority of the available literature is 20 to 40 years old, and due to the changes in PN practices in this time it is currently unknown to what degree it can now be generalised to the modern PN context. Second, with few exceptions, the research has been conducted outside of Australia and NZ and therefore the impact of different solutions, practices and this region’s vulnerability to lower baseline TE levels, such as Se and I, limit the degree to which these results can be applied to our population, although this has been extrapolated from local population information when possible. Third, the realities of nutritional research in which the elements of well-designed randomised controlled trials, notably blinding and randomisation, are not always possible due to ethical or logistical reasons limits the high level evidence available in this field. While high levels of evidence are sought to justify changes to clinical practice, lower grades of evidence often represent the best level of evidence available and this does not necessarily invalidate the recommendations. For this reason, unless otherwise indicated, the recommendations contained in this document are NHMRC Grade D recommendations. Finally, while a multidisciplinary working group was originally formed to undertake this review process, due to circumstances beyond the working group’s control the final group was limited to dietitians and pharmacists working in PN. This has attempted to be balanced by approaching a range of external reviewers, including medical and nursing practitioners and recognised experts in micronutrient research to guide the final version of the guidelines.

#### **RECOMMENDATIONS FOR CLINICIANS**

1. TEs are essential components of human nutrition and should be provided daily with PN provision from the time of commencement as standard practice in short, longer term and HPN provision.
2. Biochemical assessments of TE are expensive and many TEs do not have reliable biochemical tests available at the present time. Unless otherwise clinically indicated, monitoring of TE levels should be reserved for clinically stable, longer-term PN or HPN patients. Unless otherwise clinically indicated, annual TE monitoring should be sufficient.
3. In cases where monitoring is being performed in patients with acute issues, a CRP level in which to provide context to the level of inflammation or presence of APR that should be performed.

#### **RECOMMENDATIONS FOR INDUSTRY**

To support safe and evidence based clinical care, new multi-TE products that reflect the present recommendations are required to be available on the Australian and NZ market. Specifically:

1. Mn provision decreased to 1  $\mu\text{mol}$  (55  $\mu\text{g}$ )/day
2. Cu provision decreased to 5  $\mu\text{mol}$  (315  $\mu\text{g}$ )/day
3. Se provision increased to the higher end of the recommendations (~1.2  $\mu\text{mol}$  (~100  $\mu\text{g}$ )/day )

#### **IMPLICATIONS OF CHANGES IN PN PRACTICES ON FUTURE TE PROVISION: RECOMMENDATIONS FOR SURVEILLANCE AND FUTURE PRACTICE IN PN**

All recommendations regarding TE provision in PN to date are based on four decades of PN practice during which PN component solutions were packaged in glass bottles and glass ampoules, and drawn up in plastic syringes, metal needles and (occasionally) metal particle filters. This has been recognised to give rise to the unintentional contamination of PN solutions with a variety of TEs including boron, molybdenum, nickel, vanadium, aluminium and cadmium, at time exceeding levels that would be obtained through normal dietary sources.<sup>57,58</sup> In this setting, TE deficiencies in stabilised PN patients have been rare.

However in recent years there has been a widespread change from glass to plastic containers and to needle-less systems. With this the pattern of previously assumed contamination of TEs in PN provision has changed. Plastic is much less likely to contribute to TE contamination of PN solutions than glass, however some level of contamination may be expected to continue though at a lower level than previously seen.<sup>59</sup> The impact of these changes is yet to be described in clinical practice.

In view of the potential impact brought about by contemporary packaging changes, practitioners should now be alert to the heightened possibility of TE deficiencies amongst longer term and HPN patients. While this may suggest more frequent monitoring is warranted, the limitations on assessing TE status are acknowledged and outlined throughout this document.

#### **RECOMMENDATIONS FOR RESEARCH**

These guidelines highlight the need for further research in

PN provision. These include but are not limited to:

1. Investigation into the TE contamination profile associated with contemporary PN packaging practices;
2. Surveillance of changes to TE deficiency and toxicity patterns in longer term and HPN patients with the changes to storage and handling of PN components;
3. Development of reliable methods to facilitate TE assessment and monitoring in longer term and HPN patients; and
4. Validation of earlier poor quality studies into safe and adequate provision of TE in short, longer term and HPN patients.

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#### AUTHOR DISCLOSURES

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## Review Article

## Australasian Society for Parenteral and Enteral Nutrition guidelines for supplementation of trace elements during parenteral nutrition

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### 澳大利亚肠内肠外营养学会肠外营养补充微量元素指南

**背景：**这项工作代表了澳大利亚肠内肠外营养学会自 1999 年出台《对接受肠道外营养的成年患者微量元素补充指南》以来对该领域进展的认可按文献进行逐步综述的第一部分。**方法：**通过系统文献综述，基于现有证据并考虑对澳大利亚和新西兰执业环境的具体内容提出建议。对每项建议的证据力度进行评估。外部评审人员通过 AGREE II 针对指南提供反馈。**结果：**相比于 1999 年的指南，建议减少锰、铜、铬和钼的剂量，增加硒的剂量。目前市面上多元微量元素配方的成分是公认的指南实践中的障碍。现有文献的缺乏及监测微量元素状况的方法存在局限性，使用的肠外营养中微量元素污染对临床的影响不清楚，需要进一步研究及临床实践。**结论：**接受肠外营养的患者需要每天补充微量元素。在结合个体情况基础上，只需对接受长期肠外营养的患者进行监测，然而要个案处理。在澳大利亚和新西兰，鼓励企业根据新的研究成果修订的指南调整多元微量元素溶液。该领域需要加大研究投入。

**关键词：**微量元素、指南、肠外营养、锰、硒