Evidence Evaluations for Vitamin B6 Upper Level

Vitamin B6 Upper-Level Evaluation Report

National Health and Medical Research Council

Prepared by:

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Basis of Report

This report has been prepared by SLR Consulting Australia Pty Ltd (SLR) with all reasonable skill, care and diligence, and taking account of the timescale and resources allocated to it by agreement with National Health and Medical Research Council (the Client). Information reported herein is based on the interpretation of data collected, which has been accepted in good faith as being accurate and valid.

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Executive Summary

The National Health and Medical Research Council (NHMRC) engaged SLR Consulting Australia Pty Ltd to evaluate existing guidance and new primary evidence for the Upper Level (UL) of vitamin B6, as part of the review of the Nutrient Reference Values (NRVs) for Australia and New Zealand.

A targeted search found EFSA (2023) to be the only guidance document that met the pre-defined credibility criteria (93.8%, above the 80% threshold) and the only reassessment of the vitamin B6 UL since 2006. EFSA derived an adult UL of 12 mg/day (applicable also to pregnant and lactating women), based on peripheral neuropathy as the critical effect. EFSA's reference point of 50 mg/day is not derived from a single study but reflects a weight-of-evidence (WoE) assessment across multiple converging lines of evidence, anchored by the Dalton & Dalton (1987) case-control study and supported by a positive rechallenge case, additional case reports, and Dutch and French nutrivigilance data. The EFSA human-based derivation (uncertainty factor (UF) of 4[1], giving 12.5 mg/day) was cross-checked against an independent animal-based derivation (Phillips et al. 1978, dog LOAEL of 50 mg/kg bw/day, uncertainty factor (UF) of 300[2], giving 11.7 mg/day); the agreement between these values increased confidence in the final UL of 12 mg/day. This represents an approximately 4-fold reduction compared with the current Australian NHMRC (2006) UL of 50 mg/day, derived from different underlying studies (Bernstein & Lobitz 1988; Del Tredici et al. 1985).

Assessment of the key historical studies found that the human studies underpinning both candidate guidance values, Dalton & Dalton (1987) for EFSA, and Bernstein & Lobitz (1988) and Del Tredici et al. (1985) for Australian NHMRC, showed high risk of bias, reflecting self-reporting, lack of blinding or randomisation, absent or inadequate control groups, non-representative study populations and inherent risk of bias based on study designs (which rank low on the hierarchy of evidence). The animal study underpinning EFSA's UL (Phillips et al. 1978) was rated Low risk of bias (however, it is a non-guideline, non-GLP peer review published study that lacks the level of study reporting associated with regulatory quality studies). This pattern is a key consideration in interpreting the reliability of the vitamin B6 UL regardless of which guidance value is adopted.

An evidence review of recent literature (2022 onwards) identified primary studies across health outcome categories. Six studies relevant to peripheral neuropathy were assessed for risk of bias (RoB) and GRADE-informed confidence: four human studies (Gdynia et al. 2025; Paluszny and Qiu 2023; Stewart 2022; van Hunsel et al. 2025) received Low to Very Low final confidence, reflecting case-based or cross-sectional designs and self-reported exposure; two controlled animal studies (Sano et al. 2022; Theil et al. 2023) received Moderate confidence and remain consistent with EFSA's existing dose range. The human studies provide a qualitative signal that neuropathy may occur in some individuals at intakes below EFSA's Reference Point (RP) and UL, but this evidence is not considered sufficiently reliable to revise the existing derivation.

Hepatotoxicity and hepatocellular carcinoma study in patients with Pyridox(am)ine 5'-phosphate oxidase (PNPO) deficiency receiving very high-dose therapeutic pyridoxal-5'-

[1] The uncertainty factor of 4 comprised a factor of 2 for uncertainty regarding the duration of exposure needed to account for the inverse dose–duration relationship for peripheral neuropathy, and a further factor of 2 for limitations in the available data, including uncertainty in the LOAEL, representativeness of the Dalton and Dalton (1987) study population, interindividual variability and coverage of sensitive groups.

[2] A composite UF of 300 was applied, comprising: ×2 for interspecies toxicokinetics (reduced from the default of 4 based on evidence of shared vitamin B6 metabolism between dogs and humans); ×2.5 for interspecies toxicodynamics (default); ×10 for intraspecies variability in humans (default); ×2 for subchronic-to-chronic duration extrapolation; and ×3 to account for the absence of a NOAEL in this study.

phosphate, was identified but is not relevant to the supplement/dietary intake of vitamin B6 and general-population UL derivation consistent with the NHMRC Final NRV Methodological Framework's exclusion of non-representative clinical sub-populations from point of departure derivation (Brands 2026; Webster 2026). Similarly, studies involving high-dose therapeutic Pyridoxal 5’-phosphate (PLP) in other rare metabolic disorders (Arai 2023; Morris 2025) were excluded from dose-response assessment on the same grounds. Mechanistic evidence on individual susceptibility (Whyte et al. 2024; Zervou et al. 2025) supports toxicokinetic variability in PLP clearance as relevant to the intraspecies component of EFSA's existing uncertainty factor, given that Tissue-nonspecific alkaline phosphatase (TNSALP) carrier frequency in the general population is not negligible (approximately 1/300), though it does not warrant a quantitative change to the UF.

Overall, the new evidence identified in this review does not appear sufficient to warrant revision of EFSA's (2023) UL of 12 mg/day, which this evaluation has identified as the most appropriate current guidance value for potential adoption or adaptation in Australia and New Zealand, in place of the current NHMRC (2006) UL of 50 mg/day. The available evidence remains broadly consistent with the current weight-of-evidence basis for peripheral neuropathy as the critical endpoint, with support from both human and animal data. However, this conclusion should be considered in view of the high risk of bias and generally low to very low reliability of the human evidence base, as well as ongoing uncertainties around individual susceptibility and the absence of an established mode of action.

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Acronyms and Abbreviations

Acronym	Definition
AU/NZ	Australia and New Zealand
bw	Body weight
CBS	Cystathionine beta-synthase
CIAP	Chronic idiopathic axonal polyneuropathy
CNS	Central nervous system
DAEN	Database of Adverse Event Notifications (Australia)
EFSA	European Food Safety Authority
EU	European Union
EVM	Expert Group on Vitamins and Minerals
FAO	Food and Agriculture Organization of the United Nations
FSANZ	Food Standards Australia New Zealand
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HCC	Hepatocellular carcinoma
HPP	Hypophosphatasia
IOM	Institute of Medicine
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LOAEL	Lowest-observed-adverse-effect level
NHMRC	National Health and Medical Research Council
NIEHS	National Institute of Environmental Health Sciences
NOAEL	No-observed-adverse-effect level
NRV	Nutrient Reference Value
OHAT	Office of Health Assessment and Translation (NTP)
PLP	Pyridoxal 5'-phosphate
PNPO	Pyridox(am)ine 5'-phosphate oxidase
RoB	Risk of bias
RP	Reference point
SCF	Scientific Committee on Food
TGA	Therapeutic Goods Administration
UF	Uncertainty factor
UL	Upper Level of Intake / Tolerable Upper Intake Level
US FDA	United States Food and Drug Administration
WHO	World Health Organization

1.0 Introduction and Background

The National Health and Medical Research Council (NHMRC) engaged SLR Consulting Australia Pty Ltd (SLR) to evaluate existing guidance, primary evidence and relevant supporting information for the Upper Level (UL) of vitamin B6 (pyridoxine) as part of the review of the Nutrient Reference Values (NRVs) for Australia and New Zealand. The review was undertaken in accordance with a Research Protocol designed to support a transparent, systematic and quality-controlled approach to evaluating evidence for health-based guidance values for vitamin B6. For the vitamin B6 UL review, SLR was asked to:

- Customise and apply the Research Protocol to address the agreed research questions for the vitamin B6 UL, including consideration of critical health effects, dose–response relationships, and the suitability of existing international guidance for adoption or adaptation in the Australian and New Zealand context.
- Review and evaluate recent international guidance documents, primary human and animal health evidence, and relevant supporting information pertaining to adverse health effects associated with excess vitamin B6 intake, with a particular focus on peripheral neuropathy and other neurological outcomes.
- Collate contextual information relevant to interpretation of the UL review, including information from adverse event reporting systems in Australia, New Zealand and comparable jurisdictions, and data on vitamin B6 dietary and supplemental intake patterns in the Australian and New Zealand population.
- Produce a Technical Report and an Evidence Evaluation Report:
    - The Technical Report documents the detailed methods, evidence sources, data extraction, assessment processes, critical appraisal outputs and supporting analyses used in the review.
    - The Evidence Evaluation Report interprets, synthesises and summarises the findings of the evidence review, addresses the agreed research questions, and presents conclusions on the suitability of existing international guidance for adoption or adaptation, for consideration by NHMRC and the Vitamin B6 Expert Working Group.

These tasks were undertaken in collaboration with NHMRC and the Vitamin B6 Expert Working Group, with advice from the Working Group incorporated as required. Any amendments to the Research Protocol agreed with NHMRC and the Vitamin B6 Expert Working Group during the course of the review have been documented in the Technical Report.

The report herein is the Evaluation Report for this review.

1.1 Objectives

To identify and evaluate existing guidance and the evidence underpinning those guidance documents, together with recent scientific evidence relevant to the Upper Level (UL) for vitamin B6, and to determine whether existing international guidance particularly EFSA (2023) and other relevant jurisdictional assessments may be suitable for adoption or adaptation in the Australian and New Zealand context.

An evidence review was also be undertaken to collate supporting and contextual information relevant to interpretation of the UL review, including information available from adverse event reporting systems.

For the purposes of this review, 'general population' is defined in accordance with the NHMRC Final NRV Methodological Framework v2.0 (2015-2017) as the general healthy population, excluding individuals with genetic diseases or other conditions that predispose them to adverse effects at intake levels below those relevant to the broader population.

While evidence from potentially sensitive sub-populations including those with rare inborn errors of vitamin B6 metabolism such as Pyridox(am)ine 5'-phosphate oxidase (PNPO) deficiency or hypophosphatasia was reviewed and is discussed where relevant, it was not used to inform the point of departure for UL derivation.

2.0 Research Questions

Research questions for this review were drafted by SLR and peer reviewed and agreed upon by the NHMRC and the Vitamin B6 Expert Working Group prior to conducting the search. They are provided in **Table 1**.

Table 1 Research Questions for Evidence Evaluation of Vitamin B6 Upper Level (UL) Review

Number	Research Questions
1	Upper Level (UL) question - What excess intake of vitamin B6 is associated with adverse health effects?
2	Upper Level (UL) question - What is the critical human health endpoint that determines the UL, and what is the justification for selecting this endpoint?
3	Upper Level (UL) question - What recent ULs or equivalent health-based guidance values exist internationally (for excess vitamin B6 intake)? How were they derived, what assumptions and uncertainties were applied, and are they suitable to adopt or adapt for Australia and New Zealand?
4	Health considerations - What are the key adverse health effects associated with excess vitamin B6 intake, particularly neurological outcomes such as peripheral neuropathy?
5	Health considerations - What is the strength of evidence for a causal association for the key adverse health effects (including consideration of mode of action, dose–response relationships, and consistency of findings)? Where relevant, how do findings differ by study type (e.g. human and animal evidence) and by population group, including infants, children, pregnancy/lactation and older adults?
6	Health considerations - Are there sensitive subpopulations, exposure patterns or use scenarios that require specific consideration[3]?
7	Health considerations - How are pregnancy and other potentially sensitive life stages considered in the derivation of the UL, and are different uncertainty factors or adjustments applied for specific subpopulations where appropriate?
8	Australian and New Zealand intake profile (where relevant to interpretation of risk in Australia and New Zealand) - What are the typical dietary and supplemental sources of vitamin B6 in Australia and New Zealand?
9	Australian and New Zealand intake profile (where relevant to interpretation of risk in Australia and New Zealand) - What are the typical dietary and supplementary intakes of vitamin B6 in the Australian and New Zealand population?

[3] It is noted as per NHMRC's Final NRV Methodological Framework: "*ULs are intended for the general healthy population and exclude sub populations with genetic disease or other conditions that predispose them to adverse effects at levels below the general population. Potentially sensitive sub populations should be identified, where possible, and discussed when evaluating the evidence base for the establishment of ULs.*"

3.0 Methodology Overview

As part of the review, a number of literature searches were undertaken to target specific information relevant to answering the research questions. They consisted of the following:

- A targeted literature search of existing health-based guidance for vitamin B6. Jurisdictions and agencies searched included EFSA, FSANZ, TGA, NHMRC, WHO/FAO (including JECFA), Health Canada, US FDA, and other relevant international agencies and expert bodies identified during the review.
- An evidence scan of recent primary studies (published 2022 onwards, consistent with the evidence base underpinning EFSA 2023), with earlier pivotal studies included via backward citation searching where necessary to understand the basis of existing guidance values.
- Consultation of identified guidance documents for supporting contextual information (e.g. dietary and supplemental sources, intake patterns, sensitive subpopulation considerations).
- A review of adverse event reporting databases relevant to Australia, New Zealand and comparable jurisdictions, including DAEN, WHO VigiAccess, FDA AEMS, EudraVigilance and Canada Vigilance, to identify potential safety signals associated with pyridoxine and vitamin B6-containing products.

Results were subjected to the following steps in order to identify the most relevant information:

- A preliminary title and abstract screen, conducted by a single researcher and verified by a content expert against pre-defined inclusion and exclusion criteria; and
- A content screen where full text content of reports/reviews/articles selected to be included from the preliminary title screen step were reviewed in relation to the research questions by a subject expert to determine which to include in data extraction.

All searches and screening decisions were managed in Covidence. Relevant data were extracted by populating pre-constructed data extraction tables focused on the information needed to answer the research questions. Synthesis was conducted by presenting extracted data side-by-side in tabular format for each research question, grouped by health outcome for the recent evidence review. Risk of bias for key primary studies was assessed using a modified NIEHS Office of Health Assessment and Translation (OHAT) risk-of-bias tool, with overall certainty of evidence for each relevant health outcome assessed using a GRADE-informed approach. Expert judgement was used to highlight areas of uncertainty or areas where an organisation's methods or interpretations may differ from Australian science policy.

In addition, each candidate jurisdiction's guidance value for vitamin B6 considered for potential adoption/adaptation was evaluated against a defined set of administrative and technical credibility criteria (as set out in the Research Protocol, based on the NHMRC framework). Where a guidance document was found to meet the 80% threshold across combined 'must-have' and 'should-have' criteria, its data extractions, risk-of-bias ratings, critical effect, reference point and uncertainty factors could be relied upon directly, with review effort instead directed at identifying and synthesising new evidence published since that guidance's literature search cut-off and integrating this with its findings.

It is noted that the scope of evidence review encompasses all identified primary studies irrespective of study population, consistent with the mandate to review all relevant evidence. However, consistent with the NHMRC Final NRV Methodological Framework, ULs are intended for the general healthy population and exclude sub-populations with genetic disease or other conditions that predispose them to adverse effects at levels below those

relevant to the general population. Accordingly, studies conducted in populations with rare inborn errors of vitamin B6 metabolism (e.g. PNPO deficiency, hypophosphatasia) or other conditions conferring atypical B6 handling were included in the evidence review and are discussed where relevant to characterising potentially sensitive sub-populations but were not used to inform the point of departure for UL derivation.

Figure 1 shows an overview of the literature search process followed for vitamin B6. This is presented as a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram that describes the study selection process and numbers of records at each stage of screening (Moher et al. 2009).

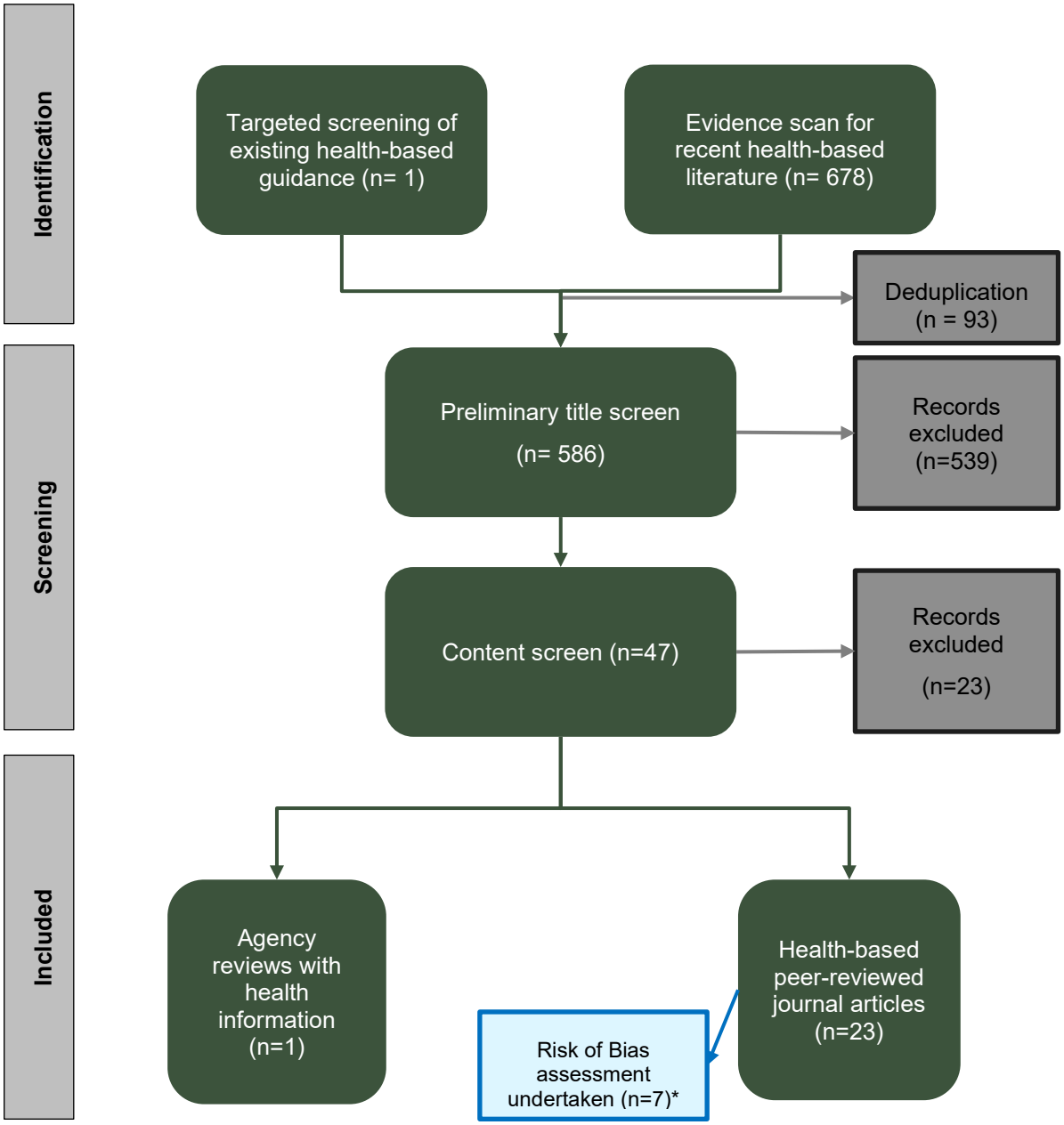

Figure 1 Overview of literature search process followed for Vitamin B6 UL (*Risk of Bias analysis was not undertaken for studies which were reviews/meta-analyses)

This report provides the summary of the findings (**Section 4.0**), a discussion of the results (**Section 5.0**), and conclusion (**Section 6.0**).

4.0 Results

4.1 Health-based guidance

The targeted screening of existing health-based guidance identified EFSA (2023) as the most recent and relevant guidance document for the vitamin B6 UL review. Upon assessment against the credibility criteria (Research Protocol, Appendix B), EFSA (2023) met the 80% threshold for combined 'must-have' and 'should-have' criteria (93.8%) and was therefore identified as the candidate guidance for potential adoption/adaptation. On this basis, the guidance documents and key studies assessed within EFSA (2023) including SCF (2000), IOM (1998), EVM (2003), WHO/FAO (2004), and NHMRC (2006) were relied upon as part of the evidence base.

EFSA (2023) derived an adult UL of 12 mg/day using peripheral neuropathy as the critical effect. The reference point (RP) of 50 mg/day was not derived from any single study but reflects a weight-of-evidence assessment across multiple converging and independent lines of evidence, consistent with EFSA Scientific Committee guidance. These included a case-control study (Dalton & Dalton 1987), in which neuropathy symptoms were reported in 48% of women consuming <50 mg/day supplemental vitamin B6 for more than six months for PMS treatment, with prevalence increasing dose-dependently at higher intakes; a positive rechallenge case in which neuropathy recurred following re-exposure to 50 mg/day after one year of recovery from neuropathy originally induced at 75 mg/day (Dalton & Dalton 1987); additional case reports documenting neuropathy at intakes of 50–300 mg/day (Dalton 1985; Blackburn & Warren 2017); Dutch nutrivigilance data comprising 33 confirmed cases with intakes at or below 50 mg/day; and French nutrivigilance data reporting cases at supplemental intakes below 25 mg/day. It was the convergence of these multiple independent lines of evidence, that led the EFSA Panel to conclude with sufficient certainty that peripheral neuropathy may occur at supplemental vitamin B6 intakes of 50 mg/day in some individuals.

It is important to note, however, that the Dalton & Dalton (1987) study, considered the key study in this body of evidence, carries substantial methodological limitations that must be acknowledged and carried forward in any interpretation of the RP. As a case-control study, it occupies a relatively low position in the hierarchy of evidence for establishing cause and effect, sitting below cohort studies and above case series and reports, and is inherently limited in its capacity to control for confounding variables. Specific limitations acknowledged in the study itself and by the EFSA Panel include reliance on patient recall of supplement dose and duration, with the authors noting potential inaccuracy for periods exceeding five years; the difficulty of separating neurological symptoms attributable to vitamin B6 from those associated with the underlying PMS condition being treated; and rechallenge procedures that were not conducted under blinded conditions. The study has also not been independently replicated. The overall risk of bias of the human evidence base was assessed as moderate to high by EFSA. Passing GRADE or credibility criteria does not eliminate these limitations rather, they are explicitly reflected in the uncertainty factor (UF) applied.

A UF of 4 was applied to the human RP of 50 mg/day to derive the human-based UL of 12.5 mg/day. This composite UF comprised two components: a factor of 2 to account for the inverse dose-time relationship (i.e., uncertainty as to whether the exposure duration in Dalton & Dalton 1987 was sufficient to capture the full range of responses, given that higher doses cause symptoms sooner); and a further factor of 2 to account for limited data and residual interindividual variability, including uncertainty about whether the RP represents a true threshold and whether sensitive subgroups were adequately represented. EFSA

considered this UF of 4 sufficient to also cover background dietary vitamin B6 intake, since the RP was derived from supplemental intake data only.

As an independent supporting derivation, EFSA also drew on a subchronic Beagle dog study (Phillips et al. 1978), in which groups of young dogs (7–8 months old; n=4–5 per group) received oral pyridoxine hydrochloride (PN-HCl) at doses of 0, 50, or 200 mg/kg bw/day for approximately 107 days. The critical effect in this study was peripheral neuropathy, specifically bilateral myelin loss in dorsal sensory nerve roots, observed in all dogs at the 50 mg/kg bw/day dose establishing this as the LOAEL. Notably, these lesions occurred in the absence of overt clinical signs at the lower dose, underscoring the sensitivity of histopathological assessment relative to clinical observation. A composite UF of 300 was applied to this LOAEL, comprising ×2 for interspecies toxicokinetics (reduced from the default of 4 based on evidence of shared vitamin B6 metabolism between dogs and humans); ×2.5 for interspecies toxicodynamics (default); ×10 for intraspecies variability in humans (default); ×2 for subchronic-to-chronic duration extrapolation; and ×3 to account for the absence of a NOAEL in this study. This gave an animal-based UL of 11.7 mg/day (50 mg/kg bw/day ÷ 300 × 70 kg). The close agreement between the human-derived value (12.5 mg/day) and the animal-derived value (11.7 mg/day) increased EFSA's confidence in the final UL of 12 mg/day, which was set as the midpoint rounded down.

4.2 New evidence reviews

In addition to the existing guidance review, an evidence review of recent literature (published 2022 onwards) identified studies for data extraction and synthesis. A key distinction must be drawn at the outset between evidence arising from dietary and general supplemental vitamin B6 exposure in the general healthy population which is directly relevant to UL derivation and evidence arising from pharmaceutical use of vitamin B6 under medical supervision, or from therapeutic administration in patients with rare inborn errors of B6 metabolism. These exposure contexts are different. Evidence from therapeutic or clinical use should therefore not be directly used to derive a population-level dietary UL.

Consistent with the NHMRC Final NRV Methodological Framework, the UL is intended for the general healthy population, and the primary evidence review was structured accordingly, with peripheral neuropathy in association with pyridoxine or supplemental vitamin B6 intake remaining the central focus. The evidence reviews additionally identified studies that fall outside the scope of UL derivation for the general population but were retained in the review for the potential contextual and mechanistic information and organised into two supplementary streams, each serving a distinct interpretive purpose.

Detailed findings tables for each research question and health outcome category are provided in the Technical Report. In this Evaluation Report, findings are summarised to focus on their relevance to UL derivation, comparison with EFSA (2023) conclusions, and identified uncertainties.

4.3 Health-based aspects

Research questions 1–9 all cover health-based aspects of the review; **Table 2** provides a summary of the agreement and disagreement between EFSA 2023 and all the previous guidance before NHMRC 2006.

Table 3 and

Table 4 provide synthesis of the results, drawing on EFSA (2023) and the recent evidence review, highlighting areas of consistency, uncertainty, or where interpretation may differ from Australian science policy.

Table 2 Summary of agreement and disagreement among guidance document based on research questions

Number	Research Questions	Is there agreement between different jurisdictions?	Any disagreement or things to note?	Any disagreement or things to note with NHMRC 2006?
1	Upper Level (UL) question - What excess intake of vitamin B6 is associated with adverse health effects?	SCF (2000), IOM (1998), EVM (2003), WHO/FAO (2004) and EFSA (2023) all agree that excess supplemental vitamin B6 (not dietary intake) causes peripheral (sensory) neuropathy. However, the specific intake levels considered to cause harm differ by jurisdiction, as each based its conclusions on different studies.	SCF (2000) derived its RP of 100 mg/day primarily from the mean supplemental intake in the Dalton & Dalton (1987) case-control study (women taking <50–500 mg/day); EFSA (2023) revisited the same study but identified a lower RP of 50 mg/day based on the lowest dose group, supported by a weight-of-evidence assessment across additional converging lines of evidence available by 2023, including a positive rechallenge case, further case reports (Dalton 1985; Blackburn & Warren 2017), and Dutch and French nutrivigilance data reporting neuropathy cases at or below 50 mg/day; IOM (1998) and WHO/FAO (2004) used studies in patients with diabetic neuropathy or carpal tunnel syndrome reporting no worsening at 100–300 mg/day (Bernstein & Lobitz 1988; Del Tredici et al. 1985); EVM (2003) used an animal study (dog LOAEL of 50 mg/kg bw/day; Phillips et al. 1978).	NHMRC (2006) drew on the same studies as IOM (1998) (Bernstein & Lobitz 1988; Del Tredici et al. 1985) but identified a higher NOAEL of 200 mg/day and applied a UF of 4 to account for the studies' limited exposure duration (5–6 months) relative to the latency period for neuropathy onset, yielding a UL of 50 mg/day.

Number	Research Questions	Is there agreement between different jurisdictions?	Any disagreement or things to note?	Any disagreement or things to note with NHMRC 2006?
2	Upper Level (UL) question - What is the critical human health endpoint that determines the UL, and what is the justification for selecting this endpoint?	Peripheral neuropathy is the critical endpoint for all assessments in guidance documents (SCF, IOM, EVM, WHO/FAO, EFSA).	EFSA (2023) could not derive a formal LOAEL from the human data and instead established an RP of 50 mg/day through a weight-of-evidence assessment across multiple converging lines of evidence, as described above. EVM (2003) relied on an animal LOAEL of 50 mg/kg bw/day from a subchronic Beagle dog study (Phillips et al. 1978), where the critical effect was peripheral neuropathy (bilateral myelin loss in dorsal sensory nerve roots, observed in all five dogs at this dose after approximately 107 days), with a composite UF of 300 applied, giving a guidance value of approximately 10 mg/day.	NHMRC (2006) also selected peripheral neuropathy as the critical endpoint, consistent with EFSA. However, NHMRC used a NOAEL of 200 mg/day (from Bernstein & Lobitz 1988 and Del Tredici et al. 1985, diabetic neuropathy/CTS patients), a different point of departure type (NOAEL vs RP) and different underlying studies than EFSA's RP.

Number	Research Questions	Is there agreement between different jurisdictions?	Any disagreement or things to note?	Any disagreement or things to note with NHMRC 2006?
3	Upper Level (UL) question - What recent ULs or equivalent health-based guidance values exist internationally (for excess vitamin B6 intake)? How were they derived, what assumptions and uncertainties were applied, and are they suitable to adopt or adapt for Australia and New Zealand?	Variation in adult UL: SCF 25 mg/day, IOM 100 mg/day, EVM 10 mg/day (0.17 mg/kg bw/day), WHO/FAO did not set a numeric UL. EFSA (2023) is the only post-2006 reassessment, setting UL = 12 mg/day for adults (including pregnant/lactating).	EFSA's UL is derived in two ways and averaged: (i) human-based: RP 50 mg/day ÷ UF 4 (×2 for inverse dose-time relationship; ×2 for limited data and interindividual variability) = 12.5 mg/day, where the RP reflects a weight-of-evidence assessment across multiple lines of evidence as described above, not a single study; (ii) animal-based: dog LOAEL 50 mg/kg bw/day ÷ UF 300 (×2 interspecies TK; ×2.5 interspecies TD; ×10 intraspecies variability; ×2 subchronic-to-chronic; ×3 absence of NOAEL) = 11.7 mg/day. Midpoint rounded down = 12 mg/day. EFSA notes that heterogeneity across agencies stems mainly from different critical studies and evidence bases used, rather than differing science policy *per se*.	NHMRC (2006) UL = 50 mg/day (NOAEL 200 mg/day ÷ UF 4), over 4× higher than EFSA's 12 mg/day. This is the key difference based on adopting different critical study and derivation approach.
4	Health considerations - What are the key adverse health effects associated with excess vitamin B6 intake, particularly neurological outcomes such as peripheral neuropathy?	Peripheral neuropathy is the consistently identified most sensitive key effect across all.	Not applicable	Not applicable

Number	Research Questions	Is there agreement between different jurisdictions?	Any disagreement or things to note?	Any disagreement or things to note with NHMRC 2006?
5	Health considerations - What is the strength of evidence for a causal association for the key adverse health effects (including consideration of mode of action, dose–response relationships, and consistency of findings)? Where relevant, how do findings differ by study type (e.g. human and animal evidence) and by population group, including infants, children, pregnancy/lactation and older adults?	The association between high-dose pyridoxine intake and peripheral neuropathy is well accepted across both human and animal evidence, with a consistent dose-response relationship and improvement upon withdrawal supporting a causal interpretation under Bradford Hill criteria. However, the underlying mechanism of action has not been established. Several hypotheses have been proposed, including inhibition of pyridoxal kinase leading to functional PLP deficiency, disruption of axonal transport, and direct dorsal root ganglia neurotoxicity, but no internationally accepted mode of action for pyridoxine-induced peripheral neuropathy is currently available. EFSA (2023) explicitly acknowledges this uncertainty. While a defined mechanism is not an absolute requirement for causal inference, its absence limits biological coherence and represents a meaningful gap in the overall evidence base.	EFSA notes that the human evidence base, while spanning multiple lines of evidence including case reports, a positive rechallenge case, additional case series, and Dutch and French nutrivigilance data, is nonetheless limited by study design constraints inherent to observational and case-based data, meaning a formal LOAEL could not be established from human data alone. The RP of 50 mg/day therefore reflects a weight-of-evidence judgement across these converging sources rather than a single study finding. The animal data from the Beagle dog study (Phillips et al. 1978) were used as an independent cross-check, with the close agreement between the human-derived (12.5 mg/day) and animal-derived (11.7 mg/day) values providing additional confidence in the final UL of 12 mg/day.	NHMRC (2006) relied on a different pair of human studies (diabetic neuropathy/CTS patients, Bernstein & Lobitz 1988; Del Tredici et al. 1985) than EFSA's case-control study; NHMRC's source population (patients with pre-existing neuropathy risk factors) may differ in applicability compared to EFSA's general PMS-treatment population (women).

Number	Research Questions	Is there agreement between different jurisdictions?	Any disagreement or things to note?	Any disagreement or things to note with NHMRC 2006?
6	Health considerations - Are there sensitive subpopulations, exposure patterns or use scenarios that require specific consideration?	All assessments identify long-term, high-dose supplement users as the primary population of concern, as dietary intake alone is considered unlikely to exceed the UL. Pharmacological use of vitamin B6 to treat conditions such as premenstrual syndrome or nausea and vomiting of pregnancy, typically at doses well above those achievable through diet or general supplementation, represents an additional exposure context of concern, though this falls within the domain of medically supervised pharmaceutical use rather than dietary exposure and is therefore outside the scope of UL derivation for the general healthy population.	Not applicable	NHMRC (2006) does not appear to have separately flagged supplement users as a distinct exposure scenario in the same explicit way EFSA (2023) does.

Number	Research Questions	Is there agreement between different jurisdictions?	Any disagreement or things to note?	Any disagreement or things to note with NHMRC 2006?
7	Health considerations - How are pregnancy and other potentially sensitive life stages considered in the derivation of the UL, and are different uncertainty factors or adjustments applied for specific subpopulations where appropriate?	SCF (2000), EFSA (2023), and WHO/FAO (2004) all apply the adult UL to pregnant and lactating women without a separate derivation. EFSA systematically reviewed developmental toxicity and a range of additional endpoints including hip fracture risk, photosensitisation, impaired memorisation, anti-lactogenic effects, and testicular toxicity. None were considered to provide sufficient evidence for a causal relationship or an independent RP, with the exception of a weak signal for hip fracture risk at 35–40 mg/day that was nonetheless insufficient to act upon, and anti-lactogenic effects observed only at approximately 600 mg/day, well above the RP. Peripheral neuropathy therefore remained the sole endpoint underpinning the UL, with no population-specific adjustments warranted for pregnancy or lactation.	Not applicable	NHMRC (2006) also applied its adult UL (50 mg/day) to pregnant/lactating women, consistent in approach with EFSA, though at a different default value for body weight.
8	Australian and New Zealand intake profile (where relevant to interpretation of risk in Australia and New Zealand) - What are the typical dietary and supplemental sources of vitamin B6 in Australia and New Zealand?	NA	Not applicable	NHMRC (2006) provides only a general/qualitative list of food sources; it does not provide AU/NZ-specific data on supplement prevalence, dose, or product types.

Number	Research Questions	Is there agreement between different jurisdictions?	Any disagreement or things to note?	Any disagreement or things to note with NHMRC 2006?
9	Australian and New Zealand intake profile (where relevant to interpretation of risk in Australia and New Zealand) - What are the typical dietary and supplementary intakes of vitamin B6 in the Australian and New Zealand population?	NA	Not applicable	NHMRC (2006) does not provide population intake data (dietary or supplemental) for Australia/New Zealand.

Table 3 Summary of findings from data extraction for health-based research questions – EFSA 2023

Number	Research Questions	EFSA 2023
1	Upper Level (UL) question - What excess intake of vitamin B6 is associated with adverse health effects?	Based on a weight-of-evidence assessment across multiple converging lines of evidence, including the Dalton & Dalton (1987) case-control study, a positive rechallenge case, additional case reports (Dalton 1985; Blackburn & Warren 2017), and Dutch and French nutrivigilance data, the EFSA Panel concluded that peripheral neuropathy may occur at supplemental vitamin B6 intakes of 50 mg/day in some individuals when consumed for more than 6 months. Within the Dalton & Dalton (1987) study, a dose-dependent increase in the prevalence of neuropathy symptoms was observed across all dose groups, including in the lowest group consuming less than 50 mg/day for more than 6 months, which contributed to but did not solely determine the RP. Symptoms were also reported at lower doses (e.g. 31 mg/day from energy drinks; nutrivigilance cases at 1.4–40 mg/day), but these were less well-confirmed.
2	Upper Level (UL) question - What is the critical human health endpoint that determines the UL, and what is the justification for selecting this endpoint?	The critical effect on which the UL is based is dorsal root sensory ganglionopathy. Peripheral axon degeneration, often presenting in a stocking-and-glove distribution, is considered secondary to dorsal root ganglion neuronal damage. The condition is predominantly, and sometimes entirely, sensory; motor nerve involvement is uncommon, and central nervous system involvement is generally limited to sensory pathways. However, motor-related complaints and balance symptoms, including gait disturbance or ataxia, have been noted in clinical case reports and pharmacovigilance datasets. These symptoms may reflect severe sensory impairment and impaired proprioception rather than primary motor neuropathy. While other adverse effects were reviewed (hip fracture risk, photosensitisation, impaired memorisation, anti-lactogenic effects, testicular toxicity), the evidence for these was considered insufficient to establish a causal relationship or derive an independent RP. Both human data and animal (Beagle dog) data agreed on peripheral neuropathy as the sensitive and relevant endpoint.

<table>
<tr>
<td>3</td>
<td>Upper Level (UL) question - What recent ULs or equivalent health-based guidance values exist internationally (for excess vitamin B6 intake)? How were they derived, what assumptions and uncertainties were applied, and are they suitable to adopt or adapt for Australia and New Zealand?</td>
<td>Summary of existing ULs for adults:
<table>
<tr><th>Body</th><th>UL (adults)[1]</th><th>Basis</th><th>Approach[2]</th></tr>
<tr><td>SCF (2000) (Europe)</td><td>25 mg/day (including pregnant and lactating women)</td><td>Dalton & Dalton (1987) case-control study; mean intake ~100 mg/day as RP</td><td>A UF of 4 was applied to the RP of 100 mg/day (mean intake in Dalton & Dalton (1987), 117 mg/day; median <100 mg/day): a factor of 2 because this intake corresponded to a possible effect level for long-term use, and a further factor of 2 to allow for deficiencies in the database. SCF considered a larger UF unnecessary, noting that the Dalton & Dalton (1987) data derived from a sub-group with high plasma concentrations and that the resulting value had not been associated with adverse effects in published studies. This gave a UL of 25 mg/day for adults, also applied to pregnant and lactating women in the absence of evidence of increased susceptibility in these groups.</td></tr>
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		IOM (1998) (USA)	100 mg/day (including pregnant and lactating women)	NOAEL of 100 mg/day from Bernstein & Lobitz (1988) and Del Tredici et al. (1985) in patients with diabetic neuropathy or carpal tunnel syndrome (CTS) in whom neuropathy did not get worse following vitamin B6 intakes of 100–300 mg/day	No UF applied
		WHO/FAO (2004)	100 mg/day	Same basis as IOM (1998)	No UF applied
		EVM (2003) (UK)	~10 mg/day (0.17 mg/kg bw per day supplemental pyridoxine equivalent to 10 mg/day for a 60-kg adult)	LOAEL of 50 mg/kg bw/day from Beagle dog study (Phillips et al., 1978)	A UF of 300 was applied to the animal LOAEL of 50 mg/kg bw/day, comprising: ×3 for LOAEL-to-NOAEL extrapolation (the LOAEL related to a histopathological change identified in a sub-chronic study, which may have underestimated toxicity during chronic exposure); ×10 for interspecies variation; and ×10 for inter-individual (human) variation. This gave a Safe Upper Level of 0.17 mg/kg bw/day supplemental pyridoxine, equivalent to 10 mg/day for a 60-kg adult.

<table>
<tr><th>Number</th><th>Research Questions</th><th colspan="4">EFSA 2023</th></tr>
<tr><td></td><td></td><td colspan="4">
<table>
<tr><td>NHMRC (2006) (Australia & New Zealand)</td><td>50 mg/day</td><td>NOAEL of 200 mg/day from Bernstein & Lobitz (1988) and Del Tredici et al. (1985)</td><td>UF of 4 applied (to account for short exposure duration; symptoms may take longer to appear).</td></tr>
</table>
(1) Children's ULs were also set by SCF, IOM, and NHMRC, derived by extrapolation from adult values on a body weight basis (Table 1 of EFSA 2023 document).
(2) The approach outlined in this table reflects EFSA's (2023) characterisation of each agency's derivation, as presented in EFSA's re-assessment, rather than a verbatim restatement of each agency's own published methodology.
Suitability for Australia and New Zealand:
The suitability of the EFSA (2023) methodology and derivation for application in the Australian and New Zealand context was considered. EFSA, as a European regulatory body, does not assess applicability to Australia and New Zealand, so this judgement is made independently here.
The critical studies underpinning EFSA's weight-of-evidence assessment were conducted predominantly in European and US populations, which are considered broadly comparable to the Australian and New Zealand population in terms of genetics, diet, and vitamin B6 metabolism. No population-specific factors have been identified in Australia or New Zealand that would render EFSA's methodological approach, choice of critical endpoint, weight-of-evidence framework, or UF derivation inappropriate for adoption or adaptation in this context.
It is noted, however, that the anchor study in EFSA's evidence base, Dalton & Dalton (1987), carries well-documented methodological limitations including reliance on patient recall of supplement intake, potential confounding with PMS symptomatology, unblinded rechallenge procedures, and lack of independent replication. These limitations are relevant to the Australian and New Zealand assessment and are carried forward as uncertainties regardless of jurisdiction.
The EFSA assessment is also explicitly scoped to dietary and supplemental vitamin B6 exposure in the general healthy population. It did not address, and was not intended to address, pharmacological use of vitamin B6 under medical supervision, including high-dose therapeutic administration in patients with inborn errors of B6 metabolism. Findings from those clinical contexts, including hepatotoxicity and hepatocellular carcinoma (HCC) signals in PNPO-deficient patients receiving therapeutic PLP, are therefore outside the scope of this UL assessment and should not be considered a limitation of EFSA's approach for Australian and New Zealand dietary exposure purposes.</td></tr>
</table>

Number	Research Questions	EFSA 2023
4	Health considerations - What are the key adverse health effects associated with excess vitamin B6 intake, particularly neurological outcomes such as peripheral neuropathy?	The principal adverse health effect is peripheral neuropathy, characterised by: - Paraesthesia (tingling sensations) - Hyperaesthesia (abnormal sensitivity) - Bone pains - Muscle weakness - Fasciculation - Numbness - Impaired proprioception, leading to sensory ataxia and loss of coordination - In severe cases, inability to walk In most cases, symptoms improved or resolved after withdrawal of vitamin B6 supplements. Recovery was reported in 55% of women after 3 months of cessation and 100% after 6 months in the Dalton & Dalton (1987) study. However, the available evidence does not clearly define whether more severe symptoms require longer recovery periods or are associated with a lower likelihood of complete recovery.

5	Health considerations - What is the strength of evidence for a causal association for the key adverse health effects (including consideration of mode of action, dose–response relationships, and consistency of findings)? Where relevant, how do findings differ by study type (e.g. human and animal evidence) and by population group, including infants, children, pregnancy/lactation and older adults?	The causal relationship between high vitamin B6 intake and peripheral neuropathy is described as "well established". Importantly, there is a lack of definitive consensus on the mode/mechanism of action of vitamin B6-induced neuropathy. However, the lack of a mode/mechanism of action is not sufficient by itself to disprove a cause-and-effect relationship. Evidence comes from multiple study types: - Human case series (Schaumburg et al. 1983): First demonstration of human vitamin B6–induced neuropathy at ≥2,000 mg/day; improvement after withdrawal. - Intervention study (Berger et al. 1992): Established the inverse relationship between dose and time to onset in humans; Quantitative sensory testing (QST) abnormalities with or without clinical symptoms at doses of 12–57mg/kg bw/day. - Case-control study (Dalton & Dalton 1987): Demonstrated peripheral neuropathy at <50 mg/day in 48% of women (n=43) consuming <50 mg/day supplemental vitamin B6 for >6 months; prevalence increased dose-dependently. - Retrospective studies (Brush et al. 1988; Chaudary et al. 2003): Mixed findings. Brush et al. (1988) reported no cases meeting a clinical diagnosis of peripheral neuropathy among women taking 40–200 mg/day for PMS. Chaudary et al. (2003) found that symptoms (tingling hands, insomnia, rash, acne) generally reduced in frequency after 3–42 months of vitamin B6 supplementation (30–230 mg/day; $p<0.001$), but among participants who were initially symptom-free, a minority (23 of 114) went on to develop new toxicity-associated symptoms after starting supplementation, predominantly at 101–150 mg/day. - Nutrivigilance data (Dutch, French systems): Reports of neuropathy at doses as low as 1.4 mg/day (though causality uncertain at very low doses); most cases at 40–100 mg/day. - Animal studies: LOAEL of 50 mg/kg bw/day established in Beagle dogs (Phillips et al. 1978); subchronic 107-day study; lesions without clinical symptoms at this dose. Rat studies showed consistent findings at higher doses. Notably, all of the human studies are observational and rank at the lower levels of the hierarchy of evidence. **Dose-response**: A dose-dependent increase in neuropathy prevalence was demonstrated, with an important inverse dose-time relationship (higher doses result in faster onset). **Risk of bias**: The overall RoB of the human evidence was assessed as moderate to high, reflecting limitations in study design (mostly observational, case reports which all rank at the lower levels of the hierarchy of evidence and are thus, due to their inherent design limitations, prone to bias and confounding effects), exposure characterisation, and outcome assessment. Meta-analysis was not feasible due to heterogeneity.

Number	Research Questions	EFSA 2023
		Population group: The primary evidence is from women (many taking supplements for PMS i.e., pharmaceutical use rather than dietary supplementation/fortification). There are no specific data on infants, children, or adolescents. **Mode of action**: The EFSA Panel notes that some hypotheses have been put forward with respect to potential mechanisms by which high vitamin B6 intakes could lead to peripheral neuropathy, but the causal mechanisms are still unknown and international consensus mode/mechanism of action is not yet available.: - High pyridoxine concentrations may inhibit pyridoxal kinase, reducing PLP availability and disrupting GABA synthesis and GABAergic neurotransmission. This may increase excitability of dorsal root ganglia sensory neurons, contributing to neuronal injury and peripheral neuropathy. - Quinone methide-type intermediates have been proposed but are considered unlikely to be responsible. The Panel also considers that it is unlikely that the aldehyde groups of PL or PLP are responsible for neurotoxic effects of vitamin B6.

Number	Research Questions	EFSA 2023
6	Health considerations - Are there sensitive subpopulations, exposure patterns or use scenarios that require specific consideration?	**Sensitive subpopulations**: Regular users of high-dose vitamin B6 supplements are the group most likely to exceed the UL in a general population context, with supplement products in some EU countries carrying doses as high as 400 mg/day. Women using high-dose vitamin B6 for PMS represent a historically important high-exposure group and formed the primary evidence base for the UL derivation. There is no specific evidence that children, adolescents, infants, pregnant women, or men are more susceptible to vitamin B6 neurotoxicity; ULs for children and infants are derived by allometric scaling from the adult value. It is important to distinguish between supplemental use within the scope of this UL and pharmacological use of vitamin B6 under medical supervision to treat disease. The latter, which includes high-dose therapeutic administration for conditions such as nausea and vomiting of pregnancy or inborn errors of B6 metabolism, involves doses substantially exceeding those relevant to the general population UL and is governed by clinical risk-benefit considerations rather than dietary safety thresholds. **Exposure patterns of concern**: - Intermediate-duration supplement use is the principal risk scenario. - Energy drinks containing vitamin B6: One case report described neuropathy in a male consuming 31 mg/day from 6 energy drinks daily. - Fortified foods: The Panel notes that some EU nutritional drinks and PMS-relief products contained up to 65 mg/serving, regulated in the EU as food supplements under Directive 2002/46/EC. This regulatory categorisation does not translate directly to Australia and New Zealand, where food fortification is regulated by FSANZ, but products making a therapeutic claim (such as PMS relief) fall instead under TGA therapeutic goods regulation[4].

[4] The TGA has already taken action on this basis, including label warnings above 10 mg/day and scheduling changes restricting products above 50 mg/day to pharmacist-only or prescription supply from 1 June 2027. Comparable high-dose B6 products marketed for PMS relief in Australia would therefore generally sit outside the food fortification framework, and this distinction should be kept in mind when interpreting relevance to the dietary UL.

Number	Research Questions	EFSA 2023
7	Health considerations - How are pregnancy and other potentially sensitive life stages considered in the derivation of the UL, and are different uncertainty factors or adjustments applied for specific subpopulations where appropriate?	**Pregnancy and lactation**: The Panel found no indication of specific risk or increased susceptibility to adverse effects of excessive vitamin B6 intake during pregnancy or lactation. Accordingly, the UL for adults of 12 mg/day is applied equally to pregnant and lactating women, consistent with the SCF (2000) approach. In reaching this position, EFSA conducted a systematic review of developmental toxicity evidence and concluded that there was no evidence of a positive relationship between vitamin B6 and congenital abnormalities (including heart malformations), intrauterine growth restriction, or impaired foetal growth, and no evidence of developmental effects in animal studies. The anti-lactogenic effect (suppression of lactation) was noted at intakes of approximately 600 mg/day, well above the RP originally used by SCF (2000) and the UL itself and was therefore not considered a limiting factor for UL derivation in lactating women. As developmental toxicity, anti-lactogenic effects, and the other additional endpoints considered (hip fracture, photosensitisation, impaired memorisation, testicular toxicity) were all assessed as having insufficient evidence to establish a causal relationship or derive an independent RP, peripheral neuropathy remained the sole endpoint underpinning the UL, with no pregnancy- or lactation-specific adjustment applied. **Children and adolescents**: No specific toxicity data exist for children. The absence of evidence of increased susceptibility in children should not be interpreted as evidence that children are not more susceptible; this represents a genuine data gap and source of uncertainty rather than a confirmed finding of equivalent sensitivity. ULs for children are extrapolated from the adult UL using allometric scaling (bw^0.75), an approach that adjusts for differences in body size but does not independently address potential differences in toxicokinetic or toxicodynamic sensitivity between children and adults. The UF of 4 applied in the adult derivation was not specifically designed to address paediatric susceptibility, and no additional UF was applied to account for this uncertainty in the extrapolation to children. **Infants (≥4 months):** No specific infant data. ULs are again extrapolated from the adult value by allometric scaling (bw^0.75). **Uncertainty factor:** No subgroup-specific uncertainty factors were applied beyond allometric scaling. The UF of 4 used in the adult derivation was considered sufficiently conservative to cover interindividual variability and sensitive groups, noting that the RP was based on supplemental intake only and the UL covers total (dietary + supplemental) intake.

Number	Research Questions	EFSA 2023
8	Australian and New Zealand intake profile (where relevant to interpretation of risk in Australia and New Zealand) - What are the typical dietary and supplemental sources of vitamin B6 in Australia and New Zealand?	The EFSA 2023 document does not contain data specific to Australia and New Zealand. According to the Australian Bureau of Statistics' 2023 Usual Nutrient Intakes release, nearly one third (32.9%) of dietary vitamin B6 intake came from three food categories: electrolyte, energy and fortified drinks; cereal-based mixed dishes such as sandwiches and pasta or noodle dishes; and poultry and feathered game. This places fortified beverages alongside everyday mixed meals and poultry as the dominant contributors to population-level intake, rather than the more vitamin B6-dense single foods such as brewer's yeast or wheat germ identified in older FSANZ assessments (FSANZ 2005a-c). Supplement use was reported separately in the ABS Dietary supplements, 2023 release, which found that one in three Australians (33.6%) took a dietary supplement in 2023, most commonly vitamin and/or mineral supplements. Based on older (2008) New Zealand dietary survey data fruits are the largest single contributor of vitamin B6 to the diet (13%) followed by vegetables, potatoes, kumara and taro (each 10%), poultry (7%) breakfast cereals (6%) and bread, non-alcoholic beverages, grains and pasta and beef and veal (each 5%, (NZANS, 2012).

Number	Research Questions	EFSA 2023
9	Australian and New Zealand intake profile (where relevant to interpretation of risk in Australia and New Zealand) - What are the typical dietary and supplementary intakes of vitamin B6 in the Australian and New Zealand population?	The EFSA 2023 document does not contain Australian or New Zealand intake data. FSANZ's Application A470 modelling, based on the 1995 Australian and 1997 New Zealand National Nutrition Surveys, estimated mean total dietary vitamin B6 intakes of around 1.2 mg/day in young children and 1.6–1.7 mg/day in adults. These were well below the adult UL of 25 mg/day used at the time, with mean adult intakes around 6–7% of the UL and 95th percentile intakes around 9–10%. More recent ABS 2023 data do not provide a directly comparable mean intake figure but show that dietary vitamin B6 intake is now close to, or below, the Estimated Average Requirement (EAR) for a substantial proportion of the population, particularly females and older adults. Around one third of intake came from electrolyte, energy and fortified drinks, cereal-based mixed dishes, and poultry/game. Compared with 2011–12, usual vitamin B6 intake shifted downward only slightly, by 0.1–0.3 mg/day, but this was enough to increase the proportion of Australians aged 2 years and over with inadequate intake from 28.9% to 46.7%. Overall, dietary vitamin B6 intake remains well below the UL, but adequacy has become a greater concern, particularly for females and older adults. Neither the FSANZ modelling nor the ABS 2023 usual intake data include vitamin B6 from dietary supplements. This is an important limitation because high-dose supplemental vitamin B6, rather than intake from foods and fortified beverages, is the main exposure source relevant to neuropathy risk and UL derivation. Based on older data (2008) the median usual daily intake of vitamin B6 was 2.2 mg for males and 1.6 mg for females (NZANS 2012)). Males aged 71+ years had lower intakes of vitamin B (1.6 mg per day) than males aged 15–18 years (2.5 mg per day) and 31–50 years (2.4 mg per day). Females aged 71+ years (1.3 mg per day) had lower intakes than females aged 19–50 years (1.6 to 2.1 mg per day). The estimated prevalence of inadequate intake was 16.9% (males 10.4%; females 22.9%).

Table 4 Summary of findings from data extraction for health-based research questions – new evidence review grouped based on health outcomes

#	Research Questions	Peripheral neuropathy	Hepatotoxicity	Individual susceptibility / B6 metabolism	Adverse pregnancy outcomes	Hypervitaminosis B6 prevalence / biomarker
1	Upper Level (UL) question – What excess intake of vitamin B6 is associated with adverse health effects?	Note: all listed primary studies are case reports, case series, or registry / pharmacovigilance data, which sit low in the hierarchy of evidence (below cohort and case-control designs) and cannot individually establish causation. They are presented as descriptive dose-exposure observations, not confirmatory evidence. Paluszny and Qiu (2023): ~8 mg/day for >10 yrs associated with neuropathy. Gdynia et al. (2025): ~10 mg/day for 13 yrs associated with sensorimotor PN in older adults. Morris et al. (2022): risk threshold ~900 mg/day in cystathionine beta-synthase (CBS) deficiency, a therapeutic, medically supervised dose in a rare metabolic disorder, not a general-population dietary/supplement exposure. Stewart et al. (2022): no association at moderately elevated plasma B6 in chronic idiopathic axonal polyneuropathy (CIAP) (null finding).	Studies (n=5): all involve high-dose therapeutic pyridoxal 5'-phosphate (PLP) (30–109 mg/kg/day) administered under medical supervision in rare paediatric metabolic disorders. This is pharmaceutical, not dietary or supplement, exposure and is not applicable to the general-population dietary/supplement UL.	Studies (n=2), both in a clinically defined hypophosphatasia (HPP) population rather than general dietary/supplement users: Whyte et al. (2024): tissue-nonspecific alkaline phosphatase (TNSALP) deficiency (HPP) resulted in impaired PLP clearance; elevated plasma B6 after low PN dose (~20 mg/day equivalent). Zervou et al. (2025): endogenous B6 elevation in HPP (233–828 nmol/L) resulted in neuropathic pain. Mechanistically informative for PLP clearance variability, relevant to the general population given TNSALP carrier frequency (~1/300), though the studies themselves were conducted in a clinical HPP population.	Study (n=1 systematic review): He et al. (2025): neurological symptoms in 164/1226 individuals using B6 pharmacologically for nausea and vomiting of pregnancy (NVP); doses 10–200 mg/day; adverse pregnancy outcomes at higher doses (limited, heterogeneous evidence). Maternal toxicity from NVP itself is a plausible unaddressed confounder (see row 4). This reflects therapeutic, not dietary/supplement, exposure.	Study (n=1): Bossard et al. (2022): ~30–40% of clinical samples had overdose PLP levels, driven by supplement use; no intake threshold quantified at individual level. Sample included bariatric surgery patients (altered absorption, high post-surgery multivitamin use), relevant when interpreting prevalence relative to the general population.

#	Research Questions	Peripheral neuropathy	Hepatotoxicity	Individual susceptibility / B6 metabolism	Adverse pregnancy outcomes	Hypervitaminosis B6 prevalence / biomarker
		vanHunsel et al. (2025): neuropathy reports persist even below Dutch 21 mg/day limit. Kościńska-Shukla et al. (2025): ≥200 mg/day from cumulative over-the-counter (OTC) supplement use associated with polyneuropathy, a supraphysiological self-administered exposure outside typical supplement use.. Reviews (Muhamad et al. 2023, Sun et al. 2025, Schellack et al. 2025) summarise this same case-level evidence and describe a dose-response pattern; risk reported at 50–100 mg/day in susceptible individuals. These reviews do not add independent primary evidence.				
2	Upper Level (UL) question – What is the critical human health endpoint that determines the UL, and what is the justification for selecting this endpoint?	Peripheral neuropathy is the critical endpoint. Justification: Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable
3	Upper Level (UL) question – What recent ULs or equivalent health-based guidance values exist internationally (for excess vitamin B6 intake)? How were they derived, what assumptions and	See **Table 3**	See **Table 3**	See **Table 3**	See **Table 3**	See **Table 3**

#	Research Questions	Peripheral neuropathy	Hepatotoxicity	Individual susceptibility / B6 metabolism	Adverse pregnancy outcomes	Hypervitaminosis B6 prevalence / biomarker
	uncertainties were applied, and are they suitable to adopt or adapt for Australia and New Zealand?					
4	Health considerations – What are the key adverse health effects associated with excess vitamin B6 intake, particularly neurological outcomes such as peripheral neuropathy?	Predominantly sensory axonal peripheral neuropathy: paresthesia, numbness, loss of vibration sense, ataxia, reported in supplement-use case series (Gdynia et al. 2025; Kościńska-Shukla et al. 2025; Muhamad et al. 2023). Sensorimotor involvement at higher doses in older adults (Gdynia et al. 2025: 7/8 patients). CNS/cognitive symptoms (memory, cognitive impairment) (Kościńska-Shukla et al. 2025). Neuropathic pain in HPP with elevated endogenous B6 (Zervou et al. 2025) is a distinct, non-supplemental mechanism (see individual susceptibility column). Modica et al. (2023, systematic review) describes altered B6 status (high and low) in Parkinson's disease patients on levodopa therapy, a clinical population on a specific pharmacological regimen, not general dietary/supplement	Elevated liver enzymes, cirrhosis, HCC in paediatric PNPO/ALDH7A1 deficiency on 30–109 mg/kg/day PLP (Brands et al. 2026; Lee et al. 2025; Stolwijk et al. 2025; Webster et al. 2026). Vomiting, elevated liver enzymes, rhabdomyolysis in infants on therapeutic PLP (Arai et al. 2023). Pharmaceutical use; not relevant to dietary/supplement UL.	Neuropathic pain in HPP from endogenous PLP accumulation (Zervou et al. 2025) demonstrates B6 metabolic dysregulation causing neuropathy independently of supplementation.	Neurological toxicity (paresthesia, ataxia) and possible miscarriage / intrauterine death reported at high doses (100–6000 mg/day) in case reports, used pharmacologically to treat NVP. It is unclear from the available evidence summary whether these outcomes were assessed independently of maternal toxicity associated with severe NVP itself (e.g. dehydration, electrolyte disturbance); a plausible confounder that should be checked directly in He et al. (2025) before this evidence is weighted. Evidence is limited and heterogeneous .	Elevated blood PLP (>100 nmol/L) associated with polyneuropathy risk, biomarker-level association without direct clinical outcome data (Bossard et al. 2022).

#	Research Questions	Peripheral neuropathy	Hepatotoxicity	Individual susceptibility / B6 metabolism	Adverse pregnancy outcomes	Hypervitaminosis B6 prevalence / biomarker
		exposure; relevance to UL derivation is limited.				
5	Health considerations – What is the strength of evidence for a causal association for the key adverse health effects (including consideration of mode of action, dose–response relationships, and consistency of findings)? Where relevant, how do findings differ by study type (e.g. human and animal evidence) and by population group, including infants, children, pregnancy/lactation and older adults?	Multiple independent case series and pharmacovigilance reports across countries describe a consistent pattern of association; however, consistent with the hierarchy of evidence, case series and case reports cannot on their own confirm causation — this evidence should be regarded as supportive, not confirmatory. Dose-response: supported by Muhamad et al. (2023, SR), Morris et al. (2025, registry), Schellack et al. (2025, consensus); null finding in Stewart (2022) CIAP cross-sectional is a counterbalance. Withdrawal response: documented in Paluszny and Qiu. (2023), Gdynia et al. (2025), Kościńska-Shukla et al. (2025), Theil et al. (2023, animal). Mode of action: a mode of action has been hypothesised, i.e. high pyridoxine intake causing functional PLP deficiency or PDXK inhibition, leading to dorsal root ganglia/sensory neuron damage, consistent with DRG-predominant pathology in Sun (2025) and	Evidence is from small case series in rare genetic conditions receiving very high therapeutic PLP doses under medical supervision. This reflects pharmaceutical use in a non-representative clinical population and cannot establish causality for general-population dietary/supplement exposure; retained for completeness only.	TNSALP controls plasma PLP clearance and provides mechanistic evidence for individual susceptibility. Zervou et al. (2025): endogenous elevated PLP results in neuropathy; asfotase alfa normalised PLP and reduced pain. vanHunsel et al. (2025): R^2=0.15 (dose–plasma correlation), significant interindividual metabolic variability confirmed.	Heterogeneous included studies; limited controlled evidence; adverse outcomes reported mostly from high-dose case reports involving pharmaceutical use for NVP, with little consideration of confounding factors such as maternal toxicity or other interacting exposures. This is very weak evidence and should be weighted accordingly.	No clinical adverse outcome.

#	Research Questions	Peripheral neuropathy	Hepatotoxicity	Individual susceptibility / B6 metabolism	Adverse pregnancy outcomes	Hypervitaminosis B6 prevalence / biomarker
		animal data from Sano et al. (2022). This remains a hypothesis, not an established mechanism; no internationally accepted mode of action for pyridoxine-induced peripheral neuropathy currently exists. Animal data (rat, Sano et al. 2022, 1200 mg/kg/day; dog, Theil et al. 2023, 100–150 mg/kg/day) use doses far higher than typical human exposure, as expected for hazard identification studies; these data remain relevant to establishing the dose-response relationship from which a point of departure and uncertainty factors are derived, consistent with standard toxicological risk assessment practice. Susceptible populations relevant to general-population supplement use may include older adults (Gdynia et al. 2025, mean age 80). Findings relating to Parkinson's disease patients on levodopa (where altered B6 status has been hypothesised as disease-relevant) and people with CBS deficiency on high-dose therapeutic B6 reflect pharmaceutical use and exploratory disease-mechanism research in				

#	Research Questions	Peripheral neuropathy	Hepatotoxicity	Individual susceptibility / B6 metabolism	Adverse pregnancy outcomes	Hypervitaminosis B6 prevalence / biomarker
		defined clinical populations; relevance to general-population UL derivation is limited and they are noted for completeness only. Refer to Appendix F – Technical Report for risk of bias assessment and confidence rating.				
6	Health considerations – Are there sensitive subpopulations, exposure patterns or use scenarios that require specific consideration?	Directly relevant to general-population supplement use: • Older adults: Gdynia et al. (2025), mean age 80; chronic low-dose neuropathy; sensorimotor involvement. • Self-medicating with multiple OTC supplements: Kościńska-Shukla et al. (2025), Gdynia et al. (2025) — unrecognised cumulative intake. • General population supplement users: vanHunsel et al. (2025) — neuropathy reports even below regulatory limits; weak dose-plasma correlation confirms variability. Of limited relevance to general-population UL sub-population characterisation: • Parkinson's disease on levodopa: Modica et al. (2023), specific clinical / pharmacological context, not	Rare genetic disorder patients (PNPO, ALDH7A1, CBS deficiency) and infants <9 months on therapeutic PLP reflect pharmaceutical use under medical supervision in non-representative clinical populations (Brands et al. 2026; Lee et al. 2025; Stolwijk et al. 2025; Webster et al. 2026; Morris et al. 2025; Arai et al. 2023). Retained for completeness and clinical-management awareness only; not evidence informing general-population UL sub-population characterisation.	TNSALP-deficient individuals (HPP and carriers, ~1/300 in Western populations) and genetically variable B6 metabolisers (vanHunsel et al. 2025) represent a mechanistically relevant general-population susceptibility factor (impaired PLP clearance);carrier frequency is not negligible and clearance variability is present in the general population. Retained as directly relevant context for UL uncertainty considerations.	Pregnant women using B6 pharmacologically for NVP (He et al. 2025) reflect a therapeutic-use context rather than general dietary/supplement exposure; relevance to general-population UL derivation is limited. Schellack et al. (2025), an expert consensus on therapeutic vitamin B6 use, explicitly excludes pregnant women from its dosing guidance. This exclusion points to a gap in the therapeutic-use literature specific to pregnancy, but it is not itself evidence relevant to general-population UL derivation.	Bariatric surgery patients and women 41–60 yrs most represented in overdose samples (Bossard et al. 2022). Bariatric surgery patients reflect a specific clinical population (altered absorption, post-surgery multivitamin use) rather than general dietary/supplement exposure; noted for contextual awareness only.

#	Research Questions	Peripheral neuropathy	Hepatotoxicity	Individual susceptibility / B6 metabolism	Adverse pregnancy outcomes	Hypervitaminosis B6 prevalence / biomarker
		general dietary / supplement exposure.				
7	Health considerations – How are pregnancy and other potentially sensitive life stages considered in the derivation of the UL, and are different uncertainty factors or adjustments applied for specific subpopulations where appropriate?	Evidence supports lower thresholds for older adults and suggests enhanced monitoring, but neither EFSA (2023) nor this evaluation has derived or applied a formal uncertainty factor for this subgroup.	Arai et al. (2023): age <9 months identified as an independent risk factor for hepatotoxicity in infants receiving therapeutic PLP, i.e. a pharmaceutical-use clinical context. Whyte et al. (2024): TNSALP activity varies with developmental stage, providing a biological basis for age-specific PLP metabolism that is generally relevant, independent of the clinical setting in which it was observed. In neither case has EFSA (2023) or this evaluation derived or applied a formal uncertainty factor.	Whyte et al. (2024): TNSALP activity determines PLP clearance capacity, providing a biological basis for a genotype-specific uncertainty factor. Since TNSALP carrier frequency in the general population is ~1/300, this rationale extends beyond the clinical HPP population studied and could support a higher uncertainty factor for individuals with reduced PLP clearance more broadly. However, neither EFSA (2023) nor NHMRC (2006) currently applies such an adjustment in their UL derivations, and this evaluation does not propose one.	Adverse neurological outcomes reported in pregnant women using B6 pharmacologically at ≥30 mg/day, with possible foetal effects at higher doses; this evidence arises from therapeutic NVP treatment rather than dietary/supplement exposure, and maternal toxicity from NVP itself is a plausible unaddressed confounder (see row 4). Caution is needed before concluding a pregnancy-specific UL is warranted on this basis alone. Schellack et al. (2025) explicitly excludes pregnant/lactating women, citing insufficient evidence, a data gap rather than a positive finding. Neither EFSA (2023) nor this evaluation has derived or applied a formal uncertainty factor for pregnancy on this basis.	Not directly relevant to UF derivation.
8	Australian and New Zealand intake profile (where relevant to interpretation of risk in Australia and New Zealand) – What are the typical dietary and supplemental sources of vitamin B6 in Australia and New Zealand?	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable

#	Research Questions	Peripheral neuropathy	Hepatotoxicity	Individual susceptibility / B6 metabolism	Adverse pregnancy outcomes	Hypervitaminosis B6 prevalence / biomarker
9	Australian and New Zealand intake profile (where relevant to interpretation of risk in Australia and New Zealand) – What are the typical dietary and supplementary intakes of vitamin B6 in the Australian and New Zealand population?	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable

4.4 Adverse key event reports

Adverse event reporting databases were reviewed as supporting contextual evidence for the vitamin B6 UL evaluation, including the Therapeutic Goods Administration's Database of Adverse Event Notifications – medicines (DAEN – medicines), the World Health Organization's VigiAccess, the United States Food and Drug Administration's FDA Adverse Event Monitoring System (AEMS) Public Dashboard, the European Medicines Agency's EudraVigilance: European database of suspected adverse drug reaction reports, and Health Canada's Canada Vigilance Adverse Reaction Online Database.

Across these databases, adverse event reports associated with pyridoxine or vitamin B6-containing products were identified, with reporting generally weighted toward recent years. This pattern may reflect increased product use, greater clinical and regulatory awareness of vitamin B6-associated neuropathy, changes in reporting practices, or stimulated reporting, rather than demonstrating a true increase in population-level risk.

The main signal across the databases was neurological, particularly neuropathy-type symptoms such as paraesthesia, peripheral neuropathy, hypoaesthesia, burning sensation, pain in extremity, gait disturbance, balance problems, muscular weakness and dizziness. This pattern is consistent with the critical effect identified in existing guidance and supports the continued focus on peripheral neuropathy as the key adverse outcome for UL evaluation.

Reports were commonly in adults, including middle-aged and older adults, and several datasets showed a higher proportion of reports in females. However, interpretation is limited by missing demographic information, differences in product use, and differences in reporting behaviour. Reports also frequently involved multi-ingredient products, including B-complex products, magnesium/vitamin B6 combinations, multivitamins, pregnancy supplements, stress or energy formulations, and injectable preparations. This highlights the practical difficulty of attributing reported effects to vitamin B6 alone and supports the need to consider cumulative exposure from multiple supplemental sources.

These data are useful for signal detection and for confirming that neuropathy-type events continue to be reported in real-world use of vitamin B6-containing products. However, spontaneous adverse event reports cannot be used to estimate incidence, population risk, causality, threshold doses or dose–response relationships. Reports are often incomplete and may lack reliable information on dose, duration, vitamin B6 form, co-exposures and underlying health conditions.

5.0 Discussion

5.1 Suitability of health-based guidance for adoption/adaptation

The key studies underpinning the EFSA (2023) and NHMRC (2006) vitamin B6 ULs were assessed to support interpretation of the suitability of existing health-based guidance for adoption or adaptation. **Table 5** summarises the main studies relied upon in these derivations, including Dalton & Dalton (1987) and Phillips et al. (1978) for EFSA, and Bernstein & Lobitz (1988) and Del Tredici et al. (1985) for NHMRC.

The assessment shows that the human evidence base underpinning both candidate guidance values is limited. Dalton & Dalton (1987), which anchors EFSA's human reference point, was rated as high risk of bias due to retrospective self-reported exposure, self-reported outcome assessment, lack of blinding or randomisation, and limitations in the study population. However, the study remains important because it provides the largest available human dataset, includes a control group, and reports duration-response and reversibility following cessation. These features support its use as part of a broader weight-of-evidence assessment, rather than as a stand-alone basis for the UL.

The two human studies underpinning the current NHMRC (2006) UL, Bernstein & Lobitz (1988) and Del Tredici et al. (1985), were also rated as high risk of bias. Both were small, uncontrolled studies conducted in clinical populations with pre-existing neuropathy-related conditions, limiting their applicability to the general healthy population. Their short exposure durations are also important given the recognised inverse relationship between vitamin B6 dose and time to onset of peripheral neuropathy.

In contrast, the Phillips et al. (1978) dog study used by EFSA as an independent animal cross-check was rated as low risk of bias, reflecting its controlled experimental design, clear dose-response and sensitive histopathological endpoint. While the animal study requires interspecies extrapolation and substantial uncertainty factors, the close agreement between EFSA's human-derived and animal-derived UL values strengthens confidence in the final UL.

Overall, it is indicated that the reliability of the EFSA vitamin B6 UL evidence base depends less on any single study and more on the consistency of the overall weight of evidence. The high risk of bias in the human studies should be recognised as an important uncertainty. However, EFSA's use of multiple converging lines of human evidence, supported by an independent low risk-of-bias animal cross-check, provides a stronger and more transparent basis for adoption or adaptation than reliance on the earlier NHMRC human studies alone.

Table 5 Summary of assessment of key studies underpinning the guidance ULs for vitamin B6

	Dalton & Dalton (1987) - basis for EFSA (2023) RP	Phillips et al. (1978) - EFSA cross-check (dog)	Bernstein & Lobitz (1988) - basis for NHMRC (2006)	Del Tredici et al. (1985) - basis for NHMRC (2006)
Study type	Case-control (humans, n=172)	Controlled experimental study (Beagle dogs, n=14)	Uncontrolled clinical study (diabetic neuropathy patients, n=16)	Uncontrolled clinical study (carpal tunnel syndrome patients, n= not stated)
Population	Women attending a PMS clinic (cases), general/healthy adult population taking B6 supplements (controls). This design compares a population using B6 pharmacologically for PMS against a population using B6 as an ordinary supplement, so it does not cleanly address the general-population question this assessment is trying to inform, and neuropathy differences may partly reflect population differences rather than a pure dose-response effect. It remains the most informative single study in EFSA's weight-of-evidence assessment, but this	Healthy female beagle dogs	Patients with pre-existing diabetic neuropathy	Patients with carpal tunnel syndrome

	Dalton & Dalton (1987) - basis for EFSA (2023) RP	Phillips et al. (1978) - EFSA cross-check (dog)	Bernstein & Lobitz (1988) - basis for NHMRC (2006)	Del Tredici et al. (1985) - basis for NHMRC (2006)
	limitation should temper the weight placed on the resulting RP.			
Dose	<50–500 mg/day (mean 117 mg/day symptomatic, 116 mg/day control)	0, 50, 200 mg/kg bw/day	150 mg/day	150 mg/day (n=16) or 300 mg/day (n=8)
Duration	Mean 2.9 ± 1.9 yr (symptomatic) vs 1.6 ± 2.1 yr (asymptomatic)	~107 days	Up to 6 months (only 4/16 completed)	4 months
Outcome assessed	Self-reported neurological symptoms elicited via structured clinical interview, considered alongside raised serum B6. This is a critical limitation: there is no objective, clinician-measured assessment of neuropathy (e.g. nerve conduction studies) in this study; the outcome itself, not just the exposure, relies on recall and self-report within an interview setting, with no blinding of the interviewer to case/control status.	Histopathology (myelin/axon loss) and clinical signs	Distal motor latency (electro-physiology)	Distal motor latency (electro-physiology)
Finding	60% with raised serum B6 reported symptoms; duration-dependent; reversible on cessation. The reversibility finding is an important piece of evidence supporting a causal interpretation, though it remains based on self-report rather than objective confirmation.	LOAEL of 50 mg/kg bw/day (histological lesions even at lowest dose tested)	No deterioration of nerve function reported	Improvement in distal motor latency reported
Control group	Yes	Yes (0 mg/kg group)	No	No
Key strengths	Largest human dataset available; control group; duration-response relationship; reversibility on cessation (supports causal interpretation). Note: exposure was self-reported throughout (see limitations). Raised serum B6 corroborates that supplementation	Controlled design; sensitive (histo-pathological) endpoint; clear dose-response	None identified	None identified

	Dalton & Dalton (1987) - basis for EFSA (2023) RP	Phillips et al. (1978) - EFSA cross-check (dog)	Bernstein & Lobitz (1988) - basis for NHMRC (2006)	Del Tredici et al. (1985) - basis for NHMRC (2006)
	occurred and relates to symptom status, but does not independently verify the dose or duration reported by participants.			
Key limitations / RoB concerns	Substantial methodological limitations: retrospective, self-reported exposure with recall bias, particularly for symptomatic participants reporting B6 use over several years; outcome assessment also self-reported via structured clinical interview, with documented concerns about leading questions in similar contemporaneous studies and no blinding of interviewers to case/control status; not randomised; no random sampling of the general population (cases drawn from a PMS clinic, i.e. pharmaceutical / therapeutic use context); does not directly address general-population dietary / supplement exposure, which is the purpose of this assessment; SCF (2000) also questioned whether “no dose difference” in the data masks a true dose-response relationship. Taken together, this is a study with substantial design weaknesses that must be weighed accordingly.	Requires interspecies extrapolation (large UF needed); relatively short duration vs chronic human exposure	No control group; tiny complete sample (n=4 at 6 months); pre-existing neuropathy population (high indirectness); short duration inconsistent with known inverse dose-duration relationship; SCF (2000) noted reporting discrepancies (patient numbers / duration)	No control group; small sample (n=24); very short duration (4 months); CTS population, i.e. outcome measure (distal motor latency) confounded by the underlying condition itself (high indirectness)
Overall RoB rating	High risk of bias. Based on OHAT-type criteria, the study was not randomised and allocation to groups was not adequately concealed; the case-control design does not	Low risk of bias (well-controlled experimental design)	High risk of bias. As a small, uncontrolled case series in a non-representative population with an unblinded design, this study design	High risk of bias. As with Bernstein & Lobitz (1988), this is a small, uncontrolled case series with no control group, unblinded

	Dalton & Dalton (1987) - basis for EFSA (2023) RP	Phillips et al. (1978) - EFSA cross-check (dog)	Bernstein & Lobitz (1988) - basis for NHMRC (2006)	Del Tredici et al. (1985) - basis for NHMRC (2006)
	control for confounding between groups; experimental / assessment conditions (clinical interview) were not standardised or blinded across groups; and both exposure and outcome relied on self-report. These design features represent a high potential for systematic error, notwithstanding the study's relatively large sample size and the supporting biomarker and dose-response signals.		carries a high potential for systematic error and sits low in the hierarchy of evidence.	assessment, and a non-representative population, all of which indicate a high risk of bias.

5.2 Overview of new evidence

This section provides an overview of the dose–response information for vitamin B6 from the evidence review of recent literature (published 2022 onwards), which may influence the findings of this Evidence Evaluation Report, along with a discussion of the overall confidence in this body of evidence. This includes consideration of RoB of individual studies (see Appendix F in the Technical Report) where appropriate. Individual RoB assessments were summarised in tables for the reported health outcome. Overall RoB ratings for each health outcome were determined using guidance from OHAT (2019) and considered alongside unexplained inconsistency, indirectness, imprecision, publication bias, magnitude of effect, and residual confounding to determine overall confidence ratings, consistent with a GRADE-informed approach.

Table 6 provides a summary of the RoB assessment for the new primary studies. The detailed rationale for selection of bias domains is provided in Appendix F in the Technical report.

5.2.1 Dose response and overall confidence by health outcomes

5.2.1.1 Neurological effects - Peripheral neuropathy

Peripheral neuropathy is the critical effect underpinning EFSA's (2023) UL derivation, so the recent literature for this outcome was reviewed primarily to test whether new evidence is consistent with, or challenges, EFSA's conclusions. Primary studies were identified, spanning human case series, a cross-sectional registry analysis, pharmacovigilance data, a systematic review, and controlled animal studies. With the exception of the controlled animal studies, these study designs sit low in the hierarchy of evidence and are inherently limited in their ability to establish causation or provide reliable quantitative estimates; the human evidence base for this outcome should therefore be considered of generally low reliability on study design grounds alone, before any consideration of the individual limitations of each study.

- Gdynia et al. 2025 (case series, high risk of bias): doses included ~10 mg/day for 13 years, plus other unspecified higher-dose multivitamin use. Notably, 10 mg/day is below EFSA's UL (12 mg/day) and far below the RP (50 mg/day), yet neuropathy was attributed to B6 in this case.
- Paluszny and Qiu 2023 (case control, high risk of bias): ~6 mg supplement/day for >10 years (estimated total ~8 mg/day with diet); authors explicitly noted this is below EFSA's 12 mg/day UL.
- Stewart et al. 2022 (cross-sectional, high risk of bias): plasma B6 categorised as normal (5–50 µg/L), mildly to extremely elevated (up to ≥300 µg/L); no dietary/supplement dose reported, exposure assessed via biomarker only, not intake.
- Zervou et al. 2025 (case series, high risk of bias): reported serum vitamin B6 levels of 233–828 nmol/L, around 2–7 times the upper reference limit. These elevations were endogenous and related to HPP, not supplement use, so no comparable mg/day dose is available.
- van Hunsel et al. 2025 (pharmacovigilance, high risk of bias): reported doses varied, with most cases occurring before 2018. Although the Dutch regulatory cap was set at 21 mg/day after 2018, reports of neuropathy continued, including some below the cap. One post-cap report involved a much higher dose of 200 mg/day.
- Sano et al. 2022 (animal, published peer-reviewed paper rather than a GLP study report; high risk of bias) used pyridoxine as a positive-control peripheral neurotoxicant in rats at 1200 mg/kg/day for one to three days. Reporting gaps drive the high RoB rating: small group sizes (n=4 per time point), incomplete outcome data for the pyridoxine (excluded from the day 8 necropsy group unlike the trimethyltin (TMT) comparator), and a dose rationale partly based on unpublished internal data. A full GLP study report with complete data may have warranted a lower risk of bias rating.
- Theil et al. 2023 (animal, moderate risk of bias): escalating pyridoxine doses up to 100–150 mg/kg/day (weeks 1–5), then 50 mg/kg/day (weeks 8–13) in juvenile beagle dogs directly comparable in magnitude to the Phillips et al. (1978) LOAEL of 50 mg/kg bw/day. This supports EFSA’s broader weight-of-evidence basis for the animal-derived UL, rather than serving as a separate basis for the animal cross-check.

The key finding is that two of the better-characterised human case studies (Gdynia et al. 2025 and Paluszny and Qiu 2023), both with biomarker-confirmed elevated serum B6, reported neuropathy at intakes of 6-10 mg/day. However, as case studies, these reports rank low on the hierarchy of evidence and are inherently prone to limitations including small sample size, absence of a control group, and an inability to fully exclude confounding factors or unreported additional sources of vitamin B6; they cannot establish a reliable population-level threshold in the way a controlled study could. With this caveat in mind, these intakes are below EFSA's UL of 12 mg/day and well below the RP of 50 mg/day, which is potentially relevant because it differs from EFSA's 2023 approach, where the RP was based on the lowest dose group in Dalton & Dalton (1987), reported as <50 mg/day. Given the low reliability of case-study evidence, this difference should be treated as a signal warranting attention rather than a finding that challenges or revises EFSA's RP on its own.

The van Hunsel et al. (2025) pharmacovigilance analysis provides a third, lower-confidence data point in the same direction, with neuropathy reports continuing below the Dutch regulatory cap of 21 mg/day. However, this evidence is also limited by the inherent uncertainties of spontaneous reporting data.

Theil et al. (2023), (Tier 2, well controlled), followed a dose-escalation pattern of exposure starting at 50 mg/kg bw per day and increasing to 150 mg/kg bw per day with a weekly dose increment of 50 mg/kg bw (consistent with the LOAEL range reported in Phillips (1978)). The dogs were then provided a treatment holiday from study weeks 6 to 10 with vitamin B6 re-treatment at 50 mg/kg bw per day recommencing on study week 10 and continuing to study week 13 (animal termination). While the study provides potentially useful mechanistic data and proof of concept for use of neurofilament light chain as a biomarker for drug-induced peripheral neuropathy, it is not useful for dose-response assessment.

Based on the assessed studies, Theil et al. (2023), while well controlled and providing useful mechanistic and biomarker proof-of-concept data, is not suitable for dose-response assessment given its reactive dose adjustment, small group sizes for the pyridoxine, and lack of formal statistical comparison, and is therefore not relied upon for this purpose. A separate group of lower-confidence human case reports and pharmacovigilance signals (Gdynia et al. 2025, Paluszny and Qiu 2023, van Hunsel et al. 2025) suggests neuropathy may occur at intakes below EFSA's RP and UL in some individuals, though, as case-based evidence, this signal warrants attention rather than being treated as a basis for revising the existing RP.

5.2.1.2 Individual susceptibility / B6 metabolism

Whyte et al. (2024) was assessed as a mechanistic study with a moderate RoB. The study used a short oral pyridoxine challenge of approximately one third mg/kg bw/day for six days, with blood collected 24 hours after the final dose. This dose is approximately equivalent to 23 mg/day for a 70 kg adult, although the study population was paediatric. The challenge dose was below EFSA’s RP on a body weight basis and was used to assess vitamin B6 metabolism and clearance, not to test toxicity.

The main finding was that individuals with impaired TNSALP activity, specifically patients with HPP, can accumulate PLP abnormally even after a modest, short-term pyridoxine dose. This supports the concept that genetic differences can affect PLP clearance and may contribute to individual susceptibility.

Although the study was conducted in a paediatric HPP population, its relevance is mechanistic rather than directly toxicological. It does not provide dose–response data for the general population and does not inform a point of departure for UL derivation. However, it supports the need to account for toxicokinetic variability in the general population, including individuals with reduced PLP clearance capacity. This is relevant to the human intraspecies uncertainty factor used in UL derivation and supports retaining, rather than reducing, this component of the uncertainty factor.

For this reason, Whyte et al. (2024) was retained in the RoB and confidence-rating tables under the “Other” health outcome category. Its value lies in characterising uncertainty around individual susceptibility, rather than in assessing toxicity or deriving a quantitative UL.

5.3 Studies excluded from RoB assessment or from further assessment due to being out of scope

Before presenting the formal RoB and confidence assessments, it is necessary to clarify which studies identified in the evidence scan were included in this quantitative assessment, and which were excluded on scope grounds. Consistent with the NHMRC Final NRV Methodological Framework, which specifies that ULs are intended for the general healthy population and exclude sub-populations with genetic disease or other conditions that predispose them to adverse effects at levels below those relevant to the general population, the following studies have been excluded from the RoB assessment tables and from further consideration in dose-response or point of departure derivation, on the basis that they reflect

pharmaceutical or therapeutic use of vitamin B6 in non-representative clinical populations rather than general dietary or supplement exposure.

5.3.1 Excluded due to therapeutic/pharmaceutical use in non-representative clinical populations

Brands et al. (2026), Webster et al. (2026), and Lee et al. (2025), all reporting hepatotoxicity/hepatocellular carcinoma in patients with PNPO deficiency receiving high-dose therapeutic PLP under medical supervision (24–109 mg/kg/day). These doses are orders of magnitude above the general-population RP and the underlying metabolic disorder itself confounds attribution of liver outcomes to PLP dosing; these studies are noted in **Section 5.2.1.2** for clinical context only, .

Arai et al. (2023) (therapeutic PLP, 10–80 mg/kg/day, in infants with epileptic spasms syndrome) and **Morris et al. (2025)** (therapeutic PLP, median ~3.8 mg/kg/day up to >900 mg/day, in patients with cystathionine beta-synthase deficiency). Both reflect high-dose clinical treatment in defined patient populations and are noted for clinical context only.

Bossard et al. (2022), provides contextual prevalence data on blood PLP status in a clinical sample (deficiency <30 nmol/L, normal 30–100 nmol/L, overdose >100 nmol/L), with overdose identified in 30–40% of samples, driven by supplement use. Exposure was not directly measured at the individual dose level, and the sample included bariatric surgery patients, a population with altered absorption; this study is retained as contextual prevalence information only and has not been included in the RoB-weighted dose-response assessment.

5.3.2 Excluded from the RoB-weighted dose-response assessment but retained as mechanistic or uncertainty-factor-relevant evidence

Zervou et al. (2025), reporting neuropathic pain associated with endogenous PLP accumulation in HPP patients. As this exposure is endogenous (arising from impaired alkaline phosphatase-mediated PLP clearance) rather than from dietary or supplemental intake, no comparable mg/day dose exists and the study cannot contribute to dose-response assessment; it is therefore not included in **Table 6** to **Table 8**of this Overall Evaluation, although it remains valuable mechanistic evidence (discussed in **Section 5.2.1.1**) supporting elevated circulating PLP, irrespective of source, as the proximate driver of neuropathy.

5.3.3 Excluded as non-primary studies with no evidence to change the evaluation

Several non-primary sources were identified (Appendix E, Technical report), including systematic reviews, narrative reviews, an expert consensus statement and a clinical reference monograph. These were not assessed for RoB but were reviewed for context.

Overall, these sources support the broader association between high-dose supplemental vitamin B6 and peripheral neuropathy, generally describing dose-related effects and improvement after stopping supplementation. However, they did not provide new primary data or quantitative evidence suitable for UL derivation. The reviews also highlighted the same limitations identified in the primary evidence base, including small sample sizes, heterogeneous data, reliance on case reports, uncertainty around toxic thresholds, and limited evidence for pregnancy and lactation.

These sources do not change the conclusions of the review. Their main value is to reinforce the consistency of the vitamin B6–neuropathy signal across independent sources and to confirm existing evidence gaps, particularly around sensitive life stages and therapeutic high-dose use.

5.4 Overall Evaluation

Following the exclusions set out above, six primary studies relevant to peripheral neuropathy were assessed for RoB and confidence (**Table 6**, **Table 7**): Gdynia et al. (2025), Paluszny and Qiu (2023), Stewart et al. (2022), van Hunsel et al. (2025), Sano et al. (2022), and Theil et al. (2023). One additional study, Whyte et al. (2024), was assessed under the 'Other' outcome category for its relevance to toxicokinetic uncertainty rather than to a specific health outcome.

Of the four human studies, all received Tier 2 to Tier 3 (moderate to high) risk of bias ratings, reflecting the predominance of case-based and cross-sectional designs, reliance on self-reported or biomarker-only exposure characterisation, absence of comparison groups in three of the four studies, and an inability to adequately control for confounding. These limitations translated into Low initial confidence ratings for all four studies (**Table 7**), which were further downgraded to Very Low in the final confidence rating (**Table 8**), reflecting an additional deduction for RoB associated with the cross-sectional and case-series designs and the absence of comparison groups, consistent with a GRADE-informed approach. This Very Low final confidence means that, while these studies provide a consistent qualitative signal that neuropathy has been reported at intakes below EFSA's RP of 50 mg/day in some individuals (Gdynia et al. 2025, Paluszny and Qiu 2023) and below the Dutch regulatory cap of 21 mg/day (van Hunsel et al. 2025), this evidence is not considered sufficiently reliable to revise EFSA's existing RP or UL. It is instead treated as a signal warranting ongoing attention, for example through continued pharmacovigilance monitoring, rather than as a basis for quantitative reassessment.

The two controlled animal studies, Sano et al. (2022) and Theil et al. (2023), received Tier 3 (high risk of bias) and Tier 2 (moderate risk of bias) ratings, respectively, and a Moderate initial confidence rating, reflecting their controlled experimental design, appropriate comparison groups, and use of objective outcome measures, including histopathology, electrophysiology and/or biomarker analysis. This Moderate confidence rating was retained in the final confidence rating following a net adjustment of zero: a one-level downgrade for indirectness, given that both studies used doses far exceeding general-population exposure, offset by a one-level upgrade for large magnitude and consistency of effects. The animal evidence remains consistent with, and supports, EFSA's existing animal-based cross-check derivation based on Phillips et al. (1978).

Considered together, the overall body of new evidence for peripheral neuropathy comprises a Very Low confidence human signal that neuropathy may, in some individuals, occur at intakes below EFSA's current RP and UL, alongside a high confidence animal evidence base that remains consistent with, and corroborates, EFSA's existing dose range. Neither component of the new evidence base is considered sufficient, on its own or in combination, to justify a quantitative revision of EFSA's RP, UF, or UL at this time. The new human evidence is most useful for identifying uncertainty around individual susceptibility, rather than for re-deriving the RP.

In relation to the studies excluded on scope grounds, the hepatotoxicity/HCC signal in PNPO-deficient patients receiving very high-dose therapeutic PLP, while a genuinely new finding not previously identified by EFSA (2023), is not considered relevant to the general-population UL, consistent with the NHMRC Final NRV Methodological Framework's exclusion of non-representative sub-populations from UL derivation, and is more appropriately addressed through clinical management guidance for this specific patient group. The mechanistic evidence from Zervou et al. (2025) and Whyte et al. (2024) is informative for understanding the role of circulating PLP and toxicokinetic variability in susceptibility and is recommended for consideration when assessing the adequacy of the existing uncertainty factor for intraspecies variability, though it does not itself warrant a

change to the UF at this time given the absence of quantitative data suitable for that purpose.

Table 6 Summary of risk of bias (RoB) assessment for new primary studies

Rating key: ++ = definitely low RoB; + = probably low RoB; NR = not reported; – = probably high RoB; –– = definitely high RoB; NA = not applicable to this study design

Tier 1 = Low risk of bias (RoB); Tier 2 = Moderate risk of bias (RoB); Tier 3 = High risk of bias (RoB)

Health Outcome	Specific Outcome	Study Type	Study	1. Randomisation	2. Allocation concealment	3. Comparison groups	4. KEY - Confounding	5. Identical conditions	6. Blinding	7. Attrition / exclusion	8. KEY - Exposure characterisation	9. KEY - Outcome assessment	10. Selective reporting	11. Other threats	**Risk of Bias Tier**
Neurological	Neuropathy severity	Human cross – sectional	Stewart et al. 2022	NA	NA	+	–	NA	NR	–	–	+	+	–	3
Neurological	Sensorimotor polyneuropathy (PN)	Human case series	Gdynia et al. 2025	NA	NA	NA	–	NA	NA	–	–	+	+	–	3
Neurological	Peripheral neuropathy	Human case control	Paluszny and Qiu 2023	NA	NA	NA	––	NA	NA	–	–	+	+	–	3
Neurological	Neuropathy reporting patterns	Pharmacovigilance study	van Hunsel et al. 2025	NA	NA	–	––	NA	NA	–	––	–	+	–	3
Neurological	Neurotoxicity / neuronal damage	Animal	Sano et al. 2022	+	NR	+	+	++	NR	+	++	–	+	–	3
Neurological	Peripheral neurotoxicity	Animal	Theil et al. 2023	+	NR	++	+	+	NR	+	+	+	+	–	2

Health Outcome	Specific Outcome	Study Type	Study	1. Randomisation	2. Allocation concealment	3. Comparison groups	4. KEY - Confounding	5. Identical conditions	6. Blinding	7. Attrition / exclusion	8. KEY - Exposure characterisation	9. KEY - Outcome assessment	10. Selective reporting	11. Other threats	**Risk of Bias Tier**
Other	Plasma B6 vitamer responses	Human cross - sectional	Whyte et al. 2024	NA	NA	+	–	–	NR	–	+	+	+	–	2

Table 7 Summary of initial confidence rating for new primary studies

Rating Key: Yes – criterion met; No – criterion not met; NA – not applicable for this study type.

Confidence rating: High confidence; Moderate confidence; Low confidence.

Health Outcome	Study Type and ID	Study design - controlled exposure	Study designs - Exposure prior to outcome	Study design - Outcome assessed on individual level	Study design - Use of comparison group	Study design - Appropriate statistical analyses	Study design - Concurrent control group	Study design - Sufficient number of tested per group	Study design - Appropriate parameters to assess adverse effects	**Initial Study confidence**	**Initial Confidence rating**
Neurological	Human cross – sectional Stewart et al. 2022	No	No	Yes	Yes	NA	NA	NA	NA	Low	Low
Neurological	Human case series Gdynia et al. 2025	No	Yes	Yes	No	NA	NA	NA	NA	Low	
Neurological	Human case control Paluszny and Qiu 2023	No	Yes	Yes	No	NA	NA	NA	NA	Low	
Neurological	Pharmacovigilance study van Hunsel et al. 2025	No	Yes	Yes	No	NA	NA	NA	NA	Low	

Health Outcome	Study Type and ID	Study design - controlled exposure	Study designs - Exposure prior to outcome	Study design - Outcome assessed on individual level	Study design - Use of comparison group	Study design - Appropriate statistical analyses	Study design - Concurrent control group	Study design - Sufficient number of tested per group	Study design - Appropriate parameters to assess adverse effects	**Initial Study confidence**	**Initial Confidence rating**
Neurological	Animal Sano et al. 2022	NA	NA	NA	NA	Yes	Yes	No	Yes	Moderate	Moderate
Neurological	Animal Theil et al. 2023	NA	NA	NA	NA	Yes	Yes	Yes	Yes	High	
Other	Human cross – sectional Whyte et al. 2024	No	No	Yes	Yes	NA	NA	NA	NA	Low	-

Table 8 Final confidence rating in the body of evidence

Health Outcome	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Neurological effects – Human studies	Low	-1 Risk of bias (cross-sectional/case series designs, no comparison groups)	Low -> Very low

Health Outcome	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Neurological effects – Animal studies	Moderate	-1 Indirectness; +1 Large magnitude of effect(1)	Moderate

(1) +1 upgrade for dose-response can only be considered for Theil et al. 2023 study.

6.0 Conclusions

This Evidence Evaluation Report has assessed the suitability of EFSA's (2023) vitamin B6 UL for adoption or adaptation in the Australian and New Zealand context and has reviewed recent primary literature published since 2022 to determine whether new evidence is consistent with, or challenges, EFSA's conclusions.

EFSA (2023) was confirmed as the only candidate guidance value meeting the pre-defined credibility threshold and remains the only post-2006 reassessment of the vitamin B6 UL internationally. EFSA's RP of 50 mg/day is not derived from a single study; it reflects a weight-of-evidence assessment across multiple converging and independent lines of evidence, comprising the Dalton & Dalton (1987) case-control study, a positive rechallenge case, additional case reports, and Dutch and French nutrivigilance data. This distinguishes EFSA's approach from SCF (2000), which relied primarily on the mean intake reported in Dalton & Dalton (1987) alone to derive its higher RP of 100 mg/day. EFSA's human-based derivation (RP of 50 mg/day, UF of 4: ×2 for the inverse dose-time relationship, ×2 for limited data and interindividual variability, giving 12.5 mg/day) was cross-checked against an independent animal-based derivation (Phillips et al. 1978, dog LOAEL of 50 mg/kg bw/day, UF of 300: ×2 interspecies toxicokinetics, ×2.5 interspecies toxicodynamics, ×10 intraspecies variability, ×2 subchronic-to-chronic extrapolation, ×3 absence of a NOAEL, giving 11.7 mg/day). The concordance between these two independently derived values increased confidence in the final UL of 12 mg/day.

This weight-of-evidence approach, together with the choice of critical effect, points of departure, and uncertainty factor derivations, is considered methodologically sound and suitable for adoption or adaptation in Australia and New Zealand. No population-specific factor has been identified that would render EFSA's approach inappropriate; regulatory differences between the EU and Australia and New Zealand relate to exposure context rather than to the underlying toxicological assessment.

The main caveats relate to the quality of the underlying evidence base rather than to jurisdictional applicability. A formal LOAEL could not be established from human data, and the anchor study within EFSA's weight-of-evidence assessment, Dalton & Dalton (1987), was rated High risk of bias, reflecting self-reported exposure and outcome assessment, absence of blinding and randomisation, and a study population in which cases were drawn from a PMS clinic using vitamin B6 pharmacologically, compared against controls using vitamin B6 as an ordinary supplement, a mismatch that does not cleanly address the general-population exposure question this assessment is trying to inform. This is not unique to EFSA's derivation: the two studies underpinning the current NHMRC (2006) UL (Bernstein & Lobitz 1988; Del Tredici et al. 1985) were also rated High risk of bias. By contrast, the animal study underpinning EFSA's cross-check, Phillips et al. (1978), was rated Low risk of bias. This pattern, uniformly high risk of bias in the human anchor studies across both candidate guidance values, contrasted with low risk of bias in the controlled animal evidence, is a key consideration in interpreting the overall reliability of the vitamin B6 UL regardless of which value is adopted. Despite these limitations, Dalton & Dalton (1987) has been retained as the anchor study in the absence of any more directly applicable general-population dataset. No internationally accepted mode of action for pyridoxine-induced peripheral neuropathy currently exists, limiting biological coherence even though this does not preclude a causal interpretation given the consistency, dose-response, and reversibility observed across the evidence base.

The review of recent literature did not identify evidence sufficient to revise EFSA's RP, UF, or UL. New human evidence (Gdynia et al. 2025; Paluszny and Qiu 2023; van Hunsel et al. 2025) provides a Very Low confidence signal that neuropathy may occur in some individuals below EFSA's current RP and UL; given small case numbers, retrospective self-reported exposure, and the possibility of unreported additional B6 sources, this is not a reliable basis

for quantitative revision but warrants ongoing pharmacovigilance monitoring. New animal evidence (Sano et al. 2022; Theil et al. 2023) received Moderate confidence ratings, with Theil et al. (2023) corroborating the broader weight-of-evidence basis for EFSA's animal cross-check rather than constituting a separate basis and remains consistent with EFSA's existing dose range.

Hepatotoxicity and hepatocellular carcinoma in PNPO-deficient patients receiving very high-dose therapeutic PLP, is not relevant to general-population UL derivation, consistent with the NHMRC Final NRV Methodological Framework's exclusion of non-representative clinical sub-populations and is more appropriately addressed through clinical management guidance. Mechanistic evidence on individual susceptibility (Whyte et al. 2024; Zervou et al. 2025) supports toxicokinetic variability in PLP clearance as relevant to the intraspecies component already built into EFSA's uncertainty factor, given that TNSALP carrier frequency may be relevant at the population level, with an estimated frequency of approximately 1 in 300.

Overall, the new evidence identified in this review does not appear sufficient to warrant revision of EFSA's (2023) UL of 12 mg/day, which this evaluation has identified as the most appropriate current guidance value for potential adoption or adaptation in Australia and New Zealand, in place of the current NHMRC (2006) UL of 50 mg/day. The available evidence remains broadly consistent with the current weight-of-evidence basis for peripheral neuropathy as the critical endpoint, with support from both human and animal data. However, this conclusion should be interpreted considering the high risk of bias and generally low to very low reliability of the human evidence base, as well as ongoing uncertainties around individual susceptibility and the absence of an established mode of action.

7.0 Review Team

Name	Position	Responsibilities
Ms Tarah Hagen, MSc DABT RACTRA	Technical Discipline Manager – Toxicology & Risk Assessment, SLR	Technical oversight and internal peer review
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Ms Emma Craven MSs	Project Consultant – Soils, Geochemistry, Toxicology & Risk, SLR	Literature searching, preliminary title screen

8.0 Declared Interests

Please refer to the Disclosure of Interest forms submitted separately to NHMRC.

9.0 Acknowledgements

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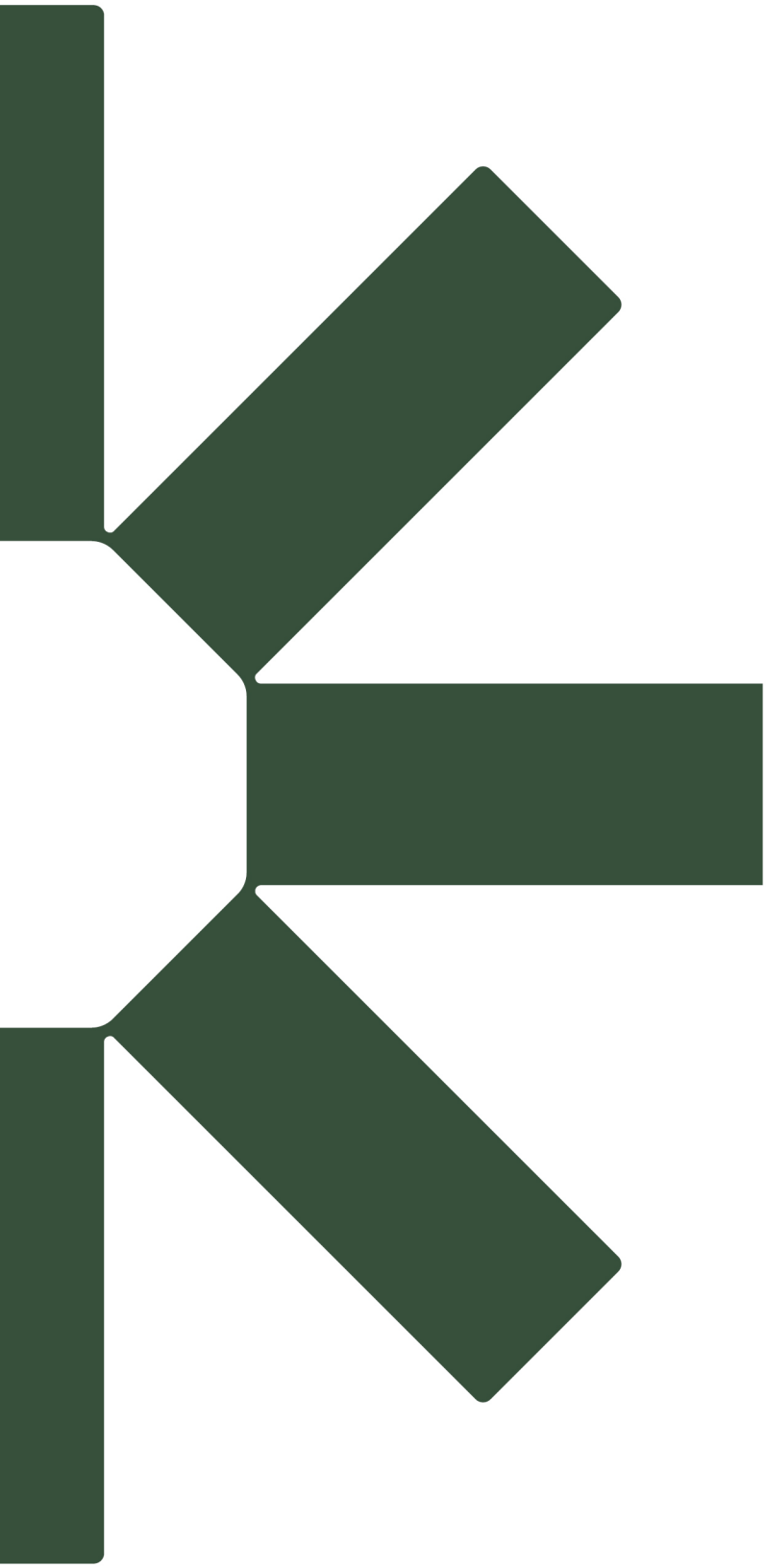

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