Evidence Evaluations for Vitamin B6 Upper Level (UL)

Vitamin B6 Upper Level (UL) Technical 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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Acronyms and Abbreviations

Acronym	Definition
ALDH7A1	Aldehyde dehydrogenase 7 family member A1
AU/NZ	Australia and New Zealand
bw	Body weight
CBS	Cystathionine beta-synthase
CIAP	Chronic idiopathic axonal polyneuropathy
CNS	Central nervous system
DRG	Dorsal root ganglia
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
GABA	Gamma-aminobutyric acid
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
MeSH	Medical Subject Headings
NHMRC	National Health and Medical Research Council
NOAEL	No-observed-adverse-effect level
NRV	Nutrient Reference Value
NTP OHAT	National Toxicology Program Office of Health Assessment and Translation
NVP	Nausea and vomiting of pregnancy
OTC	Over-the-counter
P95	95th percentile
PDXK	Pyridoxal kinase
PL	Pyridoxal
PLP	Pyridoxal 5’-phosphate
PMS	Premenstrual syndrome
PN	Pyridoxine
PN-HCl	Pyridoxine hydrochloride
PNPO	Pyridox(am)ine 5’-phosphate oxidase

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QST	Quantitative sensory testing
RoB	Risk of bias
RP	Reference point
SCF	Scientific Committee on Food
SR	Systematic review
TGA	Therapeutic Goods Administration
TNSALP	Tissue-nonspecific alkaline phosphatase
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 (**Appendix A**) 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 this Technical Report.

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

Health-based

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?

Number	Research Questions
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[1]?
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?

3.0 Evidence Evaluation Methods

3.1 Overview

This section summarises the methods used to undertake the evidence evaluation for vitamin B6. The intention is to provide sufficient detail to allow a third party to understand and, where applicable, reproduce the search and study selection process.

Some flexibility was required in applying the methodology described in the final Research Protocol to ensure relevant information could be identified efficiently and appropriately across different evidence types, including existing international guidance documents, primary human and animal health evidence, and supporting contextual information such as adverse event reporting data and intake estimates for the Australian and New Zealand population. Searches and screening records were managed in Covidence, which was used to support title and abstract screening, full-text review, and documentation of inclusion and exclusion decisions. Any deviations from the final Research Protocol methodology have been documented in this report.

Figure 1 provides an overview of the literature search and screening process for vitamin B6, presented as a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram, showing the number of records identified, screened, excluded and included at each stage of the review process (Moher et al. 2009).

[1] 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.*"

The evidence evaluation followed a two-stream approach as set out in the Research Protocol. The first stream comprised an adopt/adapt review of existing international guidance relevant to the vitamin B6 UL, including assessment of the methodological credibility and applicability of identified guidance documents using the criteria outlined in **Appendix B** of the Research Protocol. The second stream comprised an evidence scan of primary studies published since the most recent existing guidance review (i.e., from 2022 onwards), supplemented by earlier pivotal studies identified through backward citation searching where necessary to understand the basis of existing guidance values. Risk of bias and certainty of evidence assessments were applied to key primary studies and bodies of evidence relevant to the critical endpoint(s) underpinning the UL, using a modified OHAT risk-of-bias tool (NTP OHAT 2019) and a GRADE-informed approach (Alonso-Coello et al. 2016), respectively. Evidence was synthesised narratively, with integration of findings from existing guidance, newly identified primary studies, and relevant adverse event data.

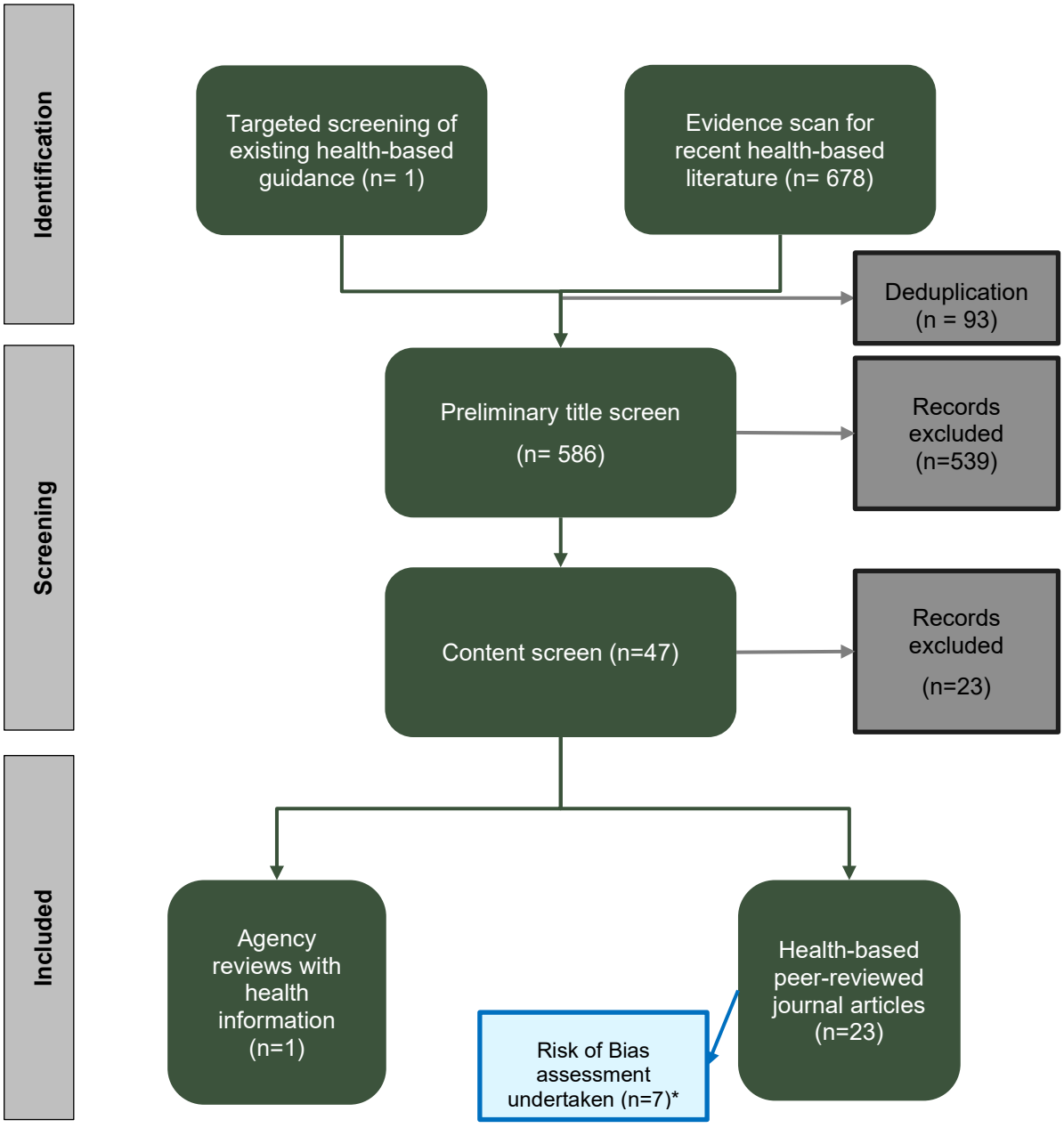

Figure 1 Overview of literature search process followed for Vitamin B6 UL

3.2 Targeted screening of existing health-based guidance

Literature search strategy

The literature search strategy for existing health-based guidance documentation for vitamin B6 is summarised in **Table 2** below.

Table 2 Search strategy for Existing Guidance/Guidelines

Parameter	Comments
Search terms	• ("Vitamin B 6"[MeSH] OR vitamin B6 OR pyridoxine OR pyridoxal OR pyridoxamine) AND ("Upper Limit"[MeSH] OR "Tolerable Upper Intake Level" OR UL OR guidance OR "Dietary Reference Values") • ("Vitamin B 6"[MeSH] OR vitamin B6 OR pyridoxine OR pyridoxal) AND ("Peripheral Nervous System Diseases"[MeSH] OR peripheral neuropathy OR neurotoxicity) • (vitamin B6 OR pyridoxine OR pyridoxal) AND (EFSA OR TGA OR Health Canada OR FSANZ OR NHMRC OR "risk assessment" OR "guidance" OR "upper intake level") The search terms above represent the core search strategy and will be adapted for each database (e.g. use of MeSH terms, truncation and field tags). They are intended to be reproducible search strategies, not just illustrative keywords. The terms may be refined based on the number and relevance of records retrieved. The proposed search terms are relatively broad and do not limit the search to specific population subgroups. Thus, additional population-specific search terms (e.g. “Aboriginal”, “Torres Strait Islander”, “Indigenous”, “Māori”) are not considered warranted.
Databases / Agency websites	Searches were conducted across the following sources: European Food Safety Authority (EFSA); NRV-related Australian and New Zealand sources including Food Standards Australia New Zealand (FSANZ), Therapeutic Goods Administration (TGA) and NHMRC; World Health Organization (WHO), including the Joint FAO/WHO Expert Committee on Food Additives (JECFA); Health Canada; United States Food and Drug Administration (US FDA); and other relevant international agencies and expert bodies identified during the review. Key publications provided by NHMRC and the Vitamin B6 Expert Working Group were also considered.
Publication Date	No strict historical cut-off was applied to the search for existing guidance documents. Priority was given to current and recent assessments relevant to the UL review. Older documents were included where necessary to understand the basis of current guidance values or the evolution of the UL.
Language	English-language documents were prioritised. Guidance documents in languages other than English were considered where relevant and a translation was accessible or could be reasonably obtained.
Study Type	Existing guidance and assessment documents relevant to the vitamin B6 UL developed by Australian and international agencies, including current guidance documents, near-publication or consultation drafts where informative, and publicly available superseded guidance where necessary to understand the basis of current values. Guidance documents were required to provide sufficient detail on the evidence base and derivation of health-based values.
Inclusion and exclusion criteria	Included: publicly available guidance relevant to vitamin B6 exposure and health outcomes; documents providing transparency of methodology and sufficient detail

Parameter	Comments
	on the derivation of health-based values; documents applicable to or informative for the Australian and New Zealand context. Excluded: documents with insufficient methodological detail to allow assessment; guidance not related to excess vitamin B6 intake or health-based values; superseded guidance unless required to understand the basis of current values.
Validation methods used	Search results were checked against key known guidance documents (e.g., EFSA 2023 and relevant TGA documents) to verify that the search strategy captured all expected key references prior to full screening.
Screening methods	Titles and source documents were screened by a single researcher (MM or SL) and verified by a content expert (TH or RC) against the inclusion and exclusion criteria outlined above. All screening decisions were recorded in Covidence. Discrepancies were resolved by consensus.
Documentation of search	All search results, screening decisions and exclusions with justifications were recorded in Covidence and are documented in this Technical Report. A list of excluded guidance documents with reasons for exclusion is provided in Appendix A. The overall search and selection process is presented as a PRISMA flow diagram in **Figure 1**.
Retrieval of publications	Full-text documents were retrieved electronically via agency websites, subscription databases or open-access repositories. Records were collated and managed in Covidence. Copies of all included documents were stored in a secure project repository.

Data Extraction and Quality Assessment

For each relevant result for which the full text was sourced:

- The full text was reviewed by a content expert to confirm relevance to the research questions and to determine whether the document contained existing health-based guidance for vitamin B6, relevant toxicity or safety information, or supporting evidence pertaining to adverse health effects associated with excess vitamin B6 intake.
- Where existing health-based guidance was identified including tolerable upper intake levels or equivalent health-based guidance values for vitamin B6, relevant data on the guidance value, derivation approach, critical endpoint, point of departure, uncertainty factors, sensitive subpopulation considerations, and applicability to the Australian and New Zealand context were extracted using a predefined data extraction framework (**Table 3**). Data extraction was undertaken by a single reviewer and subject to targeted verification by a content expert, particularly for key guidance documents and critical inputs to the UL derivation. The individual data extraction tables for existing guidance documents are provided in **Appendix D**.
- For each identified health-based guidance document, methodological credibility and transparency were assessed using the Assessment Tool described in Appendix B of the Research Protocol. This assessment informed the extent to which findings from each guidance document including underlying evidence assessments where available could be relied upon in the review. Where a guidance document met the credibility criteria (i.e., satisfying at least 80% of "must have" and "should have" criteria), its findings and certainty assessments were used to inform the review directly. The completed credibility assessment tables for all included guidance documents are provided in **Appendix C**.

Table 3 Example of data extraction table format for existing health-based key studies

Guidance Reference: ***Insert full bibliographical reference for report***

General Information

Parameter	Findings
Authors	*Intentionally blank*
Publication date	*Intentionally blank*
Document/report title	*Intentionally blank*
Literature search timeframe	*Intentionally blank*
Literature search databases	*Intentionally blank*
Publication type	*Intentionally blank*
Peer reviewed?	*Intentionally blank*
Country of origin	*Intentionally blank*
Source of funding	*Intentionally blank*
Possible conflicts of interest	*Intentionally blank*
Chemical/nutrient assessed	*Intentionally blank*
Regulatory context / purpose	*Intentionally blank*
Previous guidance value superseded	*Intentionally blank*

Health Considerations

Parameter	Findings
Exposure timeframe	*Intentionally blank*
Exposure route assessed	*Intentionally blank*
Critical human health endpoint(s) – oral exposure	*Intentionally blank*
Justification provided by agency for critical endpoint	*Intentionally blank*
Other adverse health effects considered (not selected as critical)	*Intentionally blank*
Critical study(ies) underpinning point of departure	*Intentionally blank*
Species for critical study(ies)	*Intentionally blank*
Point of departure type	*Intentionally blank*
Point of departure value (include units)	*Intentionally blank*
Uncertainty factor(s) & rationale	*Intentionally blank*
The derivation (human)	*Intentionally blank*
The derivation (animal)	*Intentionally blank*
Guidance value type	*Intentionally blank*
Guidance value (include units)	*Intentionally blank*
Mode of action for critical health endpoint	*Intentionally blank*
Genotoxic oral carcinogen?	*Intentionally blank*
Identified sensitive sub-populations	*Intentionally blank*

Parameter	Findings
Dose–response characterisation	*Intentionally blank*
Recommendations for future research	*Intentionally blank*
Any non-health-based considerations?	*Intentionally blank*

Data summary/synthesis

Extracted data from existing guidance documents have been presented in tabular format for each research question.

The methodological credibility of existing guidance was assessed using the criteria in Appendix B of the Research Protocol (completed assessment tables in **Appendix C**). Where guidance documents met at least 80% of "must have" and "should have" criteria, their findings and underlying evidence assessments were used to inform the review directly. Where limitations were identified, additional interrogation of key primary studies was undertaken as appropriate.

3.3 Evidence Review for recent studies

Literature search strategy

An evidence scan of recent literature was undertaken to identify primary studies published since the most recent credible existing guidance review, with a focus on evidence that may warrant updating, qualifying or further interrogating the findings underpinning available guidance values for vitamin B6. The search focused on studies published from 2022 onwards, consistent with the cut-off applied in the Research Protocol and aligned with the evidence search underpinning the EFSA (2023) Scientific Opinion. Earlier studies were included where identified through backward citation searching and considered pivotal to understanding the basis of existing guidance values. The aim of the evidence scan was to determine whether new evidence materially affects the conclusions of existing guidance or introduces considerations not addressed in prior assessments.

The literature search strategy for the evidence review of recent primary studies is summarised in **Table 4** below.

Table 4 Search strategy for evidence review of recent health-based studies

Parameter	Comments
Search terms	• ("Vitamin B 6"[MeSH] OR pyridoxine OR pyridoxal OR pyridoxamine) AND (toxicity OR peripheral neuropathy OR neurotoxicity) • ("Vitamin B 6"[MeSH] OR pyridoxine OR pyridoxal OR pyridoxamine) AND (supplement* OR fortified food* OR intake) • ("Vitamin B 6"[MeSH] OR pyridoxine OR pyridoxal OR pyridoxamine) AND (adverse event* OR pharmacovigilance OR safety report*) • ("Vitamin B 6"[MeSH]) AND (Australia OR "New Zealand") Search terms may be refined depending on database functionality and record yield. The search terms above represent the core search strategy and will be adapted for each database

Parameter	Comments
	(e.g. use of MeSH terms, truncation and field tags). They are intended to be reproducible search strategies, not just illustrative keywords. The terms may be refined based on the number and relevance of records retrieved. The proposed search terms are relatively broad and do not limit the search to specific population subgroups. Thus, additional population-specific search terms (e.g. “Aboriginal”, “Torres Strait Islander”, “Indigenous”, “Māori”) are not considered warranted.
Databases	MEDLINE/PubMed/TOXLINE; EMBASE; Scopus; SciFinder; Web of Science. Additional sources included reference lists of included guidance documents and key articles (backward citation searching) and articles citing key references (forward citation searching), using Semantic Scholar where appropriate. Key publications provided by NHMRC and the Vitamin B6 Expert Working Group were also considered.
Publication Date	Primary focus on studies published from 2022 onwards, consistent with the Research Protocol and the evidence search underpinning EFSA (2023). Earlier studies were included where identified as pivotal through backward citation searching or where required to provide context for interpretation of existing guidance.
Language	English-language publications were prioritised. Studies in other languages were not systematically sought; however, relevant sources identified incidentally were considered where a translation was accessible.
Study Type	All study designs were considered where they met the eligibility criteria and were relevant to the research questions. Priority was given to quantitative human studies with clearly defined exposure and outcome measures. Animal studies were considered where human data were limited in quantity or quality, or where they provided relevant supporting evidence for biological plausibility and interpretation. Qualitative studies, abstracts and conference proceedings were not a primary focus but were considered where they provided relevant contextual information.
Inclusion and exclusion criteria	Included: peer-reviewed published or in-press studies; publicly available unpublished studies (e.g., government reports, grey literature) where relevant to the research questions; studies reporting on adverse health effects associated with excess vitamin B6 intake in humans or animals; studies with clearly defined exposure (dose, duration and source) and outcome measures. Excluded: studies not reporting on vitamin B6 exposure or relevant health outcomes; in vitro studies (cell-based studies); studies lacking sufficient methodological detail to allow assessment; duplicate records. Studies conducted in populations with pre-existing neuropathy or predisposing conditions were not excluded a priori but were assessed for indirectness during evidence appraisal.
Validation methods used	Search results were checked against key known publications and regulatory documents identified during the guidance review to verify capture of expected references prior to full screening.
Screening methods	Titles and abstracts were screened by a single researcher (MM or SL or EC) and verified by a content expert (TH or RC) against the inclusion and exclusion criteria. Full-text review was conducted for all records not excluded at title and abstract screening. All screening decisions were recorded in Covidence.

Parameter	Comments
Documentation of search	All search results, screening decisions and exclusions with justifications were recorded in Covidence and are documented in this Technical Report. A list of excluded studies with reasons for exclusion is provided in Appendix B. The overall search and selection process is presented as a PRISMA flow diagram in **Figure 1**.
Retrieval of publications	Full-text articles were retrieved electronically via subscription databases or open-access repositories. Records were collated and managed in Covidence and stored in a secure project repository.

Data Extraction

For each relevant result for which the full text was sourced:

- Where deemed relevant to the research questions and potentially providing information that could alter or qualify the findings of existing guidance assessments, relevant data were extracted using a predefined data extraction framework (**Table 5**). The framework was designed primarily for epidemiological studies and was adapted as appropriate for animal studies and narrative or systematic reviews. The individual completed data extraction tables are provided in **Appendix E**.
- Data extraction was performed by the SLR review team. The initial extraction was then quality-assessed by SLR reviewers to verify accuracy and consistency of the extracted data against the source documents. Targeted verification of key data fields, particularly those directly relevant to UL derivation, including exposure metrics, outcome definitions, dose–response information and main findings, was undertaken by a content expert.
- For primary studies considered directly relevant to the critical endpoint(s) underpinning the vitamin B6 UL, risk of bias was assessed using a modified OHAT risk-of-bias tool (NTP OHAT 2019). These assessments were conducted systematically and informed interpretation of individual study findings and the overall certainty of evidence assessment. The completed risk of bias assessment tables is provided in **Appendix F.**

Table 5 Example of data extraction table format for evidence review of recent health-based studies

Publication Reference: ***Insert full bibliographical reference for report***

Study identification and design

Field	Extracted information
Citation	*Intentionally blank*
Publication status	*Intentionally blank*
Country / setting	*Intentionally blank*
Study design	*Intentionally blank*
Funding / conflicts of interest	*Intentionally blank*

Population

Field	Extracted information
Sample size	*Intentionally blank*
Patient characteristics	*Intentionally blank*
Inclusion/exclusion of alternative causes	*Intentionally blank*

Exposure

Field	Extracted information
Exposure characterisation – source	*Intentionally blank*
Exposure characterisation – dose	*Intentionally blank*
Biomarker of exposure	*Intentionally blank*
Duration of exposure	*Intentionally blank*

Outcomes

Field	Extracted information
Primary outcome	*Intentionally blank*
Outcome assessment – clinical examination	*Intentionally blank*
Outcome assessment – objective testing	*Intentionally blank*
Outcome assessment – tools used	*Intentionally blank*
Response to withdrawal	*Intentionally blank*

Results and Conclusions

Field	Extracted information
Main results	*Intentionally blank*
Authors' conclusions	*Intentionally blank*
Authors' acknowledged limitations	*Intentionally blank*

Contextual information for the AU/NZ UL review

Generalisability to AU/NZ	*Intentionally blank*

Data summary/synthesis

Data summary and synthesis for the evidence limited was limited to those studies and findings with the potential to influence the overall conclusions of existing health-based guidance relevant to the vitamin B6 UL that is, evidence directly pertaining to the health-based research questions, particularly adverse neurological effects and other critical endpoints associated with excess vitamin B6 intake. Relevant data were summarised in tabular format by research question where applicable.

Studies identified through the evidence review were used to inform interpretation of the available evidence and to determine whether any new findings may affect the assessment of existing guidance or introduce considerations not addressed in prior evaluations. Following data extraction, risk of bias assessment was undertaken for selected studies considered directly relevant to UL derivation, consistent with the agreed scope of the review and using a modified OHAT risk-of-bias tool (NTP OHAT 2019). The completed risk of bias assessment tables for individual studies is provided in **Appendix F**.

The overall confidence in the body of evidence for each relevant health outcome was assessed using a GRADE-informed approach, taking into account risk of bias findings, consistency of results across studies, directness and applicability to the Australian and New Zealand population, precision of effect estimates, and potential for publication bias, together with relevant upgrading factors such as dose–response relationships and magnitude of effect. These assessments, presented by health outcome category and study type (human and animal), are summarised in **Appendix F** alongside the individual risk of bias tables.

Table 6 provides example risk of bias assessment tables for each assessed study, showing the domain-level judgements applied to individual pieces of evidence. In addition, the overall confidence in the body of evidence for each relevant health outcome will be presented in

Appendix F, taking into account the risk of bias findings, consistency, directness, precision and other relevant considerations.

Table 6 Example of risk of bias assessment for individual new study from evidence scan

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

Study Type:	*Intentionally blank*	*Intentionally blank*
Study ID:	*Intentionally blank*	*Intentionally blank*
Health Outcome:	*Intentionally blank*	*Intentionally blank*
Bias Domain	**Rate**	**Comments**
Selection	*Intentionally blank*	*Intentionally blank*
Was administered dose or exposure level adequately randomized?	*Intentionally blank*	*Intentionally blank*
Was allocation to study groups adequately concealed?	*Intentionally blank*	*Intentionally blank*
Were the comparison groups appropriate?	*Intentionally blank*	*Intentionally blank*
Confounding – KEY DOMAIN	*Intentionally blank*	*Intentionally blank*
Does the study design or analysis account for important confounding and modifying variables?	*Intentionally blank*	*Intentionally blank*
Did researchers adjust or control for other exposures that are anticipated to bias results?	*Intentionally blank*	*Intentionally blank*
Performance	*Intentionally blank*	*Intentionally blank*
Were experimental conditions identical across study groups?	*Intentionally blank*	*Intentionally blank*
Did deviations from the study protocol have an impact on the results?	*Intentionally blank*	*Intentionally blank*
Were the research personnel and human subjects blinded to the study group during the study?	*Intentionally blank*	*Intentionally blank*
Attrition / Exclusion	*Intentionally blank*	*Intentionally blank*
Were outcome data incomplete because of attrition or exclusion from analysis?	*Intentionally blank*	*Intentionally blank*
Detection bias – KEY DOMAIN	*Intentionally blank*	*Intentionally blank*
Were the outcome assessors blinded to study group or exposure level?	*Intentionally blank*	*Intentionally blank*

Study Type:	*Intentionally blank*	*Intentionally blank*
Were confounding variables assessed consistently across groups using valid and reliable measures?	*Intentionally blank*	*Intentionally blank*
KEY - Can we be confident in the exposure characterisation?	*Intentionally blank*	*Intentionally blank*
KEY - Can we be confident in the outcome assessment?	*Intentionally blank*	*Intentionally blank*
Selective Reporting	*Intentionally blank*	*Intentionally blank*
Were all measured outcomes reported?	*Intentionally blank*	*Intentionally blank*
Other Sources of bias	*Intentionally blank*	*Intentionally blank*
Were there any other potential threats to internal validity (e.g., inappropriate statistical methods)?	*Intentionally blank*	*Intentionally blank*
Overall risk of bias for the study (Low/Moderate/High)	*Intentionally blank*	*Intentionally blank*

3.4 Adverse Event Reports

Several adverse event reporting databases were reviewed to identify reported adverse events associated with pyridoxine or vitamin B6-containing products. These databases are useful for identifying potential safety signals and the types of symptoms being reported. However, they cannot be used to estimate incidence, risk, dose–response relationships or causality, as reports may be incomplete, affected by reporting bias, and often involve multiple products or underlying health conditions.

3.4.1 Database of Adverse Event Notifications (DAEN) – medicines

The DAEN medicines dataset included 2,697 adverse event reports associated with pyridoxine or vitamin B6-related products between 1972 and May 2026. Reporting was weighted toward recent years, with more than half of reports entered from 2020 onwards. This may reflect increased awareness and reporting of vitamin B6-associated neuropathy, rather than a true increase in population-level risk.

Where age was reported, cases were mainly in adults, particularly those aged 50–69 years. Approximately 37% of reports did not include age information. Most reports involved females, who accounted for approximately 69% of cases, while males accounted for approximately 24%.

The main reported clinical pattern was neurological, most commonly symptoms associated with sensory neuropathy-type. However, some symptoms associated with motor and balance disturbance were reported. Frequently reported terms included paraesthesia, peripheral neuropathy, hypoaesthesia, burning sensation, pain in extremity, balance problems, gait disturbance, muscular weakness and dizziness. These findings are consistent with the known adverse effect profile of excess vitamin B6 exposure. Other reported symptoms included nausea, vomiting, diarrhoea, fatigue, headache, rash and pruritus, although these are less specific. Suspected products included pyridoxine or pyridoxine hydrochloride products, as well as magnesium/B6 products, B-complex products,

multivitamins, pregnancy supplements, “stress” or “energy” supplements formulations, and some injectable vitamin preparations. Death-related information was limited and did not allow the number of unique deaths or causality to be determined.

3.4.2 WHO VigiAccess

Global pharmacovigilance data were retrieved from WHO VigiAccess for pyridoxine and pyridoxine-containing search terms. The active substance search for “pyridoxine” returned 13,954 reported adverse drug reactions across 26 MedDRA System Organ Classes. Nervous system disorders, which include peripheral neuropathy-related effects, accounted for 2,437 reports and were the fourth most common reaction category after general disorders, skin disorders and gastrointestinal disorders.

Most reports originated from Asia, followed by Europe, the Americas, Africa and Oceania. Reporting increased from the 1970s, peaked in 2020 and has declined since. These data provide broad signal-level support for neurological adverse effects associated with pyridoxine, but the public VigiAccess output does not provide sufficient information on dose, duration, vitamin B6 form or causality to support dose–response assessment.

3.4.3 FDA Adverse Event Monitoring System (AEMS) Public Dashboard for Drugs and Biologics

The FDA dataset included 1,415 adverse event cases associated with pyridoxine, vitamin B6 or vitamin B-complex products from 1973 to 2026. Approximately 60% of cases were received from 2020 onwards, with the highest annual count in 2023. Most reports were submitted by healthcare professionals (74.4%), while consumers accounted for 22.3% of reports.

Most cases involved adults, particularly those aged 18–64 years and 65–85 years. Age was not specified in 27.3% of cases. Females accounted for 52.7% of reports and males for 36.3%. Product categories were mainly Vitamin B Complex and Vitamin B6, although these categories were not necessarily mutually exclusive.

Commonly reported reactions included off-label use, drug ineffective, nausea, somnolence, vomiting, fatigue, dyspnoea, headache, general physical health deterioration, hypersensitivity, abdominal pain, diarrhoea, sleep disorder, dizziness, rash and anxiety. Neuropathy-relevant terms were also reported, including paraesthesia, gait disturbance, peripheral neuropathy, hypoaesthesia, neuralgia, muscular weakness, pain in extremity, balance disorder, tremor and burning sensation. “Death” was reported as a reaction term in 49 cases, with other death-related terms reported in small numbers. However, the public output does not provide sufficient case-level outcome or causality information to determine whether vitamin B6 caused these deaths.

3.4.4 EudraVigilance – European database of suspected adverse drug reaction reports

The broader EudraVigilance pyridoxine search identified 6,196,841 individual cases. Most cases were in adults, particularly the 18–64 year age group, followed by 65–85 years. Age was not specified in 21.9% of cases. Females accounted for 57.4% of reports and males for 37.9%. Most reports were submitted by healthcare professionals (60.8%), with non-healthcare professionals accounting for 33.2%.

Reports were relatively evenly split between European Economic Area (EEA) and non-EEA sources. Within the EEA, the largest contributors were Germany, France, Italy, the Netherlands, Austria, Spain and Sweden. Reaction-term data were not available for the broader pyridoxine search.

As reaction information was not available for the broader search, a narrower exploratory search for “pyridoxine magnesium” was reviewed. This identified 463 cases up to 7 June 2026. Most cases were in adults and females, and most were from the EEA, particularly France. In contrast to the broader EudraVigilance dataset, most reports in this subset were from non-healthcare professionals. The main reaction groups were injury/poisoning/procedural complications, gastrointestinal disorders, nervous system disorders, skin disorders and general disorders. The nervous system category is relevant to potential vitamin B6-associated neuropathy, but this subset should not be considered representative of all pyridoxine or vitamin B6 reports. A search for pyridoxine hydrochloride identified only two cases and was not considered informative (low number of identified cases).

3.4.5 Canadian Vigilance Adverse Reaction Online Database

Canada Vigilance data were reviewed for the search term “pyridox” across 2000 to February 2026. Across three exported periods, there were 2,198 reported adverse reaction reports: 345 reports from 2000–2010, 909 reports from 2010–2019 and 944 reports from 2019–2026. This indicates higher reporting activity in more recent periods, although this may reflect changes in product use, awareness, reporting practices, database capture or regulatory attention rather than a true increase in risk.

The Canada Vigilance reports captured a broad range of pyridoxine-containing products and clinical contexts, including doxylamine/pyridoxine pregnancy products, B-complex products, multivitamins, vitamin/mineral supplements and multi-ingredient natural health products. Reported reactions were diverse and included gastrointestinal symptoms, hypersensitivity or skin reactions, general symptoms, pregnancy or foetal exposure-related terms, medication-use issues such as overdose or off-label use, and some neurological terms. Overall, the Canada Vigilance dataset appeared less specifically focused on vitamin B6-associated neuropathy than the DAEN dataset, although neuropathy-related terms were present.

4.0 Results

4.1 Health-based research question analysis for guidance documents

Table 7 Synthesis of extracted data for health-based research questions

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.

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?	Summary of existing ULs for adults:

Body	UL (adults)(1)	Basis	Approach(2)
SCF (2000) (Europe)	25 mg/day (including pregnant and lactating women)	Dalton & Dalton (1987) case-control study; mean intake ~100 mg/day as RP	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.
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.
NHMRC (2006) (Australia & New Zealand)	50 mg/day	NOAEL of 200 mg/day from Bernstein & Lobitz (1988) and Del Tredici et al. (1985)	UF of 4 applied (to account for short exposure duration; symptoms may take longer to appear).

(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:

Number	Research Questions	EFSA 2023
		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.
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.

Number	Research Questions	EFSA 2023
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. **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[2].
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.

[2] 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
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).
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%).

4.2 Health-based research question analysis for new evidence – grouped based on health outcomes

Table 8 Synthesis of extracted data for health-based research questions – 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	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
		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). 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 uncertainties were applied, and are they suitable to adopt or adapt for Australia and New Zealand?	See **Table 7**	See **Table 7**	See **Table 7**	See **Table 7**	See **Table 7**
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 exposure; relevance to UL derivation is limited.	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).
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,	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 —	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	TNSALP controls plasma PLP clearance and provides mechanistic evidence for individual susceptibility.	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	No clinical adverse outcome.

#	Research Questions	Peripheral neuropathy	Hepatotoxicity	Individual susceptibility / B6 metabolism	Adverse pregnancy outcomes	Hypervitaminosis B6 prevalence / biomarker
	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?	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 et al. (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 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 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.	for general-population dietary/supplement exposure; retained for completeness only.	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.	interacting exposures. This is very weak evidence and should be weighted accordingly.	
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.	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
		Of limited relevance to general-population UL sub-population characterisation: • Parkinson's disease on levodopa: Modica et al. (2023), specific clinical / pharmacological context, not 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
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

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Appendix A Research Protocol

Evidence Evaluations for Vitamin B6 Upper Level (UL)

Vitamin B6 Upper Level (UL) Technical Report

National Health and Medical Research Council

SLR Project No.: 640.032359.00001

7 August 2026

SLR

Appendix B Literature Search Screening Outcome Spreadsheet

Evidence Evaluations for Vitamin B6 Upper Level (UL)

Vitamin B6 Upper Level (UL) Technical Report

National Health and Medical Research Council

SLR Project No.: 640.032359.00001

7 August 2026

SLR

B.1 Included studies

No.	Study	Title	Notes
1	Arai et al. 2023	**Identifying risk factors for adverse events of pyridoxal phosphate in infantile epileptic spasms syndrome** *DOI: 10.1016/j.yebeh.2023.109348*	Quantitative primary study of pyridoxal phosphate (PLP) exposure in infants with epileptic spasms. It reports dose-response information, including a 40 mg/kg/day cut-off, relative risks, and clinically defined adverse outcomes.
2	Bossard et al. 2022	**Problematic rise of vitamin B6 supplementation overuse and potential risk to bariatric surgery patients** *DOI: 10.1016/j.nut.2022.111738*	Observational laboratory study relevant to supplemental vitamin B6 overexposure, particularly in bariatric surgery patients. It supports consideration of peripheral neuropathy as the critical effect, although neuropathy was not measured directly.
3	Brands et al. 2026	**Hepatocellular Carcinoma: A Critical Complication in Patients Treated with Pyridoxal Phosphate** *DOI: 10.1055/a-2773-6076*	Paediatric case series of long-term high-dose PLP treatment with hepatotoxicity outcomes, including hepatocellular carcinoma. This is relevant to non-neuropathy adverse effects and sensitive metabolic-disease populations, with indirectness to be considered during appraisal.
4	Gospe et al. 1993	**Pyridoxine-Dependent Epilepsy – ALDH7A1** *DOI: Not available*	GeneReviews chapter on pyridoxine-dependent epilepsy that discusses high-dose pyridoxine therapy and recognises reversible sensory neuropathy as an adverse effect requiring surveillance. It is useful for context on predisposing conditions and the neuropathy endpoint.
5	He et al. 2025	**The potential hazards of high doses of vitamin B6 in treating nausea and vomiting in pregnancy: A systematic review** *DOI: 10.1002/ijgo.16032*	Systematic review relevant as secondary/supporting evidence. It provides case-level information on B6-associated peripheral neuropathy in pregnancy and PMS populations, and adverse pregnancy or offspring outcomes following high-dose maternal B6 exposure.
6	Kościńska-Shukla et al. 2025	**Underestimated pyridoxine consumption and neurotoxicity: a novel manifestation with rheumatologic relevance - a case-based review** *DOI: 10.1007/s00296-025-05900-9*	Case-based review of three patients with neuropathic symptoms linked to excessive vitamin B6 intake. It provides exposure-source information and reports symptom improvement following reduction or cessation of supplementation.
7	Lee et al. 2025	**Case report: Hepatocellular carcinoma in a patient with Pyridoxamine 5-phosphate oxidase (PNPO)**	Case report of hepatocellular carcinoma in a PNPO-deficient patient receiving long-term PLP treatment. It is relevant to hepatotoxicity as a

No.	Study	Title	Notes
		deficiency undergoing pyridoxal 5-phosphate (PLP) treatment *DOI: 10.1016/j.ymgmr.2025.101224*	secondary endpoint and to sensitive metabolic-disease populations with defined PLP exposure.
8	Modica et al. 2023	**A systematic review of the potential consequences of abnormal serum levels of vitamin B6 in people living with Parkinson's disease** *DOI: 10.1016/j.jns.2023.120690*	Systematic review of abnormal vitamin B6 levels in people with Parkinson's disease, including cases of polyneuropathy with high B6. It is relevant to the neuropathy endpoint, although based on small numbers and a predisposing-factor population.
9	Morris et al. 2025	**Cystathionine β-Synthase Deficiency in the E-HOD Registry-Part II: Dietary and Pharmacological Treatment** *DOI: 10.1002/jimd.12844*	Registry analysis of patients with cystathionine beta-synthase deficiency noting that some non-responders received potentially dangerously high pyridoxine doses. It provides exposure-context information but does not report adverse health outcomes suitable for dose-response evaluation.
10	Muhamad et al. 2023	**The Role of Vitamin B6 in Peripheral Neuropathy: A Systematic Review** *DOI: 10.3390/nu15132823*	Systematic review focused on vitamin B6-related peripheral neuropathy, particularly axonal sensory neuropathy. It is directly relevant to the critical endpoint and may provide supporting dose and clinical-context information.
11	Paluszny and Qiu 2023	**Vitamin B6 Toxicity Secondary to Daily Multivitamin Use: A Case Report** *DOI: 10.7759/cureus.48792*	Case report of peripheral neuropathy associated with excessive vitamin B6 intake from daily multivitamin use. It is relevant because it includes quantitative exposure information and a clinically described adverse outcome.
12	Reddy 2022	**Preventing Vitamin B6-Related Neurotoxicity** *DOI: 10.1097/mjt.0000000000001460*	Therapeutic opinion/review addressing vitamin B6 neurotoxicity, serum PLP thresholds, and potential differences between pyridoxine and PLP-based supplements. It is relevant to vitamer-specific and biomarker-based considerations.
13	Sano et al. 2022	**Blood Neurofilament Light Chain as a Potential Biomarker for Central and Peripheral Nervous Toxicity in Rats** *DOI: 10.1093/toxsci/kfab122*	Rat study with defined high-dose pyridoxine exposure producing dorsal root ganglion and peripheral nerve changes. It provides animal evidence for the sensory neuropathy endpoint and evaluates serum neurofilament light chain as a biomarker.

No.	Study	Title	Notes
14	Schellack et al. 2025	**Expert Consensus on Vitamin B6 Therapeutic Use for Patients: Guidance on Safe Dosage, Duration and Clinical Management** *DOI: 10.2147/dhps.S499941*	Delphi consensus guidance on therapeutic vitamin B6 use, including dosage, duration, adverse events, washout periods, and monitoring. It is relevant as supporting guidance for safe-use and adopt/adapt considerations.
15	Stewart et al. 2022	**Vitamin B6 levels do not correlate with severity of neuropathy in chronic idiopathic axonal polyneuropathy** *DOI: 10.1111/jns.12480*	Cross-sectional study of patients with chronic idiopathic axonal polyneuropathy assessing plasma vitamin B6 levels and neuropathy severity. It is relevant as primary human evidence, although dose inference is limited by the cross-sectional design and use of plasma levels as an exposure proxy.
16	Stolwijk et al. 2025	**Effectiveness of Pyridoxal-5'-Phosphate in PNPO Deficiency: A Systematic Review** *DOI: 10.1002/jimd.70074*	Systematic review of PLP treatment in PNPO deficiency reporting adverse effects, with liver toxicity frequently observed. It is relevant to PLP exposure and sensitive metabolic-disease populations.
17	Sun et al. 2025	**Toxic Effects of Excess Vitamins A, B6, and Folic Acid on the Nervous System** *DOI: 10.1155/bn/7888243*	Review of neurological effects associated with excess vitamins, including vitamin B6. It is relevant as supporting evidence on neurological dysfunction from excessive supplementation.
18	Theil et al. 2023	**Neurofilament Light Chain: A Translational Safety Biomarker for Drug-Induced Peripheral Neurotoxicity** *DOI: 10.1177/01926233231180179*	Animal study using high-dose pyridoxine as a positive control for peripheral neurotoxicity in dogs. It is potentially relevant for dose-response and neurofilament light chain biomarker information.
19	vanHunsel et al. 2025	**Impact of Regulatory Action on Dose Maximalization for Vitamin B6 Dietary Supplements on the Reporting Pattern for Neuropathy** *DOI: 10.1002/pds.70108*	Pharmacovigilance study evaluating the effect of regulatory action on reported neuropathy patterns associated with vitamin B6 supplements. It is relevant to real-world supplement exposures and regulatory context.
20	Webster et al. 2026	**Liver Transplantation in PNPO Deficiency: Management Challenges and Biological Lessons** *DOI: 10.1002/jmd2.70067*	Case report in PNPO deficiency describing dose-dependent hepatotoxicity from supraphysiologic PLP treatment. It is relevant to hepatotoxicity and sensitive metabolic-disease populations.

No.	Study	Title	Notes
21	Whyte et al. 2024	**Pyridoxine challenge reflects pediatric hypophosphatasia severity and thereby examines tissue-nonspecific alkaline phosphatase's role in vitamin B(6) metabolism** *DOI: 10.1016/j.bone.2024.117033*	Pyridoxine challenge study in children with hypophosphatasia, with comparison groups. It is useful for mechanistic and context information on altered vitamin B6 metabolism, but not for deriving a general-population UL.
22	Zervou et al. 2025	**Hypophosphatasia and neuropathic pain: related to vitamin B6 metabolism?** *DOI: 10.1093/jbmrpl/ziaf086*	Case series of adults with hypophosphatasia, neuropathic pain, and elevated serum B6/PLP. It is relevant to mechanistic links between PLP excess and neuropathy in a predisposing metabolic condition.
23	Gdynia et al. 2025	**Polyneuropathy due to Vitamin B6 hypervitaminosis: A case series and call for more education** *DOI: Not available*	Case series of vitamin B6-associated sensorimotor polyneuropathy in older adults using over-the-counter supplements. It is relevant to the critical endpoint, including a low-dose chronic exposure case, but requires cautious appraisal for bias and indirectness.

B.2 Excluded studies – After full-text review

No.	Study	Title	Notes
1	-	**Vitamin B(6)**	Excluded because the article focuses on vitamin B6 adequacy and lactation transfer rather than adverse effects of excess intake or evidence relevant to UL derivation.
2	-	**Vitamin B6 Supplementation Reduces Symptoms of Depression in College Women Taking Oral Contraceptives: A Randomized, Double-Blind Crossover Trial** DOI: 10.1080/19390211.2022.2030843	Excluded because the study evaluates efficacy of vitamin B6 supplementation for depression and does not report adverse effects or neuropathy outcomes relevant to UL derivation. The available record also appears to provide insufficient methodological detail.
3	Abosamak 2026	**Vitamin B6 (Pyridoxine)**	Excluded because this is a broad clinical overview of pyridoxine use. Although adverse effects and monitoring are mentioned, it does not

No.	Study	Title	Notes
			provide specific evidence on excess intake or adverse health outcomes relevant to UL derivation.
4	Ali et al. 2022	**Dietary Vitamin B Complex: Orchestration in Human Nutrition throughout Life with Sex Differences** DOI: 10.3390/nu14193940	Excluded because the review focuses on B-vitamin adequacy, deficiency and potential protective effects across life stages. It does not provide data on adverse effects of excess vitamin B6 intake or UL derivation.
5	Ali et al. 2026	**Novel reference method for precise determination of tryptophanase activity** DOI: 10.1093/biomethods/bpag017	Excluded because this is an analytical method-development study using PLP as a cofactor. It does not address vitamin B6 intake, supplementation, adverse effects or health endpoints relevant to UL derivation.
6	Alvarez et al. 2026	**B Vitamin Deficiencies and Associated Neuropathies** DOI: 10.1007/s13668-025-00723-3	Excluded because this is a narrative review on B-vitamin deficiencies and associated neuropathies. It may provide contextual mechanistic information, but it does not provide primary quantitative toxicity or dose-response data.
7	Berger et al. 2022	**ESPEN micronutrient guideline** DOI: 10.1016/j.clnu.2022.02.015	Excluded because this clinical nutrition guideline mainly addresses deficiency, enteral/parenteral nutrition dosing and biomarkers. It restates existing toxicity information and IOM values but does not derive a new UL or provide original dose-response data.
8	Bjørke-Monsen 2023	**Vitamin B(6): a scoping review for Nordic Nutrition Recommendations 2023** DOI: 10.29219/fnr.v67.10259	Excluded because this scoping/narrative review focuses on vitamin B6 status markers and adequate intake. It does not address excess intake, neuropathy or UL derivation, although it may be useful for backward citation checking.
9	Brown et al. 2026	**Vitamin B6 Deficiency**	Excluded because the article focuses on vitamin B6 deficiency, neurotransmitter function and recommended intake rather than toxicity or adverse effects of excess intake. It does not provide sufficient evidence for UL derivation.
10	Frost et al. 2025	**Recent Advances on the Role of B Vitamins in Cancer Prevention and Progression** DOI: 10.3390/ijms26051967	Excluded because this is a narrative review of B vitamins in cancer prevention and progression. It does not provide B6-specific toxicity, neurological adverse-effect or dose-response data relevant to UL derivation.

No.	Study	Title	Notes
11	Hemminger 2026	**Vitamin B6 Toxicity**	Excluded because this is a narrative clinical overview of vitamin B6 toxicity rather than a primary study. It may be useful for background context, but it does not provide original data for risk assessment.
12	Nakano et al. 2026	**Dietary intake of one-carbon nutrients and colorectal cancer risk according to TP53 status** DOI: 10.1093/jncics/pkag009	Excluded because this cohort study examines dietary B6 intake and colorectal cancer risk by TP53 status. It does not address B6 toxicity, neurological adverse effects or excess-intake outcomes relevant to UL derivation.
13	Pan et al. 2025	**Genetic Causal Association Between 15 Micronutrients and 12 Obstetric-Related Diseases: A Mendelian Randomization Study** DOI: 10.1007/s12011-024-04479-9	Excluded because this Mendelian randomisation study examines micronutrient levels and obstetric outcomes. The B6-related finding concerns spontaneous abortion risk rather than neurological or other toxicity endpoints and does not provide dose-response data for UL derivation.
14	Tamez-Torres et al. 2023	**Safety and Tolerability of Six Months of Isoniazid Plus Pyridoxine or Three Months of Rifampicin for Tuberculosis among Subjects with Diabetes Mellitus: A Randomized Trial** DOI: 10.3390/microorganisms11081917	Excluded because the trial evaluates tuberculosis preventive treatment in people with diabetes, with pyridoxine included as part of isoniazid treatment. The setting and adverse outcomes are not suitable for assessing vitamin B6 excess toxicity or UL derivation.
15	Vyas 2026	**17-Year-Old Male Patient With Pulmonary TB Presenting With Tingling and Numbness in the Left Upper Limb** DOI: 10.1016/j.chest.2025.09.125	Excluded because this is a case of isoniazid-induced neuropathy where pyridoxine was used as treatment. It does not assess pyridoxine excess intake as the exposure or provide evidence of B6-related adverse effects.
16	Whyte et al. 2022	**Hypophosphatasia: Vitamin B(6) status of affected children and adults** DOI: 10.1016/j.bone.2021.116204	Excluded because the study describes B6 vitamer levels in patients with hypophosphatasia, a rare metabolic condition, without B6 supplementation or intervention. It does not provide evidence relevant to general-population UL derivation.
17	Wills et al. 2025	**Assessing the burden of severe nausea and vomiting of pregnancy or hyperemesis gravidarum and the associated use and experiences of medication treatments: An Australian consumer survey** DOI: 10.1371/journal.pone.0329687	Excluded because this survey examines antiemetic use and medication experiences in hyperemesis gravidarum. Pyridoxine is mentioned as one of several treatments, but no B6-specific dose-response or adverse-effect data are provided.

No.	Study	Title	Notes
18	Yadav et al. 2022	**Pyridoxine in isoniazid-induced psychosis** DOI: 10.24911/sjp.106-1584524803	Excluded because this case report concerns isoniazid-induced psychosis, with pyridoxine used as a treatment adjunct rather than the exposure. It does not address adverse effects of excess vitamin B6 intake.
19	Sikora 2024	**Assessment of the potential nutritional value of cell-cultured chicken meat in light of European dietary recommendations**	Excluded because the study is a nutritional and safety assessment of cell-cultured chicken meat. Although vitamin B6 content is discussed, it does not assess B6 supplementation, excess intake or adverse health outcomes relevant to UL derivation.
20	GarcíaGabarra 2024	**[Maximum levels of vitamins and minerals in fortified food and food supplements in the European Union]**	Excluded because the article is in Spanish and therefore outside the English-language eligibility criterion, although it appears to discuss vitamin and mineral levels in fortified foods and supplements.
21	Turck et al. 2023	**Scientific opinion on the tolerable upper intake level for vitamin B6** *DOI: 10.2903/j.efsa.2023.8006*	EFSA scientific opinion deriving a tolerable upper intake level for vitamin B6. Not a new study.
22	Turck et al. 2024	**Guidance for establishing and applying tolerable upper intake levels for vitamins and essential minerals** *DOI: Not available*	Guidance document on establishing and applying tolerable upper intake levels for vitamins and essential minerals. Not a new study.
23	Jaskólska 2022	**CASE BASED** *DOI: Not available*	Similar article as Kościńska-Shukla 2025 that has been listed in the included study.

B.3 Irrelevant studies – results from titles and abstracts screening

No.	Study	Title	Notes
1	—	Isoniazid	Excluded because it was not directly relevant to vitamers; it focused on antibiotic isoniazid.

No.	Study	Title	Notes
2	—	[Expert Consensus on the Clinical Application of Sodium Cantharidinate and Vitamin B6 Injection]	Excluded because it focused on use of Sodium cantharidinate and vitamin B6 injection for improving quality of life in cancer treatment rather than excess vitamin B6 toxicity or UL derivation.
3	Abbas-Egbariya et al. 2025	Supplementation with endogenous healthy gut metabolites reverses the disruptions of in vitro and ex vivo epithelial functions induced by fecal content from IBD patients	Excluded because this study focuses on inflammatory bowel disease and epithelial function, with pyridoxal only included as one of several gut metabolites, and it does not assess excess vitamin B6 intake, toxicity, peripheral neuropathy, or UL derivation.
4	Abdelfatah et al. 2024	A stability-indicating HPLC assay of ten different vitamins in a food supplement: Appraisal of the method's greenness, whiteness, and blueness	Excluded because this was an analytical chemistry study on HPLC measurement and stability of vitamins in a tablet formulation, not a study of vitamin B6 excess intake, adverse health effects, peripheral neuropathy, or UL derivation.
5	Abouhish et al. 2026	Modulating One-Carbon Metabolism with B-Vitamins to Protect the Retinal Barrier and Prevent Retinal Degeneration	Excluded because this study examines deficiency and supplementation of vitamins B6, B9, and B12 in relation to retinal barrier function and not excess vitamin B6 intake, toxicity, peripheral neuropathy, or UL derivation.
6	Adam et al. 2022	Metabolic and molecular signatures of improved growth in Atlantic salmon (Salmo salar) fed surplus levels of methionine, folic acid, vitamin B(6) and B(12) throughout smoltification	Excluded because this was an animal nutrition study in Atlantic salmon examining growth effects of multiple one - carbon nutrients including vitamin B6 and not excess vitamin B6 toxicity, human health outcomes, peripheral neuropathy, or human UL derivation.
7	Adhan et al. 2025	Neurotoxic Implications of Vincristine in Pediatric: Ophthalmology: A Case Series	Excluded because this case series concerns vincristine - induced neurotoxicity treated with pyridoxine as supportive therapy, rather than adverse effects from excess vitamin B6 intake or UL derivation.

No.	Study	Title	Notes
8	Agarwal 2024	Contribution of Beef to Key Nutrient Intakes and Nutrient Adequacy in Pregnant and Lactating Women: NHANES 2011-2018 Analysis	Excluded because this dietary intake study evaluates nutrient adequacy and beef consumption in pregnant and lactating women, focusing on vitamin B6 deficiency risk rather than excess intake, toxicity, peripheral neuropathy, or UL derivation.
9	Aghamohammadi et al. 2022	Modeling studies on the role of vitamins B1 (thiamin), B3 (nicotinamide), B6 (pyridoxamine), and caffeine as potential leads for the drug design against COVID-19	Excluded because this was a molecular modelling study exploring vitamin B6 as a potential antiviral candidate against COVID - 19, not a study of excess vitamin B6 intake, toxicity, peripheral neuropathy, or UL derivation.
10	Ahmad et al. 2024	Protective Role of Vitamin B6 Against Teratogenic Effects Induced by Lead in Chick Embryo	Excluded because this animal study evaluates vitamin B6 as a protective treatment against lead toxicity in chick embryos, not adverse effects from excess vitamin B6 intake or UL derivation.
11	Ahmed et al. 2026	Vincristine-Induced Neurotoxicity in Acute Lymphoblastic Leukemia: A Comprehensive Systematic Review	Excluded because this review concerns vincristine - induced neurotoxicity and mentions pyridoxine only as a possible symptomatic treatment, not vitamin B6 excess intake, vitamin B6 - induced neuropathy, or UL derivation evidence.
12	Ahmed 2025	Vincristine-induced ptosis in pediatric patients: a systematic review and practice recommendations	Excluded because this review focuses on vincristine - induced ptosis/neurotoxicity with pyridoxine used as treatment, rather than adverse effects from excess vitamin B6 intake or UL derivation.
13	Akbarzadeh et al. 2025	Short-Term Effects of Folate Supplementation in Combination With Vitamin B6 for Treating Acute Manic Episodes in Bipolar I Disorder: A Randomized Controlled Trial	Excluded because this clinical trial evaluates vitamin B6 as adjunct therapy for bipolar disorder treatment, not adverse effects from excess vitamin B6 intake, peripheral neuropathy, or evidence relevant to establishing the vitamin B6 UL.
14	Akiyama et al. 2025	Vitamin B6 Status in Hypophosphatasia: Association With Clinical Severity, Diagnostic	Excluded because this study investigates vitamin B6 vitamer biomarkers in hypophosphatasia and treatment response not

No.	Study	Title	Notes
		Utility, and Effects on Vitamin B6 Metabolism by Supplementation and Enzyme Replacement Therapy	excess vitamin B6 intake, toxicity, peripheral neuropathy, or UL derivation.
15	Aktaşoğlu et al. 2026	Gyrate atrophy of the choroid and retina: a tertiary center experience	Excluded because this study concerns pyridoxine as part of treatment for gyrate atrophy/metabolic control, not adverse effects from excess vitamin B6 intake or UL derivation.
16	AlHariri 2026	Tuberculous Peripancreatic Lymphadenitis Presenting as Obstructive Jaundice Due to Extrinsic Common Bile Duct Compression: A Case Report	Excluded because it did not assess vitamin B6 toxicity; vitamin B6 was considered as a treatment.
17	AlMughram et al. 2022	Elucidating the Interaction between Pyridoxine 5'-Phosphate Oxidase and Dopa Decarboxylase: Activation of B6-Dependent Enzyme	Excluded due to wrong outcome: this biochemical/mechanistic study examined PLP transfer between B6-salvage enzymes and apoDDC, and did not assess vitamin B6 intake, adverse effects, or a health endpoint relevant to UL derivation.
18	Al-Awaida et al. 2023	Modulation of wheatgrass (Triticum aestivum Linn) toxicity against breast cancer cell lines by simulated microgravity	Excluded because this study examined phytochemical changes in wheatgrass under simulated microgravity, with pyridoxine identified only as one of many compounds; it was not relevant to excess vitamin B6 intake, human adverse effects, or UL derivation.
19	Alfian et al. 2025	Inverse embryonic responses of In vivo and In vitro fertilized mouse embryos to vitamin B supplementation during preimplantation period with limited long-term risks	Excluded because it was an IVF-related study and the exposure route was not relevant to vitamin B6 UL derivation.

No.	Study	Title	Notes
20	Ali et al. 2025	Conservation of Verbascum sinaiticum Benth using innovative tissue culture technique and DNA barcoding	Excluded due to wrong population; the study was in vitro and not directly relevant to excess vitamin B6 toxicity or UL derivation.
21	Aljaadi et al. 2022	Riboflavin intake and status and relationship to anemia	Excluded due to wrong nutrient and direction of effect; this narrative review focused on riboflavin deficiency and anemia, with vitamin B6 mentioned only in passing, and did not address adverse effects from excess vitamin B6 intake.
22	Almaraz-Postigo et al. 2024	Ocoxin Oral Solution Triggers DNA Damage and Cell Death in Ovarian Cancer	Excluded due to wrong nutrient and wrong outcome; vitamin B6 was not assessed as a relevant exposure and no relevant adverse health effect was reported.
23	Alsaeedi et al. 2023	Impact of lifestyle factors on dietary vitamin B(6) intake and plasma pyridoxal 5'-phosphate level in UK adults: National Diet and Nutrition Survey Rolling Programme (NDNS) (2008-2017)	Excluded due to wrong direction of effect; the study assessed dietary vitamin B6 intake and plasma PLP status in relation to deficiency risk, not adverse effects from excess intake relevant to the UL.
24	Alshaikh et al. 2026	Hyperemesis gravidarum revisited: from GDF15 biology to precision multimodal therapy	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxine mentioned as first line pharmacotherapy.
25	Althubity 2026	Homocystinuria: Advances in metabolic and molecular therapies targeting homocysteine pathways (Review)	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 mentioned as a treatment.
26	Alvarez et al. 2025	Vitamin B6 challenge as a tool for detecting ALPL mutations and diagnosing hypophosphatasia	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 supplementation can help detect ALPL.

No.	Study	Title	Notes
27	Ambrose et al. 2026	A novel therapy for pyridoxine-dependent epilepsy due to biallelic pathogenic variants in ALDH7A1: secondary mitochondrial energy deficiency and improvements of neurodevelopmental outcomes on triheptanoin treatment	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxine mentioned as a medication.
28	Andac-Ozturk et al. 2022	Investigation of the vitamins B(1), B(2), and B(6) vitamers bioaccessibilities of canned, dried legumes after in vitro gastrointestinal digestion system	Excluded due to wrong population: in vitro. Wrong exposure - bioavailability in veg and legumes.
29	Andraos et al. 2021	Plasma B Vitamers: Population Epidemiology and Parent-Child Concordance in Children and Adults	Excluded because wrong setting - correlation of B vitamers from parent to child.
30	Anjani et al. 2025	Lyophilised reservoirs in combination with hydrogel-forming microarray patches for transdermal delivery of isoniazid and pyridoxine hydrochloride	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; no adverse effects of B6 mentioned.
31	Antherjanam 2023	Electrochemical preparation and the characterizations of poly(3,5-diamino 1,2,4-triazole) film for the selective determination of pyridoxine in pharmaceutical formulations	Excluded because wrong setting - technique to measure pyridoxine in pharmaceuticals.
32	Arjeh et al. 2022	Synthesis and characterization of novel Spirulina protein isolate (SPI)-based hydrogels through dual-crosslinking with genipin/Zn(2)	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; mentions rate of B6 release.

No.	Study	Title	Notes
33	Asadi et al. 2024	The injection of maternal B complex vitamin during the transition period: The impact on performance, thyroid hormones levels and immunological parameters in the Sannen goats and their kids, as well as the faeces status of newborn kids	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; discusses benefits of vit B in goats and their kids.
34	Aslanli et al. 2022	Decarboxylases as hypothetical targets for actions of organophosphates: Molecular modeling for prediction of hidden and unexpected health threats	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; discusses PLP dependant enzymes not B6 itself.
35	Atia et al. 2025	Contribution of vitamin B 6 deficiency to anemia in children on regular hemodialysis	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 was not found to prevent anemia in children on HD.
36	Atreya 2022	Neurological Consequences of Sphingosine Phosphate Lyase Insufficiency	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; sPLIS mechanisms during insufficiency.
37	Ayen et al. 2025	Pott's disease presenting with bilateral psoas abscesses in a resource-poor setting: Case report and literature review	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - pyridoxine as therapeutic agent.
38	B et al. 2024	Characteristics of isoniazid-induced psychosis: a systematic review of case reports and case series	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 therapeutic effect to treat polyneuropathy from isoniazid.
39	Baart et al. 2023	Efficacy and utility of a tool for both measurement of vitamin B6, B12, D, folate and iron status and assessment of diet quality in athletes	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; tool to measure B6 status.

No.	Study	Title	Notes
40	Babor et al. 2023	4'-Deoxypyridoxine disrupts vitamin B(6) homeostasis in Escherichia coli K12 through combined inhibition of cumulative B(6) uptake and PLP-dependent enzyme activity	Excluded due to wrong population: e Coli K12.
41	Badrinath et al. 2026	Isoniazid Toxicity	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no adverse health effect from B6 reported) - studies the adverse health effect from isoniazid.
42	Bahalul-Yarchi et al. 2025	Drugs and Nutrients in Epilepsy: Vitamin B6 and the Ketogenic Diet	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - discusses supplementing with B6.
43	Banihani 2026	Role of Vitamin B_6 in Testosterone Synthesis	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; but highlighting the need to research B6 in testosterone synthesis.
44	Bao et al. 2025	Dietary patterns, nutrients, and risk of expiratory airflow limitation in children and adolescents	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - pyridoxine in diet helped protect lung function.
45	Barros et al. 2023	Dietary Intake of Micronutrients and Disease Severity in Patients with Amyotrophic Lateral Sclerosis	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - lower B6 intake was associated with increased severity of disease.
46	Bartella et al. 2026	HPLC-Orbitrap-MS for the Determination of B-Vitamins in Fruit Juices and Food Supplements	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 in fruit juice.

No.	Study	Title	Notes
47	Barzegari et al. 2025	Effects of Vitamin B6 on the Expression and Development of Tolerance to Morphine Stimulating Effects on Locomotor Activity in Mice	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; vitamin B6 may be considered as a nutritional supplement in reducing morphine tolerance.
48	BasualdoAllende et al. 2024	A case series of low-level laser therapy treatment in patients with peripheral facial palsy	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 supplementation may improve facial palsy.
49	Bayzaei et al. 1993	Tyrosinemia Type II	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - pyridoxine may be beneficial for skin treatment.
50	Besag et al. 2023	Current evidence for adjunct pyridoxine (vitamin B6) for the treatment of behavioral adverse effects associated with levetiracetam: A systematic review	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxine supplementation for treatment of adverse behaviour.
51	Bhargava 2024	The 3 HP regimen for tuberculosis preventive treatment: safety, dosage and related concerns during its large-scale implementation in countries like India	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; benefits of B6 supplementation alongside 3 HP.
52	Bicalho-Silva et al. 2026	β-caryophyllene mitigates metabolic dysfunction in the testes of gerbils perinatally exposed to BPA	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxine as a biomarker in testes.
53	Bird et al. 2023	Micronutrient intakes in the Dutch diet: foods, fortified foods and supplements in a cross sectional study	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; no B6 above the UL were found in Dutch population.

No.	Study	Title	Notes
54	Bjørke-Monsen et al. 2026	Exclusive Breastfeeding Is Not Ensuring an Adequate Vitamin B Status in Premature Infants with Very Low Birth Weight	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; do babies get enough B6 from breastmilk.
55	Bjørklund et al. 2022	The role of B vitamins in stroke prevention	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; role of B vitamins in stroke prevention.
56	Blau et al. 1993	Aromatic L-Amino Acid Decarboxylase Deficiency	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 included as treatment.
57	Blonk et al. 2024	Micronutrient deficiencies and anemia in the follow-up after gastroesophageal cancer surgery	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 should be supplemented after surgery.
58	Bloomer et al. 2024	Randomized Trial to Assess the Safety and Tolerability of Daily Intake of an Allulose Amino Acid-Based Hydration Beverage in Men and Women	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; the product contained B6.
59	Bo et al. 2022	Intakes of Folate, Vitamin B6, and Vitamin B12 in Relation to All-Cause and Cause-Specific Mortality: A National Population-Based Cohort	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - B6 reduced mortality rate from CVD.
60	Bonino et al. 2025	Thiamine hydrochloride, riboflavin, pyridoxine hydrochloride, and biotin hard gelatin capsules prepared in advance and stored for the treatment of pediatric metabolic diseases: a safer alternative	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; do vitamin B6 gummies stay stable?

No.	Study	Title	Notes
61	Bottino et al. 2025	Lactic acidosis, rhabdomyolysis, and hyperammonemia: Atypical presentation in a new patient with PDE-ALDH7A1 defect	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; treatment with pyridoxine.
62	Boyer et al. 2022	Nutrition interventions in congenital disorders of glycosylation	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 as treatment option.
63	Braadland et al. 2023	Clinical and biochemical impact of vitamin B6 deficiency in primary sclerosing cholangitis before and after liver transplantation	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; focuses on negatives of B6 deficiency.
64	Brasky et al. 2023	Supplemental B-Vitamins and Risk of Upper Gastrointestinal Cancers in the Women's Health Initiative	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 supplementation did not lead to adverse effects and increased risk of GI cancer.
65	Bråtveit et al. 2024	Association between dietary macronutrient composition and plasma one-carbon metabolites and B-vitamin cofactors in patients with stable angina pectoris	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 just a bio - measurement in study.
66	Brenner et al. 2024	7,8-Dihydroxyflavone is a direct inhibitor of human and murine pyridoxal phosphatase	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - addresses the need for B6 supplementation when inhibited by 7,8 - DHF.
67	Brossfield et al. 2025	The Effects of the AGE Inhibitor Pyridoxamine on Bone in Older Women With Type 2 Diabetes: A Randomized Clinical Trial	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - Pyridoxamine improved bone health (no adverse effects).

No.	Study	Title	Notes
68	Brown et al. 2025	Neglected micronutrients-considering a broader set of vitamins and minerals in public health nutrition programs worldwide: a narrative review	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; discusses supplementation to prevent deficiency of B6.
69	Buzatu et al. 2025	The Role of Vitamin B Complex in Periodontal Disease: A Systematic Review Examining Supplementation Outcomes, Age Differences in Children and Adults, and Aesthetic Changes	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - low B6 was linked to worse periodontal symptoms.
70	Bzikowska-Jura et al. 2023	Maternal diet during breastfeeding in correlation to calcium and phosphorus concentrations in human milk	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; materal diet included pyridoxine.
71	Cai et al. 2023	Optimization of Gamma-Aminobutyric Acid Production by Lactiplantibacillus plantarum FRT7 from Chinese Paocai	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake;, wrong setting - PLP used in synthesis.
72	Cai et al. 2024	A novel and apparent de novo ALAS2 missense variant associated with congenital sideroblastic anemia	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; anemia was B6 responsive and symptoms were helped by B6.
73	Calmarza et al. 2023	Musculoskeletal pain and muscular weakness as the main symptoms of adult hypophosphatasia in a Spanish cohort: clinical characterization and identification of a new ALPL gene variant	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake or otherwise lacked a relevant vitamin B6 exposure.
74	Camacho et al. 2025	Pyridoxal and Salicylaldehyde Derivatives: Synthesis, Characterization, and Antifungal Potential Against Opportunistic Yeast Pathogens	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - pyridoxal derivates in antifungal medication.

No.	Study	Title	Notes
75	Camargo et al. 2025	Comparison of Nutrient Intake Across Different Dietary Patterns in Brazilian Community-Dwelling Older Adults	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake;, Wrong outcome - certain diets improved the intake of B6.
76	Cansino et al. 2023	Nutrient effects on working memory across the adult lifespan	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - memory correlates with B6 consumption.
77	CastruccioCastracani et al. 2025	An erythroid-specific lentiviral vector improves anemia and iron metabolism in a new model of XLSA	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; treatments are limited to pyridoxine and no adverse effects discussed.
78	Chambliss et al. 2025	Reported Awareness and Use of Pyridoxal-5'-Phosphate Supplementation in Alanine Aminotransferase and Aspartate Aminotransferase Assay Reagents: A Survey by the College of American Pathologists Clinical Chemistry Committee	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; study shows B6 benefits and hospital behaviour in ALT and AST reagents.
79	Chancharoenthana et al. 2026	Management of latent tuberculosis infection in patients with kidney disease	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - therapeutic effect of B6 supplementation.
80	Chang 2023	Update current understanding of neurometabolic disorders related to lysine metabolism	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake;, Wrong outcome - discusses treatment of pyridoxine dependant epilepsy.

No.	Study	Title	Notes
81	Chen et al. 2025	Computational Study on the Catalytic Mechanism of UstD Catalyzing the Synthesis of γ-Hydroxy-α-Amino Acids	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake;, wrong setting - discusses mechanism of pyridoxine dependant UstD.
82	Chen et al. 2022	Metabolomic and transcriptomic responses of mouse testis to the dextran sulfate sodium induced colitis	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 levels decreased from induced IBD.
83	Chen et al. 2024	Association of methyl donor nutrients dietary intake and sleep disorders in the elderly revealed by the intestinal microbiome	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 as part of MDN can help regulate sleep.
84	Chen et al. 2026	Vitamin B6 attenuates aortic dissection by inhibiting pathological remodeling of the aortic extracellular matrix	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 can prevent AD.
85	Chen et al. 2024	A synthetic microbial consortium protects against obesity by regulating vitamin B6 metabolism	Excluded due to wrong population: in vitro. Wrong exposure - regulating obesity with B6 metabolism.
86	Chen et al. 2025	Systems metabolic engineering and process optimization for efficient l-tyrosine production from high-purity glucose syrup in Escherichia coli	Excluded due to wrong population: bacteria/ cell.
87	Chen et al. 2023	Association of vitamins with hearing loss, vision disorder and sleep problem in the US general population	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake;, Wrong outcome (no adverse effects) - B6 inversely related to health issues.

No.	Study	Title	Notes
88	Chen et al. 2026	A case report of congenital sideroblastic anemia caused by a novel ALAS2 mutation in conjunction with thalassemia	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; the population responded to B6 therapy.
89	Cheng et al. 2025	Exploring the effects of Tianma Gouteng granules on L-NAME-induced hypertensive rats based on 16S rDNA gene sequencing and metabolomics	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 metabolism affected by TG.
90	Cheng et al. 2023	Association between B-vitamins intake and frailty among patients with chronic obstructive pulmonary disease	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake;, Wrong outcome - less B6 increased chance of frailty.
91	Cheraghmakani et al. 2022	Pyridoxine for treatment of levetiracetam-induced behavioral adverse events: A randomized double-blind placebo-controlled trial	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; blind study on whether the pyridoxine medication relieves psychiatric symptoms.
92	Chi et al. 2022	Drosophila carrying epilepsy-associated variants in the vitamin B6 metabolism gene PNPO display allele- and diet-dependent phenotypes	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pLP supplementation reduced seizures in flies.
93	Chidambaram et al. 2023	Pyridoxine Therapy: Not Just the Dose, the Duration Matters Too	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; benefits of pyridoxine in PDE patients.
94	Chu et al. 2024	Factors influencing vitamin B6 status in domestic cats: age, disease, and body condition score	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; discusses B6 deficiency.
95	Chun et al. 2024	Traditional Korean diet high in one-carbon nutrients increases global DNA methylation: implication for epigenetic diet	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; k (plant - based) group consumed more B6 in their diet.

No.	Study	Title	Notes
96	Cifelli et al. 2022	Association between Intake of Total Dairy and Individual Dairy Foods and Markers of Folate, Vitamin B(6) and Vitamin B(12) Status in the U.S. Population	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; dairy consumption reduced risk of B6 deficiency.
97	Clements et al. 2022	A 2-Year Randomized Controlled Trial With Low-Dose B-Vitamin Supplementation Shows Benefits on Bone Mineral Density in Adults With Lower B12 Status	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; not excess B6 intake but LOW DOSE.
98	Cominacini et al. 2025	Unlocking Relief: Investigating the Impact of a Fixed Combination of Acetyl-L-Carnitine and Palmitoylethanolamide on Traumatic Acute Low Back Pain	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - B6 may help reduce lower back pain.
99	CorreaGuzmán et al. 2022	Validation of an instrument to assess food diversity in women of childbearing age in Medellín, Colombia	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; instrument to measure deficiencies.
100	Costeira et al. 2023	Metabolomic biomarkers of habitual B vitamin intakes unveil novel differentially methylated positions in the human epigenome	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; effect of B6 on the human epigenome (not relevant to dose).
101	Coughlin 2023	Pyridoxine-dependent epilepsy: Current perspectives and questions for future research	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; no adverse health effects from pyridoxine, pyridoxine used as treatment for PDE.

No.	Study	Title	Notes
102	Coughlin et al. 2022	Association Between Lysine Reduction Therapies and Cognitive Outcomes in Patients With Pyridoxine-Dependent Epilepsy	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - pyridoxine treatment in first 6 months helped development.
103	Crawford et al. 2023	Micronutrient Gaps and Supplement Use in a Diverse Cohort of Pregnant Women	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; study finds dietary intake of micronutrients and minerals in pregnant women.
104	Crowther et al. 2023	Metabolomics analysis of antiquitin deficiency in cultured human cells and plasma: Relevance to pyridoxine-dependent epilepsy	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxine dependant epilepsy.
105	Cui et al. 2023	Can vitamin B6 alleviate the adverse reactions of quadruple anti-Helicobacter pylori regimen? : randomized controlled trial	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 supplementation benefitted the regimen.
106	Cuyubamba et al. 2025	The Combination of Neurotropic Vitamins B1, B6, and B12 Enhances Neural Cell Maturation and Connectivity Superior to Single B Vitamins	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; benefits of combined B supplementation on Peritheral neuropathy compared to B12 treatment alone.
107	D'Ambrosio 2022	Lumasiran in the Management of Patients with Primary Hyperoxaluria Type 1: From Bench to Bedside	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxine used to be used to treat PH1.
108	D'Haese et al. 2024	Pyridoxamine Alleviates Cardiac Fibrosis and Oxidative Stress in Western Diet-Induced Prediabetic Rats	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; less risk of cardiac disease with B6 supplementation.

No.	Study	Title	Notes
109	Dahir et al. 2024	Safety, pharmacokinetics, and pharmacodynamics of efzimfotase alfa, a second-generation enzyme replacement therapy: phase 1, dose-escalation study in adults with hypophosphatasia	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 as a biomarker and mentioned as a treatment for HPP.
110	Dattagupta et al. 2022	A Case of Spondylodysplastic Ehlers-Danlos Syndrome With Comorbid Hypophosphatasia	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 measurement can be used as a diagnosis for syndrome.
111	Dattilo et al. 2022	Modulation of Human Hydrogen Sulfide Metabolism by Micronutrients, Preliminary Data	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; / outcome (no adverse effects to excess B6) - B6 supplementation was beneficial.
112	deCarvalho et al. 2022	Management of Hyperhomocysteinemia, Low Vitamin Levels, and Low Cortisol in Cannabis Users: A Report of 2 Cases	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 management effect on cannabis users.
113	dePuyraimond et al. 2026	Should PNPO Deficiency Be Treated In Utero? Clinical Findings From Prenatal Pyridoxine Therapy	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - therapeutic effect of B6 on PNPO in utero.
114	DeSimoni et al. 2024	Role of antioxidants supplementation in the treatment of atopic dermatitis: a critical narrative review	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; /exposure (not adverse effects to excess B6) - pyridoxine used as a treatment.
115	De-Mul et al. 2024	[Management of patients with kidney stones]	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 was sometimes used as a treatment (B6 mentioned as context).

No.	Study	Title	Notes
116	Delgado-García et al. 2024	A Randomized Control Trial of Dexketoprofen/Vitamin B (Thiamine, Pyridoxine and Cyanocobalamin) Fixed-Dose Combination in Post-Traumatic Grade I-II Cervical Sprains	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 supplementation was used as an analgesic.
117	Deng et al. 2022	Antenna effect of pyridoxal phosphate on the fluorescence of mitoxantrone-silicon nanoparticles and its application in alkaline phosphatase assay	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxal as feature in chemical experiment.
118	Deruelle et al. 2022	[Expert consensus from the College of French Gynecologists and Obstetricians: Management of nausea and vomiting of pregnancy and hyperemesis gravidarum]	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; touches on benefit of B6 in this specific case.
119	Dhanshri 2023	Fluorescence Turn-on Detection of Alkaline Phosphatase Activity and Al(3+) Using Vitamin B(6) Cofactor Conjugated GSH Capped Mn-doped ZnS Quantum Dots	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxal effect in fluorescence.
120	DiasDuartedeCarvalhoSouza et al. 2024	The Dietary Inflammatory Index is associated with diet quality and nutrient intake during the gestational period	Excluded because wrong setting - pyridoxine as a measurement of diet quality.
121	Dias et al. 2025	Biological properties of vitamins of the B-complex, part 2 - vitamins B(6) and B(7) (biotin, vitamin H)	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; only briefly discusses symptoms of B6 toxicity not likely to go into dosing.

No.	Study	Title	Notes
122	Didangelos et al. 2024	Efficacy and Safety of the Combination of Palmitoylethanolamide, Superoxide Dismutase, Alpha Lipoic Acid, Vitamins B12, B1, B6, E, Mg, Zn and Nicotinamide for 6 Months in People with Diabetic Neuropathy	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; combination of vitamins helped prevent diabetic neuropathy.
123	Ding et al. 2023	Pyridoxal 5'-phosphate alleviates prenatal pyridaben exposure-induced anxiety-like behaviors in offspring	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pY may disrupt B6 metabolism in offspring.
124	Dkhillon et al. 2023	B Vitamins as Adjunctive Treatment for Chronic Heart Failure	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - B6 improved heart function.
125	Donge et al. 2025	Advancing Neonatal Screening for Pyridoxine-Dependent Epilepsy-ALDH7A1 Through Combined Analysis of 2-OPP, 6-Oxo-Pipecolate and Pipecolate in a Butylated FIA-MS/MS Workflow	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; good response to high dose B6 in PDE patients.
126	Dou et al. 2025	Synergistic Effect Evaluation and Mechanism Investigation of Vitamin B6 and B12 in Models of Neuroinflammation	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; using nanocarriers to more effectively deliver B6.
127	Douglas et al. 2025	Acute kidney failure from ingestion of "wood bleach" beekeeping miticide	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - pyridoxal used as treatment for toxicity.

No.	Study	Title	Notes
128	Du et al. 2025	Advanced Applications of Vitamin B Complex in Plastic and Cosmetic Surgery: Mechanisms and Therapeutic Benefits	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - B6 supplementation helps in cosmetic procedures.
129	Du 2025	Association between vitamin B(6) status and eczema in children and adolescents: results from the NHANES database	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - quick metabolism of B6 can increase risk of eczema.
130	Duan et al. 2025	Effects of a food supplement containing phosphatidylserine on cognitive function in Chinese older adults with mild cognitive impairment: A randomized double-blind, placebo-controlled trial	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 improved symptoms.
131	Ducamp et al. 2024	Murine models of erythroid 5ALA synthesis disorders and their conditional synthetic lethal dependency on pyridoxine	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; discusses harm from B6 deficiency.
132	Edwards et al. 2024	Effects of an Acute Dose of Zinc Monomethionine Asparate and Magnesium Asparate (ZMA) on Subsequent Sleep and Next-Day Morning Performance (Countermovement Jumps, Repeated Sprints and Stroop Test)	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 level was not deficient from medication (ZMA).
133	Edwards et al. 2023	Dietary factors potentially impacting thiaminase I-mediated thiamine deficiency	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; mentions pyridoxine effect on thiamine in fish.

No.	Study	Title	Notes
134	Ehrmann et al. 2024	Engineering Saccharomyces cerevisiae for fast vitamin-independent aerobic growth	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; growth rate of cultures with/out B6 (Wrong population).
135	Ekundayo et al. 2024	Synergistic Effect of Donepezil and Neurotropic B Vitamins on Dysregulated Antioxidant, Inflammation and Neurotransmitter Status in Aluminium Chloride-Induced Neurotoxicity in Rats	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - B6 increased therapeutic effects of donepezil.
136	ElMesmoudi et al. 2022	Validation of a quantitative web-based food frequency questionnaire to assess dietary intake in the adult Emirati population	Excluded due to wrong exposure: not directly relevant to excess vitamin B6 toxicity or UL derivation; method validation study on diet questionnaire.
137	Elebiju et al. 2024	In Silico Design of Potential Small-Molecule Antibiotic Adjuvants against Salmonella typhimurium Ortho Acetyl Sulphydrylase Synthase to Address Antimicrobial Resistance	Excluded due to wrong exposure: not directly relevant to excess vitamin B6 toxicity or UL derivation; pLP binding used as a comparison to different binder (brief mention).
138	Elgharably et al. 2023	Vitamin B group levels and supplementations in dermatology	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - B6 deficiency should be assessed when treating skin conditions.
139	Elhusseiny et al. 2023	Regression of treatment-resistant gyrate atrophy-associated intraretinal cystic spaces using long-term diet restriction: A case report	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - B6 supplementation helped the child.

No.	Study	Title	Notes
140	Elkhateeb et al. 2023	Paracetamol toxicity in classic homocystinuria: Effect of N-acetylcysteine on total homocysteine	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; the woman's disease was pyridoxine unresponsive but this was not the focus.
141	Ellis et al. 2026	Inpatient initiation of tuberculosis preventive therapy with 1 month of isoniazid and rifapentine for adults with advanced HIV disease and cryptococcal meningitis (IMPROVE): a non-inferiority, randomised controlled trial	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 taken at 25 mg/kg was taken alongside medication and no adverse effects reported from B6.
142	Ene et al. 2023	The effectiveness of citrates and pyridoxine in the treatment of kidney stones	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; pyridoxines may prevent kidney stones.
143	Eom et al. 2022	Metabolic profiling of serum and urine in lactating dairy cows affected by subclinical ketosis using proton nuclear magnetic resonance spectroscopy	Excluded because wrong setting - pyridoxine as a biomarker.
144	Faccin et al. 2023	Industry survey of added vitamins and trace minerals in U.S. swine diets	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - amount of pyridoxine in swine diets.
145	Falsaperla et al. 2025	Is Vitamin B6 a Precision Therapy for Neonatal Seizures?	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; therapeutic effects of B6.
146	Fang et al. 2024	Vitamin B6 alleviates osteoarthritis by suppressing inflammation and apoptosis	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 alleviates osteoarthritis.

No.	Study	Title	Notes
147	Felippe et al. 2026	Vitamin B6 (Pyridoxal 5' Phosphate) antagonises carotid body P2X3 receptors in hypertension	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - B6 may have a calming effect on the nervous system.
148	Feng et al. 2024	Bacterial vitamin B6 is required for post-embryonic development in C. elegans	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 derivative as an important player in post - embryonic development.
149	Field et al. 2022	High-dose Vitamin B6 supplementation reduces anxiety and strengthens visual surround suppression	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 reduces anxiety and helps produce GABA.
150	Filipic et al. 2026	Branched-chain amino acid transferase 2 (BCAT2) deficiency: A case series and systematic review	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 supplementation trialled to help.
151	Flores-Torres et al. 2023	Long-Term Intake of Folate, Vitamin B6, and Vitamin B12 and the Incidence of Parkinson's Disease in a Sample of U.S. Women and Men	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; study was trying to find the benefit of B6 on reducing PD however this was not found.
152	Fortin et al. 2023	Pearls & Oy-sters: Delayed Response to Pyridoxine in Pyridoxine-Dependent Epilepsy	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 supplementation helped prevent seizures.
153	Freercks et al. 2026	Safety and Effectiveness of Long-Term Isoniazid Treatment for the Prevention of Tuberculosis in High-Risk Dialysis Patients	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; side effects were treated with B6.

No.	Study	Title	Notes
154	Fu et al. 2025	A cell-autonomous role for the vitamin B6 metabolism gene PNPO in Drosophila GABAergic neurons	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 mechanisms to active vitamer in PNPO genes.
155	Fulmali 2022	Phosphate moiety in FDA-approved pharmaceutical salts and prodrugs	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxal phosphate mentioned in passing as a prodrug.
156	Gaither et al. 2026	Consensus Guideline for Care of Patients in the Prehospital and Aerospace Settings with Exposures to Hydrazine and Hydrazine Derivatives	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 therapeutic effect for exposure to hydrazine.
157	Gálvez et al. 2023	Gastroparesis associated to isoniazid. First description	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - pyridoxine supplementation has therapeutic effect.
158	Gálvez-Navas et al. 2024	Molecular Mechanisms Linking Genes and Vitamins of the Complex B Related to One-Carbon Metabolism in Breast Cancer: An In Silico Functional Database Study	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; /outcome (no toxicity of B6 intake) - B vitamin supplementation is vital in the one carbon metabolism process than that can prevent cancer.
159	Gao et al. 2023	Lacticaseibacillus rhamnosus Probio-M9 enhanced the antitumor response to anti-PD-1 therapy by modulating intestinal metabolites	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxine concentration as a bioresponse.
160	Gao et al. 2022	Genome-wide identification of SHMT family genes in cucumber (Cucumis sativus L.) and functional	Excluded due to wrong population: plants.

No.	Study	Title	Notes
		analyses of CsSHMTs in response to hormones and abiotic stresses	
161	Gao et al. 2025	High-performance biocatalyst Nicotiana attenuata α-glucan phosphorylase facilitates the robust synthesis of amylose from cellobiose	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 catalysis is affected in study.
162	Gao et al. 2025	The Application of Quantitative (1)H-NMR for the Determination of Melatonin and Vitamin B6 in Commercial Melatonin Products	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; determining the amount of B6 in melatonin products.
163	Gao et al. 2026	Association between serum PLP levels and the natural resolution of nausea and vomiting in pregnancy: a secondary analysis	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - specific study - PLP as biomarker for NVP would be hard to obtain info on UL.
164	Garg et al. 2026	Hippophae rhamnoides: Way to Ameliorate Depressive Augury by Cyanocobalamin	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - correlation of vitamin B12 on depression.
165	Geusens et al. 2026	YouTube as a source of (mis)information for morning sickness self-help - A content analysis and literature review of recommendations for nausea and vomiting in pregnancy	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; misinformation for pregnancy symptoms in YouTube.
166	Gholizadeh et al. 2022	Production performance, egg quality and some blood parameters of heat-stressed laying hens as affected by dietary supplemental Vit B6, Mg and Zn	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - B6 helped performance of egg laying hens.

No.	Study	Title	Notes
167	Ghosh et al. 2023	In vivo 'turn on' fluorescence detection of free cysteine in zebrafish kidney and liver	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake;, wrong setting - pyridoxal as part of the system to detect free cysteine.
168	Ghosh et al. 2026	B vitamins in dermatology	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; b vitamins have dermatological benefits.
169	Ghosh-Jerath et al. 2022	Indigenous Foods to Address Malnutrition: An Inquiry into the Diets and Nutritional Status of Women in the Indigenous Community of Munda Tribes of Jharkhand, India	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxine levels were normal in population.
170	Giudici et al. 2023	Effect of a 1-Year Nutritional Blend Supplementation on Plasma p-tau181 and GFAP Levels among Community-Dwelling Older Adults: A Secondary Analysis of the Nolan Trial	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; / Wrong exposure - in fact B6 did not affect the progression of Alzheimer's.
171	Głąbska et al. 2022	Analysis of the Nutritional Value of the Diets Presented in Women's and Sports Magazines before and during the COVID-19 Pandemic	Excluded because wrong setting - B6 amount in meals in magazines.
172	Gnocchini et al. 2022	Vitamin B6 Deficiency Promotes Loss of Heterozygosity (LOH) at the Drosophila warts (wts) Locus	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 deficiency may promote loss of Heterozygosity.
173	Godfrey et al. 2023	Maternal B-vitamin and vitamin D status before, during, and after pregnancy and the influence of supplementation preconception and during	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; deficiency not toxicity.

No.	Study	Title	Notes
		pregnancy: Prespecified secondary analysis of the NiPPeR double-blind randomized controlled trial	
174	Goedeke et al. 2024	Assessing the Nutrient Composition of a Carnivore Diet: A Case Study Model	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; carnivore diet met RDI for B6.
175	Göktaş 2024	Adherence to medical treatment for Wilson's disease in children and adolescents: a cohort study from Turkey	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; does not study effects of B6.
176	Goorden et al. 2025	Two new cases of KYNU deficiency: Further delineation of the phenotypic and biochemical spectrum and exploration of treatment options	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 supplementation mya be used as medication.
177	Gopinath et al. 2023	Reduced serum pyridoxine and 25-hydroxyvitamin D levels in adults with chronic pruritic dermatoses	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; / Wrong outcome (no adverse effects from B6) - low B6 is harmful and B6 supplementation may help patients with CPD.
178	Groborz et al. 2025	New insights into the mechanisms and prevention of central nervous system oxygen toxicity: A prospective review	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 administration to be administered alongside HBOT to help therapeutic effects.
179	Gu et al. 2026	A lung microbial signature for postoperative recurrence in stage I-II non-small cell lung cancer	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; mentions B6 metabolic pathways in relation to cancer.

No.	Study	Title	Notes
180	Gu et al. 2024	Intestinal commensal bacteria promote Bactrocera dorsalis larval development through the vitamin B6 synthesis pathway	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 beneficial to larval growth.
181	Gundogan et al. 2022	Serum micronutrient levels in critically ill patients receiving continuous renal replacement therapy: A prospective, observational study	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 levels measured after renal replacement therapy.
182	Gunes et al. 2024	Assessment of Impact of Dietary Patterns on Obstructive Sleep Apnea Patients	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; relating sleep apnea to nutritional patterns (involving B6).
183	Guo et al. 2026	Combined B-vitamin supplementation on homocysteine and vascular outcomes in coronary heart disease: a meta-analysis	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; b vitamin supplementation reduced symptoms of CHD.
184	Guo et al. 2025	MC-LR triggers trophoblast ferroptosis at the maternal-fetal interface by directly targeting PKM2 to reprogram metabolism	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - pyridoxine restored liver function.
185	Gupta et al. 2024	A retrospective study to assess adolescent nutritional deficiencies and the association with post-COVID-19 status	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; adolescence don't get enough B6.
186	Gupta et al. 2022	Treatment of primary hyperoxaluria type 1	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; talks about patients having pyridoxine sensitivity.

No.	Study	Title	Notes
187	Haesen et al. 2024	Pyridoxamine Attenuates Doxorubicin-Induced Cardiomyopathy without Affecting Its Antitumor Effect on Rat Mammary Tumor Cells	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; pyridoxamine may improve heart function.
188	Hake et al. 2023	Combined strategy employing MutMap and RNA-seq reveals genomic regions and genes associated with complete panicle exsertion in rice	Excluded due to wrong population: rice.
189	Hakola et al. 2024	Intake of B vitamins and the risk of developing islet autoimmunity and type 1 diabetes in the TEDDY study	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 led to lower risk of developing autoimmunity changes that lead to type 1 diabetes.
190	Hamouda et al. 2022	Assessment of Antioxidant and Anticancer Activities of Microgreen Alga Chlorella vulgaris and Its Blend with Different Vitamins	Excluded due to wrong population: in vitro. Wrong exposure - not excess intake.
191	Han et al. 2025	Exploring neuropsychiatric manifestations of vitamin B complex deficiencies	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; discussing importance of supplementation in deficiencies rather than risks of toxicity.
192	Hansen et al. 2025	Acute non-alcoholic nutritional neuropathies in high-income countries - a systematic review	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; nutritional neuropathy patients were B6 deficient.
193	Harb et al. 2023	Micronutrient inadequacy and urinary stone disease: an analysis of the National Health and Nutrition Examination Survey 2007-2018	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; inadequate amount of B6 lead to health complications.

No.	Study	Title	Notes
194	Hashim et al. 2026	Comprehensive Review of L-Lysine: Chemistry, Occurrence, and Physiological Roles	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; benefits of lysine and how lysine can affect pyridoxine - dependant epilepsy.
195	Hasken et al. 2023	Maternal dietary intake among alcohol-exposed pregnancies is linked to early infant physical outcomes in South Africa	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; women were below the B6 RDI.
196	He et al. 2024	Vitamin B6 Competition in the Tumor Microenvironment Hampers Antitumor Functions of NK Cells	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 supplementation has antitumor properties.
197	He et al. 2026	Common Adverse Reactions and Management Strategies of First-Line Anti-Tuberculosis Drugs	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - pyridoxine as treatment for peripheral neuropathy.
198	Heilfort et al. 2023	A Systematic Review of the Benefit of B-Vitamins as a Complementary Treatment in Cancer Patients	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; "Evidence of B - vitamins in cancer patients is low and supplementation cannot be recommended" No real outcome.
199	Helland et al. 2022	Consumption of a light meal affects serum concentrations of one-carbon metabolites and B-vitamins. A clinical intervention study	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; light breakfast does not provide enough B vit.
200	Hernandez-Unzueta et al. 2023	Improving the Antitumor Effect of Chemotherapy with Ocoxin as a Novel Adjuvant Agent to Treat Prostate Cancer	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake or otherwise lacked a relevant vitamin B6 exposure.

No.	Study	Title	Notes
201	Herrera et al. 2024	Effects of the PREMEN-CALM® in the Management of the Premenstrual Syndrome: A Randomized, Double-Blind, Placebo-Controlled Pilot Study	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; a medication that contains B6 may help PMS.
202	Hess et al. 2023	Modeling Ovo-vegetarian, Lacto-vegetarian, Pescatarian, and Vegan USDA Food Patterns and Assessing Nutrient Adequacy for Lactation among Adult Females	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; shows that vegetarian diets can lack in some B6. Does not discuss toxicity.
203	Heysell et al. 2026	Immediate or high-dose antituberculosis therapy for HIV-related sepsis in Tanzania and Uganda (ATLAS): a phase 3, open-label, randomised, controlled, 2 × 2 factorial, superiority trial	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxine taken alongside medication, effects of pyridoxine not discussed.
204	Hikichi et al. 2025	Scavenging methylglyoxal improves bone quality and defect healing in diabetic mice	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - pyridoxamine supplementation ameliorated impairments.
205	Højfeldt et al. 2026	Nicotinamide and Pyridoxine Supplementation Enhances Muscle Stem Cell Activity and Muscle Regeneration in Humans: A Randomized Placebo-Controlled Clinical Trial of High Force Eccentric Contraction Recovery in Healthy Young Men	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 may be therapeutic in muscle regeneration.
206	Horowitz et al. 2026	Gyromitra Mushroom Toxicity	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; the mushroom effects pyridoxal in the body.

No.	Study	Title	Notes
207	Hu et al. 2024	Effects of different energy levels in low-protein diet on liver lipid metabolism in the late-phase laying hens through the gut-liver axis	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxine was affected by LL diet.
208	Hu et al. 2022	Vitamins and their derivatives synergistically promote hair shaft elongation ex vivo via PlGF/VEGFR-1 signalling activation	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxine supplementation improved hair shaft formation.
209	Hu et al. 2022	Effect of ginger in the treatment of nausea and vomiting compared with vitamin B6 and placebo during pregnancy: a meta-analysis	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; shows that ginger is more effective than B6 for alleviating symptoms.
210	Huang 2023	Quantification of the Relationship of Pyridoxine and Spirometry Measurements in the United States Population	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; / Wrong outcome (no adverse effects from B6) - Increased vitamin B6 intake is associated with improvement in lung function.
211	Huang et al. 2023	Scavenging dicarbonyls with 5'-O-pentyl-pyridoxamine increases HDL net cholesterol efflux capacity and attenuates atherosclerosis and insulin resistance	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 acting like protective drug and reducing stress and inflammation.
212	Huang et al. 2025	Cardiac Manifestations of Nutritional Deficiencies	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; discusses deficiencies not toxicity.
213	Huo et al. 2026	Dietary Intake and Plasma Concentration of B Vitamins in Relation to Incident Coronary Artery Disease in African-American Adults: The Jackson Heart Study	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; no strong correlation between B vitamins and CAD found.

No.	Study	Title	Notes
214	Hussein et al. 2023	LC/MS analysis of mushrooms provided new insights into dietary management of diabetes mellitus in rats	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - mushroom supplementation reduced plasma glucose levels through the bioactive compound pyridoxine.
215	Işık 2026	Assessment of the nutritional status of Syrian refugee women in the lactation period	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; the need for B6 supplementation.
216	Ito et al. 2023	d-amino acid auxotrophic Escherichia coli strain for in vivo functional cloning of novel d-amino acid synthetic enzyme	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake or otherwise lacked a relevant vitamin B6 exposure.
217	Jadidi et al. 2022	Therapeutic effects of magnesium and vitamin B6 in alleviating the symptoms of restless legs syndrome: a randomized controlled clinical trial	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; therapeutic effect of B6 on supplementation.
218	Jafari et al. 2025	Combination Therapy with Pyridoxine and Arginine Supplementations along with a Lysine-Restricted Diet in Individuals with Pyridoxine-Dependent Epilepsy: A Comprehensive Systematic Review	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - pyridoxine treatment was highly effective.
219	Jahner et al. 2026	Quantitation of Vitamin B6 Vitamers and Glycosides in German Alcohol-Free and Full-Strength Beer by a Stable Isotope Dilution LC-MS/MS Method	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; levels of B6 in german beer.

No.	Study	Title	Notes
220	Jarrett et al. 2022	Vitamin B-6 and riboflavin, their metabolic interaction, and relationship with MTHFR genotype in adults aged 18-102 years	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 dependency on riboflavin biomechnaism.
221	Jaruan et al. 2025	Pyridoxine exerts antioxidant effects on kidney injury manifestations in high-fat diet-induced obese rats	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 may help medicate kidney failure in obese patients.
222	Jayaram 2022	Computational Molecular Modeling Studies of Some Mycobacterium Tuberculosis Alanine Racemase Inhibitors	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxal is a description for the enzyme.
223	Jayawardena et al. 2023	The effects of pyridoxine (vitamin B6) supplementation in nausea and vomiting during pregnancy: a systematic review and meta-analysis	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 helped reduce symptoms of NVP.
224	Jiang et al. 2025	DOPA Decarboxylase (DDC) in Pacific Oysters: Characterization and Role in Tyrosine Metabolism and Melanogenesis	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxamine is a biological component.
225	Jiang et al. 2022	Lactobacillus casei modulates inflammatory cytokines and metabolites during tuberculosis treatment: A post hoc randomized controlled trial	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxamine as a measurement.
226	Jiao et al. 2022	The Effect of Supplemental Concentrate Feeding on the Morphological and Functional Development of the Pancreas in Early Weaned Yak Calves	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; not B6, Wrong outcome - supplementation helped.

No.	Study	Title	Notes
227	Jin et al. 2025	Off-label use of sodium cantharidinate and vitamin B6 injection in cancer: a protocol for a systematic review and meta-analysis	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 as part of cancer treatment.
228	Johnson et al. 2023	Vincristine-induced ptosis in a leukemia patient treated with pyridoxine and pyridostigmine	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; pyridoxine treatment had no adverse side effects.
229	Jové-Solavera et al. 2025	The role of genetic testing in accurate diagnosis of X-linked sideroblastic anemia: novel ALAS2 mutations and the impact of X-chromosome inactivation	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxal as a medication and there was variable response shown in terms of effectiveness.
230	Kamchatnov et al. 2024	[B vitamins and diseases of the peripheral nervous system]	Excluded because wrong language (not English).
231	Kamphuis et al. 2022	Increased fermentable carbohydrate intake alters colonic mucus barrier function through glycation processes and increased mast cell counts	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - IBS effects were reduced by pyridoxamine.
232	Karlsson 2024	Manganese- and Platinum-Driven Oxidative and Nitrosative Stress in Oxaliplatin-Associated CIPN with Special Reference to Ca(4)Mn(DPDP)(5), MnDPDP and DPDP	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake or otherwise lacked a relevant vitamin B6 exposure.
233	Karmeli et al. 2026	Vitamin A acts as a potent suppressor of selenoprotein P with potential relevance for multivitamin supplementation	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - B6 was not found to correlate with SELENOP.

No.	Study	Title	Notes
234	Karolczak et al. 2025	Estimated Amounts of β-Carotene, Vitamin B6, Riboflavin and Niacin in the Daily Diet of Older Subjects Associate Negatively with ADP-Induced Aggregation of Blood Platelets Independently of Cardiovascular Risk Factors	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; adequate supplementation led to decreased platelets which would reduce risk of disease.
235	Kato et al. 2024	Does Vitamin B6 Act as an Exercise Mimetic in Skeletal Muscle?	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; discusses benefits of exercise - mimetic roles of B6 in skeletal muscle.
236	Kaur et al. 2022	Case Report: Isoniazid-Associated Delirium in an Elderly Female with Spinal Tuberculosis	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; pyridoxine augmentation improved patients' illness.
237	Kazlauskaite et al. 2025	Development of 3D-Printed Gel-Based Supplement-Containing Tablets with Tailored Release Profiles for Neurological Pain Management	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 in tablet has therapeutic effect.
238	Kędzierska-Kapuza et al. 2023	Demand for Water-Soluble Vitamins in a Group of Patients with CKD versus Interventions and Supplementation-A Systematic Review	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - B6 supplementation may have positive impact for CKD patients.
239	Keller et al. 2024	Factors influencing survival in sphingosine phosphate lyase insufficiency syndrome: a retrospective cross-sectional natural history study of 76 patients	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 mentioned as a treatment option.

No.	Study	Title	Notes
240	Kendir-Demirkol et al. 2023	The Protective Effects of Pyridoxine on Linezolid-Induced Hematological Toxicity, Hepatotoxicity, and Oxidative Stress in Rats	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; pyridoxine found as an effective therapeutic alongside medication.
241	Key et al. 2024	Knockout Mouse Studies Show That Mitochondrial CLPP Peptidase and CLPX Unfoldase Act in Matrix Condensates near IMM, as Fast Stress Response in Protein Assemblies for Transcript Processing, Translation, and Heme Production	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; not vitamin B6.
242	Key et al. 2024	CLPP-Null Eukaryotes with Excess Heme Biosynthesis Show Reduced L-arginine Levels, Probably via CLPX-Mediated OAT Activation	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; the CLPX promotes pyridoxal binding.
243	Khan 2026	Computational insights into pyridoxal 5-phosphate for cataract therapy: targeting TNF-α, IL-6, and IL-1β through network pharmacology, molecular docking, and dynamics approaches	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake;, wrong setting, Wrong population - computational study on PLP mechanics.
244	Khobrani et al. 2023	Impact of vitamin B6 deficiency on the severity of diabetic peripheral neuropathy - A cross sectional study	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 deficiency effects.
245	Kholmukhamedov et al. 2022	A new fluorescent sensor mitoferrofluor indicates the presence of chelatable iron in polarized and depolarized mitochondria	Excluded because wrong setting - pyridoxal as a chelate in mechanism.

No.	Study	Title	Notes
246	Ki et al. 2023	Crystal Structure and Functional Characterization of Acetylornithine Aminotransferase from Corynebacterium glutamicum	Excluded because wrong setting - developing biochemical structure that involves PLP (B6).
247	Kim et al. 2022	Associations of Vitamin B6 Intake and Plasma Pyridoxal 5'-Phosphate with Plasma Polyunsaturated Fatty Acids in US Older Adults: Findings from NHANES 2003-2004	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; sufficient vitamin B6 status may positively influence PUFA metabolism in older adults.
248	Kim et al. 2026	Adjunctive and supportive strategies to mitigate drug toxicities in the treatment of nontuberculous mycobacterial disease with future directions	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; alternatives to B6 supplementation as medication.
249	Kim et al. 2022	An Atypical Presentation of Pyridoxine-Dependent Epilepsy Diagnosed with Whole Exome Sequencing and Treated with Lysine Restriction and Supplementation with Arginine and Pyridoxine	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - tolerated high dose of B6 well.
250	Kim et al. 2025	Suppression of stress granule assembly by pyridoxal hydrochloride attenuates oxidative damage in skin fibroblasts	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; / Wrong exposure (not excess B6 intake) - pyridoxal.. used as a treatment method.
251	Kim et al. 2025	Moonlighting activity of threonine synthase in cyanobacterial cell death	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxine dependant mechanism.
252	Kishida et al. 2025	Dietary intake of folate, vitamin B6, vitamin B12, and riboflavin and the risk of incident dementia	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - B6 reduced risk of dementia.

No.	Study	Title	Notes
253	Kothari et al. 2024	AGA Clinical Practice Update on Pregnancy-Related Gastrointestinal and Liver Disease: Expert Review	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; mentions treatment with B6.
254	Krusinski et al. 2024	Fatty acids and secondary metabolites can predict grass-finished beef and supplemental cattle feeds	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxine levels changed upon diet.
255	Kumar et al. 2026	Silently Gradually Progressing Paraparesis Pott's Spine Lumbar Vertebra with Bilateral Psoas Abscess	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; adverse effects not related to B6, B6 just used as side effect medication.
256	Kumar et al. 2024	Alarming levels of inadequate intake of B group vitamins in tribal lactating women from South India	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; discusses deficiency in group and need for supplementation.
257	Lai et al. 2023	Association Between Vitamin B6 and the Risk of Colorectal Cancer: A Meta-analysis of Observational Studies	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 reduced risk of cancer.
258	Lalley et al. 2024	Ramen noodle neuropathy: an atypical case of partial paralysis from malnutrition	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; malnutrition and therefore lack of B6.
259	Landi et al. 2022	Effects of a New Multicomponent Nutritional Supplement on Muscle Mass and Physical Performance in Adult and Old Patients Recovered from COVID-19: A Pilot Observational Case-Control Study	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - B6 supplementation improved symptoms of covid19 fatigue.

No.	Study	Title	Notes
260	Le et al. 2024	Vitamin B(1), B(2), and B(6) Intakes and Risk of Gastric Cancer: Findings from a Case-Control Study	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 reduced risk of cancer.
261	Leal-Martinez et al. 2024	Nutritional Support System (NSS) as a New Therapeutic Strategy for Cerebral Palsy	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; mentions pyridoxal is one of the most studied supplement effects in cerebral palsy.
262	Lee et al. 2025	Mendelian randomization study of micronutrients and development of CKD in a Korean population	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 inversely related to development of CKD.
263	Lee et al. 2025	Pyridoxamine inhibits dopamine-induced α-synuclein oligomerization through scavenging neurotoxic dopamine quinone	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 had therapeutic effect.
264	Lee et al. 2023	Lipid hydroperoxide-derived insulin resistance and its inhibition by pyridoxamine in skeletal muscle cells	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxamine can inhibit the formation of advanced glycation/lipoxidation end products by scavenging reactive carbonyl species.
265	Lee et al. 2023	Medicinal benefits, biological, and nanoencapsulation functions of riboflavin with its toxicity profile: A narrative review	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; riboflavin helps metabolise pyridoxine.
266	Lee et al. 2023	Characterization of a Potential Probiotic Lactiplantibacillus plantarum LRCC5310 by Comparative Genomic Analysis and its Vitamin B(6) Production Ability	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; probiotic may help supplement B6.

No.	Study	Title	Notes
267	Lellig et al. 2024	Pyridoxal-5'-phosphate: A cost-effective treatment candidate for hypertensive patients?	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; pLP may be cost effective drug against hypertension.
268	Li et al. 2024	Association between Vitamin E, Vitamin B6, and Vitamin B12 with coronary heart disease	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - possible therapeutic effect of B6 on CHD.
269	Li et al. 2023	Association between Vitamin B(6) and Risk of Gastric Cancer: A Systematic Review and Meta-Analysis of Epidemiological Studies	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 may reduce gastric cancer but inconclusive.
270	Li et al. 2022	[Clinical characteristics and CBS gene analysis of 13 cases with classic homocystinuria]	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; most patients did not respond to B6.
271	Li et al. 2023	Probiotic Bacillus subtilis contributes to the modulation of gut microbiota and blood metabolic profile of hosts	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 was affected by the probiotic (B6=dependant variable).
272	Li et al. 2025	Relationship between vitamin B6 intake and thyroid function in US adults: NHANES 2007-2012 results	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - B6 can improve thyroid function.
273	Li et al. 2025	Effects of B Vitamins on Homocysteine Lowering and Thrombotic Risk Reduction-A Review of Randomized Controlled Trials Published Since January 1996	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - B6 supplementation to reduce risks of diseases.

No.	Study	Title	Notes
274	Li et al. 2025	Exploring the Causal Effects of Micronutrient Supplementation on Susceptibility to Viral Pneumonia: A Mendelian Randomization Study	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 supplementation may be used as a therapy for viral pneumonia.
275	Li et al. 2024	Vitamin B6, B12, and Folate's Influence on Neural Networks in the UK Biobank Cohort	Excluded because wrong setting - B6 effect on neural networks related to Alzheimer's disease. B6 actually impaired activity in some neural networks but study does not focus on toxicity.
276	Li et al. 2025	High prediagnostic dietary intake of vitamin B(2) and vitamin B(6) is associated with favorable prognosis of colorectal cancer among Chinese colorectal cancer patients	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 may be associated with improved survivals in colorectal cancer patients.
277	Li et al. 2025	Association between methyl donor nutrients' dietary intake with phenotypic aging among US adults: a cross-sectional study from NHANES 2005-2018	Excluded because wrong setting - B6 as a vital micronutrient.
278	Li et al. 2025	Dietary protein sources in concentrate supplementation influence growth performance by manipulating gut microbiota and serum metabolites in suckling Donkey foals	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; soy diet improved B6 levels.
279	Lin et al. 2022	A nitrous oxide abuser presenting with cerebral venous thrombosis: A case report	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; pyridoxine at 50 mg/day helped alleviate symptoms.
280	Lin et al. 2024	Elucidation of the beneficial role of co-fermented whole grain quinoa and black barley with	Excluded because wrong setting - pyridoxine as a metabolite marker.

No.	Study	Title	Notes
		Lactobacillus on rats fed a western-style diet via a multi-omics approach	
281	Liu et al. 2025	Effect of Nutritional Supplements for Reducing Homocysteine Levels in Healthy Adults: A Systematic Review and Network Meta-Analysis of Randomized Trials	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; benefit of supplement combinations.
282	Liu et al. 2024	Trimethylamine N-oxide, β-alanine, tryptophan index, and vitamin B6-related dietary patterns in association with stroke risk	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 as a biomarker.
283	Liu et al. 2026	Vitamin B intake and post-stroke depression: Results from the US national health and nutrition examination surveys (NHANES) 2007-2018	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 inversely associated with PS depression.
284	Liu et al. 2026	The mitigation mechanism of exogenous pyridoxal-5-phosphate on Pb stress damage in Polygonatum Cyrtonema Hua by multi-omics combined analysis	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 had protective effect against Pb poisoning in plants, Wrong population - plants.
285	Liu et al. 2022	PDX1.1-dependent biosynthesis of vitamin B(6) protects roots from ammonium-induced oxidative stress	Excluded due to wrong population: roots in plants.
286	Liu et al. 2022	Transcriptomics integrated with metabolomics reveals the effect of Bisphenol F (BPF) exposure on intestinal inflammation	Excluded due to wrong population: cell study.

No.	Study	Title	Notes
287	Llop et al. 2026	Mutational analyses reveal PLP-independent functions at PipY, the cyanobacterial paradigm for pyridoxal-phosphate binding proteins	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; highlights that proper handling of vitamin B6 (PLP) is crucial Genetic mutations affecting this system can lead to neurological problems like epilepsy It's about B6 dysfunction, not B6 adverse effects.
288	Lob et al. 2022	Vitamin B6 decreases the risk of levetiracetam discontinuation in children with epilepsy: A retrospective study	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - B6 reduces bad side effects.
289	Long et al. 2022	The consistency of aminotransferase analysis in China: a comparison of six mainstream aminotransferase routine methods and recalibration using human pooled serum preparations supplemented with human recombinant aminotransferases	Excluded because wrong setting - measurement of aminotransferase.
290	Lu et al. 2025	Effects of dark septate endophyte on root growth, physiology and transcriptome of Ammopiptanthus mongolicus seedlings under drought stress	Excluded due to wrong population: desert plants (B6 metabolism in the plants).
291	Lu et al. 2022	Multiple forms of vitamin B(6) regulate salt tolerance by balancing ROS and abscisic acid levels in maize root	Excluded due to wrong population: plants.
292	Lu et al. 2024	Clinical Efficacy of Sodium Cantharidate Vitamin B6 Combined with Concurrent Chemoradiotherapy in the Treatment of Local Advanced Cervical Cancer and its Influence on Tumor Markers	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 alongside medication helped alleviate symptoms.

No.	Study	Title	Notes
293	Lu et al. 2024	Associations of Dietary Intake of Vitamin B6 and Plasma Pyridoxal 5'-Phosphate Level With Depression in US Adults: Findings From NHANES 2005-2010	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 supplementation helped reduce depression.
294	Lu et al. 2026	Severe ethylene glycol toxicity leading to persistent kidney disease	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 as treatment for ethylene glycol toxicity.
295	Lu et al. 2022	Integrated metabolomics and transcriptomics analysis reveals new biomarkers and mechanistic insights on atrazine exposures in MCF-7 cells	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxine as a biomarker.
296	Luo et al. 2024	B vitamins and bone health: a meta-analysis with trial sequential analysis of randomized controlled trials	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 did not strongly help bone health however there was no adverse reactions.
297	Lykstad 2026	Biochemistry, Water Soluble Vitamins	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; biochemistry of vitamin B6.
298	Ma et al. 2022	Application of the deep learning algorithm in nutrition research - using serum pyridoxal 5'-phosphate as an example	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake;, wrong setting - study is trying to predict blood PLP levels through different modelling.
299	Ma et al. 2022	One-carbon metabolism-related nutrients intake is associated with lower risk of preeclampsia in pregnant women: a matched case-control study	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; /outcome (not excess B6 intake and no adverse effects) - B6 as a micronutrient can prevent PE in pregnant women in population.

No.	Study	Title	Notes
300	Machover et al. 2024	Treatment of patients with carcinomas in advanced stages with 5-fluorouracil, folinic acid and pyridoxine in tandem	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; no adverse effects found.
301	Machover et al. 2022	Pharmacologic modulation of 5-fluorouracil by folinic acid and pyridoxine for treatment of patients with advanced breast carcinoma	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - high dose B6 can increase anti - tumor properties.
302	Madhubalaji et al. 2022	Unraveling of Chlorella-associated bacterial load, diversity, and their imputed functions at high- and low-yield conditions through metagenome sequencing	Excluded because wrong setting - pyridoxine mentioned as a biosynthesis marker in bacteria.
303	Mahajan et al. 2025	Hypocupraemia-related drug-refractory seizures in Wilson disease	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wilsons disease can cause B6 deficiency.
304	Mahdavi et al. 2026	Hepatoprotective effect of pyridoxal phosphate against lead poisoning by inhibiting Kupffer cell hyperplasia due to a decrease in oxidative stress associated with hepatic NF-kβ	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; and Wrong outcome (no adverse effect of B6) - PLP may help prevent Pb poisoning.
305	Mandal et al. 2023	Polypyridyl-based Co(III) complexes of vitamin B(6) Schiff base for photoactivated antibacterial therapy	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 complexes in antibacterial therapy.
306	Mangel et al. 2022	Natural Variation in Vitamin B(1) and Vitamin B(6) Contents in Rice Germplasm	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 in rice germplasm.

No.	Study	Title	Notes
307	Manzoor et al. 2025	Vitamin-B profiling and Vit-GWAS in buckwheat (Fagopyrum spp.): a first report	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; measuring concentration of B6 in buckwheat.
308	Marrón-Ponce et al. 2023	Ultra-processed foods consumption reduces dietary diversity and micronutrient intake in the Mexican population	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - processed foods lacked in pyridoxine.
309	Martedì et al. 2026	De novo cysteine biosynthesis in Pseudomonas aeruginosa: Characterization of the two main cysteine synthase isoforms	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxal dependant enzyme in mention.
310	Martínez-Galindo et al. 2026	Clinical Approaches and Emerging Therapeutic Horizons in Primary Hyperoxaluria	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxine mentioned as a therpeutic.
311	Martínez-Mendiola et al. 2024	Effect of pyridoxine or cobalamin supplementation on apoptosis and cell cycle progression in a human glioblastoma cell line	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; shows benefits of vitamin B6 not toxicity.
312	Maruyama et al. 2022	Phase I studies of the safety, tolerability, pharmacokinetics, and pharmacodynamics of DS-1211, a tissue-nonspecific alkaline phosphatase inhibitor	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxal as pharmakokinetic marker.
313	Mascolo et al. 2022	Vitamin B6 rescues insulin resistance and glucose-induced DNA damage caused by reduced activity of Drosophila PI3K	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 as an effective natural remedy.
314	Massimino et al. 2023	Dietary micronutrient adequacies and adherence to the Mediterranean diet in a population of older	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health

No.	Study	Title	Notes
		adults with type 2 diabetes: A cross-sectional study	effect reported) - patients with T2D did not adhere to diet and therefore were deficient in B6.
315	Mastrangelo et al. 2023	Epilepsy Phenotypes of Vitamin B6-Dependent Diseases: An Updated Systematic Review	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; therapeutic effect of B6 on B6 - dependant diseases.
316	Matlapeng et al. 2026	Adjunctive Multicomponent Crystals of Two Anti-Tubercular Drugs with Pyridoxine	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - discusses B6 supplementation to prevent deficiency from anti - tubercular drugs.
317	Mato-López et al. 2022	Relationship between structure and cytotoxicity of vanadium and molybdenum complexes with pyridoxal derived ligands	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; complexes derived from pyridoxal.
318	Matsuo et al. 2024	Identification of YigL as a PLP/PNP phosphatase in Escherichia coli	Excluded due to wrong population: in vitro cell/ bacteria.
319	Matta et al. 2024	GABA synthesizing lactic acid bacteria and genomic analysis of Levilactobacillus brevis LAB6	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pLP was measured in the study.
320	Mbala et al. 2023	Evaluation of vitamin B(6) supplementation in Wilson's disease patients treated with D-penicillamine	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 may not be needed for WD patients however adverse effects not mentioned.
321	Meng et al. 2026	Jinlida ameliorates diabetic kidney disease via gut microbiota-dependent production of pyridoxamine targeting renal AGEs/RAGE and TGF-β pathways	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; /exposure (no excessB6 and

No.	Study	Title	Notes
			no adverse health effects) - B6 had enhanced renoprotective effects.
322	Menichini et al. 2022	Oral supplementation of α-lipoic acid (ALA), magnesium, vitamin B6 and vitamin D stabilizes cervical changes in women presenting risk factors for preterm birth	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - B6 counteracted risk factors for preterm birth.
323	Messina et al. 2023	Hyperphosphatasia with mental retardation syndrome 3: Cerebrospinal fluid abnormalities and correction with pyridoxine and Folinic acid	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 supplementation helped normalise symptoms.
324	Michels et al. 2023	Multivitamin/Multimineral Supplementation Prevents or Reverses Decline in Vitamin Biomarkers and Cellular Energy Metabolism in Healthy Older Men: A Randomized, Double-Blind, Placebo-Controlled Study	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; therapeutic effects of supplementation in older men.
325	Mikkelsen et al. 2023	High-Dose Vitamin B6 (Pyridoxine) Displays Strong Anti-Inflammatory Properties in Lipopolysaccharide-Stimulated Monocytes	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 high dose therapeutic effects.
326	Milliner et al. 1993	Primary Hyperoxaluria Type 1	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxine mentioned as a therapy.
327	Mirrafiei et al. 2024	Higher dietary methyl donor micronutrient consumption is associated with higher muscle strength in adults: a cross-sectional study	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; / Wrong exposure (not excess B6) - B6 had a secondary relation to increased muscle strength.

No.	Study	Title	Notes
328	Mo et al. 2022	Effects of the Probiotic, Lactobacillus delbrueckii subsp. bulgaricus, as a Substitute for Antibiotics on the Gastrointestinal Tract Microbiota and Metabolomics Profile of Female Growing-Finishing Pigs	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxine levels affected by trial drug.
329	Mokhtari et al. 2024	Taurine, alpha lipoic acid and vitamin B6 ameliorate the reduced developmental competence of immature mouse oocytes exposed to methylglyoxal	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; not vitamin B6.
330	MolaeiRamshe et al. 2024	A Novel Ornithine Aminotransferase Splice Site Mutation Causes Vitamin B6-Responsive Gyrate Atrophy	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 supplementation may help.
331	Mondésert et al. 2025	Branched-chain amino acid transferase type 2 (BCAT2) deficiency: Report of an eighth case and literature review	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - pyridoxine may help prevent harmful mechanisms of disease.
332	Monge-Rojas et al. 2024	A Landscape of Micronutrient Dietary Intake by 15- to 65-Years-Old Urban Population in 8 Latin American Countries: Results From the Latin American Study of Health and Nutrition	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; population does not have adequate B6 intake.
333	Moon et al. 2022	Concurrent zinc and vitamin B(6) deficiencies in acutely exacerbated inflammatory bowel disease: Case reports	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 to help IBD.

No.	Study	Title	Notes
334	Moya-López et al. 2024	[Epilepsy and inborn errors of metabolism]	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxamine sensitive epilepsy mentioned as a type of epilepsy.
335	Mruga et al. 2024	Amperometric Biosensor Based on Glutamate Oxidase to Determine Ast Activity	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake;, wrong setting - - pyridoxal as a coenzyme in mechanism.
336	Naghavi et al. 2024	Late-onset drug-resistant epilepsy in pyridoxamine 5'-phosphate oxidase deficiency: a case report	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 alleviated symptoms of seizure instantly.
337	Nakamura et al. 2025	Late-onset Vitamin B6-dependent epilepsy caused by compound heterozygous pathogenic PLPBP variants	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; shows case note of a girl with vitamin B6 dependant epilepsy and how these patients can have adverse reactions to B6 supplementation however full text focuses more on therapeutic effect of B6 and mainly on getting the correct diagnosis.
338	Nakao et al. 2025	Vitamin B6 Deficiency May Not Always Present As Microcytic Hypochromic Anemia	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 deficiency must be addressed in diagnosis.
339	Narayana et al. 2022	Children with functional abdominal pain disorders successfully decrease FODMAP food intake on a low FODMAP diet with modest improvements in nutritional intake and diet quality	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; (B6 one of the dependant variables of change of diet).

No.	Study	Title	Notes
340	Nascimento et al. 2026	Association Between Habitual Food Intake and Energy Metabolism-Related Urine Metabolites in Female Soccer Players	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake;, wrong setting - B6 used as a nutrient marker measurement.
341	Nasir et al. 2024	Vitamin B6 Via p-JNK/Nrf-2/NF-κB Signaling Ameliorates Cadmium Chloride-Induced Oxidative Stress Mediated Memory Deficits in Mice Hippocampus	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 as a neurotherapeutic.
342	Nathan et al. 2025	New Onset Medically Refractory Seizures in an Adult With Parkinson's Disease and Vitamin B6 Deficiency Case Report	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; seizures resolved with B6.
343	Nayak et al. 2026	NBD Integrated and Vitamin B6-Driven Charge-Reversible Peptide-Based Nanocarriers for Targeted Therapeutic Delivery	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 as effective part of nanocarrier for therapeutic delivery.
344	Nelson-Piercy et al. 2024	The Management of Nausea and Vomiting in Pregnancy and Hyperemesis Gravidarum (Green-top Guideline No. 69)	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - pregnant women benefit from B6.
345	Nematgorgani et al. 2022	B vitamins and their combination could reduce migraine headaches: A randomized double-blind controlled trial	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 supplementation helped reduce migraine symptoms.
346	Nguyen et al. 2025	The anti-inflammatory effects of vitamin B6 on neuroinflammation and neuronal damage caused by 1,2-diacetylbenzene in BV2 microglial and sH-SY5Y cells	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) Wrong population - in vitro.

No.	Study	Title	Notes
347	Norton et al. 2025	Leucine, pyridoxine and resveratrol supplementation alter metabolic parameters in ponies with equine metabolic syndrome	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; ponies benefited from pyridoxine supplementation.
348	Oikawa et al. 2022	(+)-Sesamin, a sesame lignan, is a potent inhibitor of gut bacterial tryptophan indole-lyase that is a key enzyme in chronic kidney disease pathogenesis	Excluded because wrong setting - pyridoxal mentioned as a binding site.
349	Olaso-Gonzalez et al. 2022	Impact of supplementation with vitamins B(6) , B(12) , and/or folic acid on the reduction of homocysteine levels in patients with mild cognitive impairment: A systematic review	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - B6 may reduce homocysteine levels which would be beneficial.
350	Ong et al. 2025	Deprescribing vitamin B6 in a Singapore community hospital	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; focus is on reducing the pill burden (and cost) from overprescribing B6.
351	Ortega et al. 2025	[Nutrition in improving sleep quality and fighting insomnia]	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - adequate pyridoxine can help prevent sleep disturbance.
352	Oto et al. 2024	A case report of odonto-hypophosphatasia with a novel variant in the ALPL gene	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pLP (pyridoxal) was a biomarker measurement.
353	Ouyang et al. 2024	Dietary vitamin B6 supplementation alleviates heat stress-induced intestinal barrier impairment by	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 can alleviate heat - stress induced symptoms.

No.	Study	Title	Notes
		regulating the gut microbiota and metabolites in broilers	
354	Ozgodek et al. 2026	A Comparative Evaluation of the Therapeutic Effects of Adenosine Triphosphate, Coenzyme Q10, Pyridoxine, and Thiamine Pyrophosphate in a Linezolid-Induced Peripheral Neuropathic Pain Model in Rats	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 partially alleviated pain from peripheral neuropathy.
355	Paez-Hurtado et al. 2023	Mechanisms of action of vitamin B1 (thiamine), B6 (pyridoxine), and B12 (cobalamin) in pain: a narrative review	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 as an analgesic.
356	Pages-García et al. 2024	Effectiveness of a Saffron and Withania Supplement on Mood in Women With Mild-to-Moderate Anxiety During the COVID-19 Lockdown	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - B6 helped reduce anxiety.
357	Pande et al. 2025	Novel Homozygous MTHFR Variant Causing Homocystinuria: Subtle Phenotypic Clues in Carriers	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; management included pyridoxine therapy.
358	Panteghini 2025	Supplementation of pyridoxal-5'-phosphate in aminotransferase reagents: a matter of patient safety	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - supplementation of B6 is essential in aminotransferase reagents.
359	Park et al. 2025	Association Between Dietary Intake and Blood Concentrations of One-Carbon-Metabolism-Related Nutrients in European Prospective Investigation into Cancer and Nutrition	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; diet influences B6 levels in the blood.

No.	Study	Title	Notes
360	Paruthi et al. 2025	Acute vision loss associated with vincristine therapy in T cell lymphoma	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 had therapeutic effect.
361	Patel et al. 2025	Neuropsychiatric manifestations after gastric bypass progressing to status epilepticus resolving with pyridoxine: a case report and literature review	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 was vital in alleviating neuropsychiatric symptoms.
362	Pavlak et al. 2024	Dietary Intake of Micronutrients and Use of Vitamin and/or Mineral Supplements: Brazilian National Food Survey	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; found that people who use supplements are usually the ones with the best dietary intake already anyway.
363	Paxhia 2022	Pyridoxal and α-Ketoglutarate Independently Improve Function of Saccharomyces cerevisiae Thi5 in the Metabolic Network of Salmonella enterica	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - pyridoxine improved function of Thi5 so it was beneficial.
364	Peruzzi 2025	Lumasiran at birth changes the trajectory of primary hyperoxaluria type 1: same disease, different outcomes in two affected siblings	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; vitamin B6 not mentioned.
365	Petersen et al. 2023	Periconceptional intakes of methyl donors and other micronutrients involved in one-carbon metabolism may further reduce the risk of neural tube defects in offspring: a United States population-based case-control study of women meeting the folic acid recom	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; (no adverse effects from excess B60 - high doses of B6 helped reduce defects.

No.	Study	Title	Notes
366	Pfeiffer et al. 2022	Calmangafodipir for Prevention of Oxaliplatin-Induced Peripheral Neuropathy: Two Placebo-Controlled, Randomized Phase 3 Studies (POLAR-A/POLAR-M)	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake or otherwise lacked a relevant vitamin B6 exposure.
367	Philipp et al. 2026	Structure-activity relationship of S-adenosylmethionine analogs as pharmacological chaperones for cystathionine beta-synthase-deficient homocystinuria	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; alternatives to B6 supplementation.
368	Pilesi et al. 2023	A gene-nutrient interaction between vitamin B6 and serine hydroxymethyltransferase (SHMT) affects genome integrity in Drosophila	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 deficiency negatively effects genome integrity.
369	Pilesi et al. 2024	Vitamin B6 deficiency cooperates with oncogenic Ras to induce malignant tumors in Drosophila	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; pLP deficiency can impact on cancer by increasing genome instability.
370	Piyathilake et al. 2022	The consumption of micronutrients in relation to calorie intake and risk of insulin resistance	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; dRIs for pyridoxine were met.
371	Plecko 1993	PNPO Deficiency	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; adverse side effects briefly mentioned however not in the focus or conclusion of the study rather the focus is how B6 supplementation is necessary for PNPO deficiency. Old study - 1993.

No.	Study	Title	Notes
372	Pokushalov et al. 2024	Effect of Methylfolate, Pyridoxal-5'-Phosphate, and Methylcobalamin (Soloways(TM)) Supplementation on Homocysteine and Low-Density Lipoprotein Cholesterol Levels in Patients with Methylenetetrahydrofolate Reductase, Methionine Synthase, and Methionine Syn	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 reduced homocysteine levels which is useful for specific disease.
373	Powers et al. 2023	Over-the-Counter Medications in Pregnancy	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 mentioned as treatment for pregnancy symptoms.
374	Prakash et al. 2025	Markedly discordant hypophosphatasia in a young girl	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - pyridoxal levels as a biochemical signature for HPP.
375	Prasad et al. 2024	Nutrient Composition, Physical Characteristics and Sensory Quality of Spinach-Enriched Wheat Bread	Excluded because wrong setting - B6 in nutrients in spinach enriched bread.
376	Prombood et al. 2025	Vitamin B(6) Status Assessed by Plasma Vitamers and Homocysteine in Lactating Dairy Cows and Its Relationship to Rumen Fermentation, Plasma Metabolites, and Milk Production in Different Environmental Conditions	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; specific scenario B6 status in milked cows not useful for UL in humans.
377	Prus 2026	Moxifloxacin-Induced Peripheral Neuropathy: A Rare Side Effect of Fluoroquinolone Therapy in Tuberculosis Management	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxal treatment to alleviate symptoms no adverse symptoms of B6.

No.	Study	Title	Notes
378	Pulluru et al. 2024	Seizures due to pyridoxine deficiency in Parkinson's disease	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - making sure patients with PD have adequate pyridoxine levels.
379	Qing et al. 2025	Gut dysbiosis-induced vitamin B6 metabolic disorder contributes to chronic stress-related abnormal behaviors in a cortisol-independent manner	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - B6 supplement can be used as treatment.
380	Qu et al. 2022	Profound Perturbation in the Metabolome of a Canine Obesity and Metabolic Disorder Model	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxal as a measured metabolite.
381	Quan et al. 2025	From Virulence to Vulnerability: New Insights on Disrupting the d-Alanine Pathway and Its Influences on Polymyxin Resistance in Riemerella anatipestifer	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxal critical in particular synthesis.
382	Rabinovich et al. 2025	Hair straightening and acute kidney injury: a case series from a medical toxicology service	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; /exposure (not B6 excess intake, no adverse health effects from B6) - pyridoxine used as a treatment.
383	Raghuvanshi et al. 2023	Relationship Between Vitamins and Diabetes	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - benefits of B supplementation.

No.	Study	Title	Notes
384	Rajasekar et al. 2024	Dietary intake with supplementation of vitamin D, vitamin B6, and magnesium on depressive symptoms: a public health perspective	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; low B6 lead to depressive symptoms.
385	Rane et al. 2022	Low Serum Pyridoxine Levels Worsen Seizure Control in Adult Epilepsy Patients	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - low pyridoxine levels may increase risk of seizures.
386	Raynor et al. 2022	[Usual transaminase values: should they be reviewed and adjusted?]	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; sample supplementation with B6 can ensure comparability.
387	Renting et al. 2024	Vitamin B6 status and chronic chemotherapy-induced peripheral neuropathy: a prospective cohort study among patients with non-metastatic colorectal cancer receiving oxaliplatin-based chemotherapy	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - higher levels of B6 reduced bad side effects.
388	Restrepo-Mesa et al. 2023	Food and nutrient intake of adolescent women in Medellín, Colombia	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; population was B6 deficient.
389	Reyes-Alvarez et al. 2026	Hydroxocobalamin, thiamine, and pyridoxine as an adjunct to standard treatment in chronic low back pain: a randomized clinical trial	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 trialled to help with treating back pain.
390	Ribeiro et al. 2023	Evaluation of a ruminally protected blend of pantothenic acid, pyridoxine, folic acid, biotin, and vitamin B12 on finishing steer growth performance, efficiency of dietary net energy	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; role of B6 on finishing performance, dietary efficiency and carcass trait response in beef steers.

No.	Study	Title	Notes
		utilization, carcass trait responses, and liver abscess prevalence and s	
391	Ricci et al. 2021	Mechanisms of Neuronal Damage in Acute Hepatic Porphyrias	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxal deficiency as an effect of oxidative damage.
392	RivasNavarrete et al. 2025	Inhibition of advanced glycation end-products by the vitamin B6 vitamer pyridoxamine prevents systemic and skeletal muscle diet-induced metaflammation through modulation of S1P/RhoA/ROCK signalling	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; pyridoxine supplementation may reduce inflammation that would lead to obesity.
393	Rizzo et al. 2022	Use of Nutritional Supplements Based on L-Theanine and Vitamin B6 in Children with Tourette Syndrome, with Anxiety Disorders: A Pilot Study	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 can help alleviate Tic disorder symptoms.
394	Rodríguez-Araya et al. 2026	The Challenge of Hypophosphatasia Diagnosis in Patients with Fibromyalgia	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - B6 as a biomarker.
395	Rossmann et al. 2022	Validated UPLC-MS/MS method for the analysis of vitamin B(6) pyridoxal 5́-phosphate, pyridoxal, pyridoxine, pyridoxamine, and pyridoxic acid in human cerebrospinal fluid	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; method for determining B6 concentrations.
396	Roy et al. 2025	Enhanced rivastigmine delivery through nanoemulsion and pyridoxine supplementation: An in-vivo study on Alzheimer's disease intervention	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake;, Wrong outcome (no relevant adverse health effect reported) - pyridoxine helped the transportation and therefore effectiveness of medication.

No.	Study	Title	Notes
397	Ruan et al. 2024	Association of vitamin B6 intake with the risk and prognosis of diabetic retinopathy: a NHANES-based study	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 may reduce risk of death from cardiovascular diseases.
398	Rubinos et al. 2023	Association of Serum Pyridoxal Phosphate Levels with Established Status Epilepticus	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; epilepticus patients may need more B6 supplementation as their levels are lower.
399	Rudnicki-Velasquez et al. 2025	A Simultaneous Determination of the B(1) and B(6) Vitamers Reveals Their Loss During a Single Peritoneal Dialysis Session: Chromatographic and Chemometric Approach	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; focuses on how B6 concentration is reduced during peritoneal dialysis and one may need to supplement.
400	RuizdeGalarreta et al. 2023	Antifibrogenic and apoptotic effects of Ocoxin in cultured rat hepatic stellate cells	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; not vitamin B6.
401	Ryback 2023	Coenzyme biosynthesis in response to precursor availability reveals incorporation of β-alanine from pantothenate in prototrophic bacteria	Excluded due to wrong population: bacteria.
402	Sacharow 1993	Homocystinuria due to Cystathionine Beta-Synthase Deficiency	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 as therapeutic.
403	Saldanha et al. 2023	A case study: Correlation of the nutrient composition in Chinese Hamster Ovary cultures with cell growth, antibody titre and quality attributes using multivariate analyses for guiding medium and feed optimization in early upstream process development	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; concentration of pyridoxal governed initial cell growth.

No.	Study	Title	Notes
404	Salehi-Sahlabadi et al. 2022	Nutrient patterns and non-alcoholic fatty liver disease in Iranian Adul: A case-control study	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; measuring pyridoxine as a nutrient pattern for NAFLD.
405	ŠalkováKráľová et al. 2023	Dietary habits and dietary nutrient intake in patients with age-related macular degeneration: A case-control study	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 nutrient increased in different diet.
406	Sankar et al. 2024	Isoniazid-historical development, metabolism associated toxicity and a perspective on its pharmacological improvement	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - reviews how isoniazid can cause B6 deficiency.
407	Sarkar et al. 2026	Sterol Endoperoxides and Their Antileishmanial Effects: Influence on Viability, Oxygen Metabolism and Sterol Synthesis	Excluded due to wrong population: in vitro.
408	Sas et al. 2024	Natural history of urine and plasma oxalate in children with primary hyperoxaluria type 1	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; measuring effect of pyridoxamine on urine etc. no adverse effects reported.
409	Sawhney et al. 2022	Isolated Pyridoxine Deficiency Presenting as Peripheral Neuropathy Post-chemotherapy	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 deficiency causing PN.
410	Sayedahmed et al. 2026	An integrated in vitro antioxidant/in vivo metabolomics approach unravels the synergistic effects between oregano essential oil and vitamin C as a nutritional strategy for alleviating heat stress in rabbits	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 was reduced by specific treatment.

No.	Study	Title	Notes
411	Schichtl et al. 2025	Pyridoxamine promotes heat-induced protein modifications in whey as evaluated by structure- and binding site-specific profiling using high-performance liquid chromatography-tandem mass spectrometry in scheduled multiple reaction mode	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxamine in whey protein production.
412	Schorgg et al. 2022	Increased vitamin B6 turnover is associated with greater mortality risk in the general US population: A prospective biomarker study	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - patients with increased PLP turnover may need increased B6 supplementation.
413	Schuurmans et al. 2025	Targeting AASS alleviates neurotoxicity and improves mitochondrial function in astrocyte models for pyridoxine-dependent epilepsy	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 to help prevent neurotoxicity.
414	Seale et al. 2025	Dietary Micronutrient Intake and the Prevalence of Metabolic Conditions among Children from the United States-Affiliated Pacific Region in the Children's Healthy Living Program	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 as a micronutrient measurement in obesity study.
415	Sedillo et al. 2024	Prevalence estimate of sphingosine phosphate lyase insufficiency syndrome in worldwide and select populations	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; pyridoxine supplementation may be therapeutic.
416	Seefried et al. 2026	A randomized Phase 1b trial evaluating the pharmacodynamics of ilofotase alfa in adults with hypophosphatasia	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxal levels used as a biomarker in study.

No.	Study	Title	Notes
417	Sekine et al. 2025	Oxygen needs sulfur, sulfur needs oxygen: a relationship of interdependence	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; not vitamin B6.
418	Sengupta et al. 2022	Comparative Study to Evaluate the Effect of Low-Protein Diet Supplementation with Taurine and N-Acetylcysteine, N-Acetylcysteine and Pyridoxamine Dihydrochloride in Preventing the Progression of Chronic Renal Failure in Patients with Non-Diabetic Kidney D	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; therapeutic benefit of pyridoxamine.
419	Shah et al. 2023	Mass Poisoning From Ethylene Glycol at a U.S. Military Base	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; patients were given B6 as part of treatment.
420	Shajani-Yi et al. 2022	Urine phosphoethanolamine is a specific biomarker for hypophosphatasia in adults	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 as genetic marker.
421	Shang et al. 2024	microRNA maintains nutrient homeostasis in the symbiont-host interaction	Excluded due to wrong population: in vitro not relevant.
422	Shemer et al. 2025	Biotin or Pyridoxine Versus Combined Regimen in the Treatment of Onychoschizia	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - no adverse effects reported and B6 was beneficial.
423	Sheng et al. 2025	Study of the association of niacin and vitamin B6 intake with endometriosis: Evidence from NHANES 2003-2006	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - vitamin B6 had negative correlation to endometriosis.

No.	Study	Title	Notes
424	Sheng et al. 2025	The association of dietary nutrients consumption with hepatic steatosis and fibrosis from NHANES 2017-2020	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake;, Wrong outcome (no adverse effects of B6) - Higher intake of pyridoxine is associated with lower levels of liver fat.
425	Shi et al. 2022	Alterations of gut microbial pathways and virulence factors in hemodialysis patients	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxamine was increased in HD patients which effects virulence factors.
426	Shikh et al. 2022	[The effectiveness of BIFIFORM KIDS in the prevention of the incidence of acute respiratory infections in children]	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - B6 was part of the treatment but not elaborated on effects.
427	Shrateh et al. 2024	Comparing pyridoxine with dopaminergic agonists (cabergoline and bromocriptine): Unveiling the strategy for lactation inhibition - A systematic review of clinical trials	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - B6 mentioned as an inferior medication to others for lactation.
428	Shtyrlin et al. 2023	Synthesis and biological evaluation of fluoroquinolones containing a pyridoxine derivatives moiety	Excluded due to wrong population: in vitro.
429	Sillis et al. 2026	Medication, Vaccine, and Folic Acid Use Among Pregnant Women in Belgium: Insights from the BELpREG Cohort	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - shows frequency of use of pyridoxine not effect.

No.	Study	Title	Notes
430	Śliwiński 2024	Circulating B vitamins metabolites in depressive disorders - connections with the microbiota-gut-brain axis	Excluded due to wrong outcome and direction of effect; this narrative review addressed B vitamins and depression via the gut-brain axis, not adverse effects from excess vitamin B6 intake.
431	Sofyan et al. 2022	B Vitamins, work-related stress and emotional mental disorders: a cross-sectional study among nurses in Indonesia	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; nurses emotional state was helped by B6.
432	Song et al. 2022	Association between Micronutrient Intake and Breast Cancer Risk According to Body Mass Index in South Korean Adult Women: A Cohort Study	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; vitamin B6 supplements reduced risk of breast cancer.
433	Song et al. 2024	Vitamin B-6 Prevents Heart Failure with Preserved Ejection Fraction Through Downstream of Kinase 3 in a Mouse Model	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) - B6 helped mice prevent heart failure.
434	Song et al. 2024	Genome-Wide Approach of Gene-Nutrient Intake Interaction Study for Essential Hypertension in a Large Korean Cohort (KoGES)	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; briefly mentions B6 may influence HTN risk.
435	Sousou et al. 2023	Pyridoxine Deficiency and Neurologic Dysfunction: An Unlikely Association	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; the study showed that an ill man with peripheral neuropathy had his symptoms reduced by the supplementation of B6.
436	Stolwijk et al. 2022	A vitamin a day keeps the doctor away: The need for high quality pyridoxal-5'-phosphate	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake;, Wrong outcome - shows benefits of PLP in seizures and highlights need for HQ medication.

No.	Study	Title	Notes
437	Stoś et al. 2021	Assessment of Food Supplement Consumption in Polish Population of Adults	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; polish population use B6 and sometimes in excess (over the UL) but no adverse health effects studied.
438	Subbotin et al. 2026	PDXK-Related Neuropathy: A Case With a Novel Splice-Altering Missense Variant and Literature Review	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; neuropathy can be managed with pyridoxal 5' - phosphate supplementation.
439	Sukmak et al. 2025	Monosodium Glutamate Consumption Disrupts Vitamin B6 Status in Rat Kidney	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; mSG effects B6 levels in kidney.
440	Sun et al. 2021	Effects of Compound Probiotics on Cecal Microbiome and Metabolome of Shaoxing Duck	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; the pathways of Vitamin B6 metabolism were benefited by probiotics.
441	Sun et al. 2023	Protective effect of vitamin B(6) against doxorubicin-induced cardiotoxicity by modulating NHE1 expression	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome (no relevant adverse health effect reported) B6 has antioxidative and antiapoptosis effects to improve cardiac function.
442	Sunder et al. 2026	Synergistic DLP bioprinting of high-fidelity nerve guidance conduits using a chitosan-collagen methacryloyl conductive bioink with neurotrophic factors	Excluded due to wrong population: (in vitro / cell study).
443	Sureja et al. 2023	Efficacy and Tolerability Evaluation of a Nutraceutical Composition Containing Vitex agnus-castus Extract (EVX40™), Pyridoxine, and	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake;, Wrong outcome - B6 supplementation can help PMS.

No.	Study	Title	Notes
		Magnesium in Premenstrual Syndrome: A Real-World, Interventional, Comparative Study	
444	Syring et al. 2024	One-carbon metabolite supplementation increases vitamin B12, folate, and methionine cycle metabolites in beef heifers and fetuses in an energy dependent manner at day 63 of gestation	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake or otherwise lacked a relevant vitamin B6 exposure.
445	Ta et al. 2023	Metabolomics analysis reveals amelioration effects of yellowhorn tea extract on hyperlipidemia, inflammation, and oxidative stress in high-fat diet-fed mice	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxine level was affected after yellowhorn tea.
446	Talli et al. 2025	Measurement of AST and ALT with Pyridoxal-5'-Phosphate according to IFCC: A decades-long gap seems to be filled	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; talks about correlations to patients with low B6.
447	Tanwar et al. 2026	Reduction of glycation stress as a geroscience intervention: protocol for a pilot RCT in postmenopausal women	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxal supplementation can help postmenopausal women.
448	Thananowan et al. 2025	Pyridoxine supplementation for levetiracetam-related neuropsychiatric adverse events in pediatric and adolescent epilepsy: a prospective, double-blind, randomized, placebo-controlled trial	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; no adverse effects from pyridoxal treatment.
449	Thanuma et al. 2025	Metabolomic analysis of bioactive compounds in dill (Anethum graveolens L.) extracts	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; shows dill can increase pyridoxal levels.

No.	Study	Title	Notes
450	Thavornnart et al. 2026	Cocrystal Formation of Quercetin and Nutraceutical Coformers via a Facile Technique with Improved Solubility and Biological Properties	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; focus is on solubility of pharmaceutical compounds.
451	Tian et al. 2024	Vitamin B(6) and folate intake are associated with lower risk of severe headache or migraine in adults: An analysis based on NHANES 1999-2004	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 may help with migraines.
452	Titcomb et al. 2023	Inadequate Niacin Intake Disrupts Growth and Retinol Homeostasis Resulting in Higher Liver and Lower Serum Retinol Concentrations in Male Rats	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 only mentioned in passing as a measurement.
453	Todorović et al. 2025	Effects of vitamin B6 on cardiometabolic biomarkers, cardiac oxidative stress and enzymes activities, and cardiovascular histomorphometric parameters in hyperhomocysteinemic rats	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 supplementation benefit in cardiovascular systems.
454	TorcidaSedano et al. 2022	Status epilepticus after gastric bypass surgery	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; benefit of B6 supplementation after gastric bypass surgery.
455	Tribble et al. 2025	Dysfunctional one-carbon metabolism identifies vitamins B(6), B(9), B(12), and choline as neuroprotective in glaucoma	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 supplementation to be neuroprotective.
456	Tripathi et al. 2024	From A to E: Uniting vitamins against stroke risk-A systematic review and network meta-analysis	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; supplementation of vitamins against stroke.

No.	Study	Title	Notes
457	Trotter et al. 2023	Large-scale genetic characterization of the model sulfate-reducing bacterium, Desulfovibrio vulgaris Hildenborough	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; talks about synthesis of pyridoxal in passing.
458	Tseng et al. 2022	Timing of therapy and neurodevelopmental outcomes in 18 families with pyridoxine-dependent epilepsy	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxine may help neurodevelopmental outcomes.
459	Tummolo et al. 2023	Micronutrient Deficiency in Inherited Metabolic Disorders Requiring Diet Regimen: A Brief Critical Review	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; deficiencies in different diets.
460	Tyrberg et al. 2022	The effect of vitamin B supplementation on neuronal injury in people living with HIV: a randomized controlled trial	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; effect of vitamin B6 supplementation.
461	Ülger et al. 2025	The effect of dietary carbohydrate quality on depression and anxiety levels in adolescents	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; adolescence with poor nutrients at higher risk of anxiety and depression.
462	Ureta-Velasco et al. 2023	Associations of Dietary Intake and Nutrient Status with Micronutrient and Lipid Composition in Breast Milk of Donor Women	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; pyridoxal as a weak correlation in unrelated study of breast milk.
463	Ureta-Velasco et al. 2024	Day-to-Day Fluctuation in Micronutrient Content in Human Milk Relative to Maternal Diet	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; micronutrient variations in breast milk compared to maternal diet.

No.	Study	Title	Notes
464	Vahid et al. 2023	Mental Health Conditions, Including Depression and Stress, Are Associated with Increased Odds of Gastric Cancer-Insights into the Role of Diet: A Case-Control Study	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; wrong outcome - B6 supplementation can help reduce gastric cancer and possibly depression and anxiety.
465	vanKarnebeek et al. 2025	New treatment for pyridoxine-dependent epilepsy due to ALDH7A1 deficiency: first proof-of-principle of upstream enzyme inhibition in the mouse	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 supplementation not helping in resistant patients on seizure medication.
466	Vargas-Quesada et al. 2025	Adherence to the EAT-Lancet diet and its association with micronutrient intake in the urban population of eight Latin American countries	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; study showed LA countries had fine levels of B6 in their diet.
467	Vasconcelos et al. 2025	Folic acid and autism: updated evidences	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; focuses on folic acid intake in relation to autism.
468	Ventura et al. 2022	Hyperhomocysteinemia in acute hepatic porphyria (AHP) and implications for treatment with givosiran	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; and Wrong outcome - benefits of B6 supplementation at certain homocysteine levels.
469	Vera et al. 2022	The ALT upper reference interval debate: Blame it on the alcohol	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; vit B vitamer was used as a measurement in the study not main topic.
470	Vernì 2024	Vitamin B6 and diabetes and its role in counteracting advanced glycation end products	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; but vitamin B6 supplementation benefits in diabetes.

No.	Study	Title	Notes
471	Vernì et al. 2026	From Fly to Human: Translational Relevance of Drosophila Models in the Study of Vitamin B6 and Cancer Relationship	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; and Wrong outcome - B6 deficiency can lead to cancer.
472	Vohra et al. 2024	A 19-year longitudinal assessment of gyromitrin-containing (Gyromitra spp.) mushroom poisonings in Michigan	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake or otherwise lacked a relevant vitamin B6 exposure.
473	Vorobieva et al. 2023	[The results of the use of a combined probiotic (Lactobacillus rhamnosus GG and Bifidobacterium animalis spp. lactis BB-12) in children with gastrointestinal and skin manifestations of food allergy]	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; vitamin B6 helped children with gastrointestinal issues and skin issues.
474	Wang et al. 2026	Genetic vitamin B6 deficiency exacerbates alcohol behavioral responses, metabolism, and toxicity in Drosophila	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; shows correlation between B6 and alcohol behaviour. Does show that increased alcohol use leads to deficiency however it is unrelated to toxicity.
475	Wang et al. 2022	Colorimetric detection of alkaline phosphatase activity based on pyridoxal phosphate-induced chromatic switch of polydiacetylene nano-liposomes	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; discusses mechanisms of alkaline phosphatase related to B6.
476	Wang et al. 2024	Intratumoral CXCL13(+) CD160(+) CD8(+) T cells promote the formation of tertiary lymphoid structures to enhance the efficacy of immunotherapy in advanced gastric cancer	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; shows benefits of B6 in cancer prevention.

No.	Study	Title	Notes
477	Wang et al. 2026	The alleviating effects of vitamin B6 and choline on β-lactoglobulin Maillard reaction: Insight into the mechanisms via mass spectrometry and interaction analysis	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake;, Wrong context - Discusses the biomechanisms of B6 - VB6 and choline decreased the extent of glycation at specific sites, showed the inhibitory effects of VB6 and choline on glycation but not in relation to B6 toxicity and dose supplementation.
478	Wang et al. 2023	Association of B vitamin intake and total homocysteine levels with all-cause and cause-specific mortality in central obesity	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; presents benefits of B6 supplementation.
479	Wang et al. 2025	Vitamin B6 allosterically activates AMPK to promote postischemic angiogenesis in mice	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; shows benefits of B6 supplementation in mice.
480	Wang et al. 2024	Associations among dietary 1-carbon metabolism nutrients, genetic risk, and Alzheimer disease: a prospective cohort study	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; study found OCMs in diet decreased risk of AD.
481	Wassie et al. 2022	Microbiome-metabolome analysis reveals alterations in the composition and metabolism of caecal microbiota and metabolites with dietary Enteromorpha polysaccharide and Yeast glycoprotein in chickens	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; shows benefits of B6 in chickens diets.
482	Welan 2023	Effect of Vitamin B6 on Osteoporosis Fracture	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; but benefits of B6 supplementation for osteoporosis.

No.	Study	Title	Notes
483	Whyte et al. 2024	Pediatric hypophosphatasia: avoid diagnosis missteps!	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; B6 accumulation mentioned as symptom of HPP.
484	Wiedeman et al. 2023	Children Aged 5-6 Years in Vancouver, Canada Meet Dietary Recommendations for Folate and Vitamin B12 but not Choline	Excluded because wrong focus (vitamin B6 does not appear in conclusions) and study focuses on children meeting dietary requirements not the toxicity of B6.
485	Wilke et al. 2026	Functional Characterization of Two Novel Biallelic PIGV Variants in a Patient With Myoclonic Seizures and Elevated Alkaline Phosphatase: A Case Report	Excluded because wrong Focus/topic (not vitamin B6 toxicity) - vitamin B6 mentioned in passing.
486	Wimer et al. 2025	Glycation-lowering compounds inhibit ghrelin signaling to reduce food intake, lower insulin resistance, and extend lifespan	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; discusses B6 deficiency reducing food intake.
487	Wise et al. 2022	Refractory Seizures Secondary to Vitamin B6 Deficiency in Parkinson Disease: The Role of Carbidopa-Levodopa	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; discusses vitB6 deficiency.
488	Wu et al. 2025	Dysregulation of astrocyte-derived matrix gla protein impairs dendritic spine development in pyridoxine-dependent epilepsy	Excluded due to wrong exposure: the study did not assess excess vitamin B6 intake; focus is alternatives for PDE.
489	Wu et al. 2025	Oral preventive medications for migraine in adults aged 18-65: a network meta-analysis	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported.

No.	Study	Title	Notes
490	Wu et al. 2022	Food additive sodium bisulfite induces intracellular imbalance of biothiols levels in NCM460 colonic cells to trigger intestinal inflammation in mice	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; vitamin B(6) (VB(6)) supplementation successfully ameliorated NaHSO(3) - induced damage in NCM460 cells and the colon of Balb/c mice.
491	Wu et al. 2023	Associations of dietary B vitamins intakes with depression in adults	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 helps reduce/ prevent depression.
492	Wu et al. 2025	Vitamin B(6) form produced by Lactobacillus induces metabolic disorder and suppresses multi-pathogenic bacteria	Excluded due to wrong population: (in vitro / cell study) - B6 induces metabolic disorder and suppresses bacteria.
493	Wu et al. 2022	Associations of dietary vitamin B1, vitamin B2, vitamin B6, and vitamin B12 with the risk of depression: a systematic review and meta-analysis	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 inversely affected depression in females.
494	Xiaozhe et al. 2022	Pyridoxine Is Effective for Preventing Hand-Foot Syndrome Induced by Pegylated Liposomal Doxorubicin for Multiple Myeloma: The Results of a Randomized Study	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 improved symptoms.
495	Xie et al. 2023	Dietary supplementation of pyridoxine can enhance the growth performance and improve the protein, lipid utilization efficiency of mandarin fish (Siniperca chuatsi)	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; fish grew from B6 supplementation.

No.	Study	Title	Notes
496	Xiong et al. 2023	Folate, vitamin B(6), and vitamin B(12) intakes are negatively associated with the prevalence of hypertension: A national population-based study	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; shows benefits of B6 for hypertension.
497	Xu et al. 2022	Vitamin B(6), B(9), and B(12) Intakes and Cognitive Performance in Elders: National Health and Nutrition Examination Survey, 2011-2014	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 was not found to have a correlation in conclusions. Wrong direction of effect - looking at B6 improving cog. per.
498	Xu et al. 2024	Analysis of differentially expressed proteins in lymph fluids related to lymphatic metastasis in a breast cancer rabbit model guided by contrast-enhanced ultrasound	Excluded because wrong focus/topic - breast cancer in rabbits. B6 mechanism mentioned in passing.
499	Xu et al. 2025	Vitamin B6 resensitizes mcr-carrying Gram-negative bacteria to colistin	Excluded because wrong focus/topic - B6 affected in study but not related to B6 toxicity.
500	Xue et al. 2024	Pyridoxine supplementation before puberty ameliorates MAM-induced cognitive and sensorimotor gating impairments	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; benefit of B6 supplementation for cognitive etc. impairments.
501	Xue 2023	Investigation of enzymatic quality and quantity using pyridoxal 5'-phosphate (PLP) regeneration system as a decoy in Escherichia coli	Excluded due to wrong population: in vitro. Wrong focus - enzyme quality from B6 related system.
502	Xue et al. 2024	The marine environmental microbiome mediates physiological outcomes in host nematodes	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; B6 accelerated growth in fish.

No.	Study	Title	Notes
503	Yan et al. 2024	Disrupted de novo pyrimidine biosynthesis impairs adult hippocampal neurogenesis and cognition in pyridoxine-dependent epilepsy	Excluded because wrong focus - study says we need more than B6 to treat illness.
504	Yan et al. 2025	Vitamin B6 Alleviates Aflatoxin B1-Induced Impairment of Testis Development by Activating the PI3K/Akt Signaling Pathway	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; benefit of B6 supplementation not toxicity.
505	Yang et al. 2024	Effects of Exposure to Different Types of Metal-Organic Framework Nanoparticles on the Gut Microbiota and Liver Metabolism of Adult Zebrafish	Excluded because wrong focus - effect of B6 from MOF NP in fish.
506	Yasuda et al. 2022	Vitamin B6 deficiency as a cause of polyneuropathy in POEMS syndrome: rapid recovery with supplementation in two cases	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; polyneuropathy treated with B6 supplementation.
507	Yasuda et al. 2022	Vitamin B6 Deficiency Anemia Attributed to Levodopa/Carbidopa Intestinal Gel Therapy for Parkinson's Disease: A Diagnostic Pitfall for Myelodysplastic Syndrome with Ring Sideroblasts	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; benefits of B6 supplementation.
508	Yin et al. 2025	Integrative analysis of microbiome and metabolome reveals the effect of deoxynivalenol on growth performance, liver and intestinal health of largemouth bass (Micropterus salmoides)	Excluded because wrong focus of discussion - B6 as a biomarker.

No.	Study	Title	Notes
509	Yu et al. 2024	Dietary Pyridoxine Requirements of Coho Salmon (Oncorhynchus kisutch) Post-Smolts	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; benefits of supplementing salmon with B6.
510	Yu et al. 2022	Theoretical study of myriocin-binding mechanism targeting serine palmitoyltransferase	Excluded because wrong focus - biomechanics involving B6 for unrelated binding mechanism.
511	Yuan et al. 2024	Immunotoxicity of 2-Acetyl-4-tetrahydroxybutylimidazole in BALB/c mice with different vitamin B6 nutritional statuses	Excluded because wrong context - B6 as an independent variable for mouse neurotoxicity.
512	Yuan et al. 2026	Comparative analysis of brain transcriptomics, intestinal metabolomics and intestinal microbial diversity between two body weight-differentiated groups of mandarin fish (Siniperca chuatsi) after artificial feed acclimation	Excluded because wrong focus - nutrients in brain of fish.
513	Zhang et al. 2023	Associations of dietary folate, vitamin B6 and B12 intake with cardiovascular outcomes in 115664 participants: a large UK population-based cohort	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; studies benefits of B6 supplementation for CVD not toxicity from excess use.
514	Zhang et al. 2024	Plasma vitamin levels and pathway analysis in boys with autism spectrum disorders	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; and Wrong outcome - studying if B6 supplementation can help ASD in boys, outcome inconclusive (further study needed). Does not relate to toxicity of B6.

No.	Study	Title	Notes
515	Zhang et al. 2025	Pyridoxal 5'-phosphate and risk of stroke: triangulation of evidence from a nationally representative cohort and bidirectional Mendelian randomization analysis	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; shows how B6 supplementation can prevent stroke. Does not discuss toxicity.
516	Zhang et al. 2023	Associations of Dietary Zinc-Vitamin B6 Ratio with All-Cause Mortality and Cardiovascular Disease Mortality Based on National Health and Nutrition Examination Survey 1999-2016	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; study showed that vitamin B6 intake is associated with a lower risk of CVD mortality. Does not evaluate toxicity.
517	Zhang et al. 2024	Dosage exploration of combined B-vitamin supplementation in stroke prevention: a meta-analysis and systematic review	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; discusses benefits of B6 supplementation in stroke prevention.
518	Zhang et al. 2025	Association of pyridoxal 5'-phosphate (PLP) with lipid profiles: a population-based cohort study	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; discusses benefits of supplementation not toxicity associated with overdose.
519	Zhang et al. 2025	Intake of one-carbon metabolism nutrients and risk of rheumatoid arthritis: a prospective UK biobank cohort study	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; study showed that OCM nutrients (that included B6) could help reduce risk of RA. Does not discuss toxicity of B6 overdose.
520	Zhang et al. 2026	Intake of Folate, Vitamin B6, and Vitamin B12 Before and After Disease Diagnosis and the Risk of Death in Individuals with Parkinson's Disease	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; discusses how B6 supplementation can help prevent death from PD if taken before diagnosis.

No.	Study	Title	Notes
521	Zhao et al. 2026	Congenital sideroblastic anemia: Unravelling molecular pathogenesis and advancing precision therapeutics	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; discusses how B6 can help CSA not the toxicity assosicated.
522	Zhen et al. 2022	Effect of different dosages of sodium butyrate and niacin on growth, faecal microbiota and Vitamin B metabolism in weaned piglets	Excluded because wrong focus - discusses sodium butyrate and niacin effect on B6 metabolism in weaned piglets.
523	Zheng et al. 2025	Integrative Multi-Omics Analysis of the Rumen in Tan Sheep with Contrasting Average Daily Gain	Excluded because wrong focus - discusses B6 to elucidate the molecular mechanisms behind growth differences in Tan sheep not toxicity related to the UL.
524	Zheng et al. 2024	Human-derived fecal microbiota transplantation alleviates social deficits of the BTBR mouse model of autism through a potential mechanism involving vitamin B(6) metabolism	Excluded because wrong focus and direction of effect - discusses benefits of B6 metabolism on ASD.
525	Zhou et al. 2022	How to Maintain a Healthy Gut Microbiome in Children with Cancer? Gut Microbiome Association with Diet in Children with Solid Tumors Postchemotherapy	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; study found that group that took B6 had increased microbiome. Does not discuss toxicity.
526	Zhou et al. 2022	[Relationship between peripheral blood micronutrients and four kinds of oral mucosal diseases in children: clinical analysis of 217 cases]	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; B6 may need to be supplemented to prevent deficiencies.

No.	Study	Title	Notes
527	Zhu et al. 2023	Folate, Vitamin B6, and Vitamin B12 Status in Association With Metabolic Syndrome Incidence	Excluded due to wrong outcome: no relevant adverse health effect for vitamin B6 toxicity was reported; vitamin B6 decreased risk of metabolic syndrome incidence.
528	Zhu et al. 2025	Vitamin B6 status, type 2 diabetes mellitus, and periodontitis: evidence from the NHANES database 2009-2010	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; benefit of supplementation does not discuss toxicity.
529	Zhu et al. 2022	Age-dependent alteration in metabolism of vitamin B(6) , neurotransmitters, and amino acids after 4'-O-methylpyridoxine administration in rats	Excluded because wrong focus - study discusses the antivitamin of B6 (MPN) and it's toxicity.
530	Zhu et al. 2024	Joint B Vitamin Intake and Type 2 Diabetes Risk: The Mediating Role of Inflammation in a Prospective Shanghai Cohort	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; and outcomes not related to excess vitamin B6 intake - Study showed that Vitamin B6 had a large role to play in decreasing the likelihood of Type 2 Diabetes.
531	ZilliVieira et al. 2024	Detrimental impact of solar and geomagnetic activity on plasma B-complex vitamins in the VA normative aging study cohort	Excluded because outcomes not related to excess vitamin B6 intake - Study conclusions did not find a correlation between solar and geomagnetic activity on vitamin B6 levels in the body.
532	Zimmern 2022	Updates on the diagnostic evaluation, genotype-phenotype correlation, and treatments of genetic epilepsies	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; not adverse effects from excess intake relevant to the UL but a benefit of B6 supplementation in genetic epilepsies.

No.	Study	Title	Notes
533	McInerney et al. 2024	MR1 presents vitamin B6-related compounds for recognition by MR1-reactive T cells	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; measurement strategy of B6 by biochemical mechanisms.
534	Mathala et al. 2026	A Novel Approach in Cancer Immunotherapy: CART-CELL Therapy	Excluded because wrong topic - cancer immunotherapy.
535	Fillah et al. 2025	Vitamins Supplementation for Nerve Regeneration: A Systematic Review of Clinical Evidence	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; nerve regeneration effects of supplementation not adverse effects from excess intake relevant to the UL.
536	Burgard et al. 2025	Ernährung in der Schwangerschaft	Excluded because wrong Language (not English).
537	BogatajJontez et al. 2024	Does Dietary Supplement Use Increase Micronutrient Intake Adequacy in Healthy Adults with Habitual Omnivorous, Vegetarian, Vegan, and Low-Carbohydrate High-Fat Diets?	Excluded due to wrong direction of effect: the study did not assess adverse effects from excess vitamin B6 intake; studies micronutrient uptake related to supplement use not B6 supplement UL toxicity.
538	Drohovoz et al. 2023	Можливість нейротоксичної дії препаратів вітамінів та умови її профілактики	Excluded because of wrong Language.
539	Dedov et al. 2023	Anemia: epidemiology, clinical-pathogenetic associations, risk of development, selenium deficiency, prevention, selenium-containing drugs	Excluded due to wrong nutrient; the study was not relevant to vitamin B6.

Appendix C Existing Guideline/Guidance Assessment Tables – Credibility Assessment

Evidence Evaluations for Vitamin B6 Upper Level (UL)

Vitamin B6 Upper Level (UL) Technical Report

National Health and Medical Research Council

SLR Project No.: 640.032359.00001

7 August 2026

SLR

C.1 Criteria for assessing existing guidance or guidelines

Administrative and technical criteria for assessing existing guidance or guidelines

The criteria outlined in this Appendix will be used to assess the methodological credibility and transparency of existing guidance documents. This assessment will inform the extent to which findings from existing guidance can be relied upon in the review. Where guidance documents are considered methodologically robust and applicable [i.e. meeting at least 80% of “must-have” and “should-have” criteria], their findings (including underlying evidence assessments where available) may be used to inform the review. Where limitations are identified, additional interrogation of the underlying evidence may be undertaken, as appropriate.
The EFSA 2023 guidance document was assessed below.

Criteria have been colour-coded to assess minimum requirements as follows: 'Must have (M)', 'Should have (S)' or 'May have(-)'

C.1.1 Overall guidance/advice development process – EFSA 2023

Criteria		Y/N/partially met/?/NA	Notes
	Overall guidance/advice development process		
M	Are the key stages of the organisation's NRV development processes compatible with NHMRC processes? (i.e., relevant and useful, transparent, overseen by a guideline development group/committee, COI management, focussed on health-related outcomes, evidence informed, actionable recs, up to date and accessible)?	Y	EFSA's process is compatible with NHMRC processes. The opinion was developed by the EFSA Panel with a dedicated Working Group on Upper Levels. It follows EFSA's established methodology framework (EFSA, 2020) and the draft Panel guidance for establishing ULs (EFSA Panel, 2022). It is health-outcome focused (peripheral neuropathy as critical effect for the UL), evidence-informed via systematic review, with a documented protocol (EFSA Panel 2023, Annex A), clear actionable recommendations (UL of 12 mg/day for adults plus age-specific values), recently published (29 March 2023, doi:10.2903/j.efsa.2023.8006), and freely accessible via EFSA Journal.
M	Are the administrative processes (e.g. the NRV development process and associated governance, principles and procedures) documented and publicly available?	Y	Yes. The methodology is documented in Section 2 of the opinion and the protocol is published as Annex A. The opinion explicitly references the EFSA framework documents that govern the process: EFSA (2010) on systematic review methodology, EFSA (2015) on principles and processes for dealing with data and evidence, EFSA Scientific Committee (2011, 2017a, 2017b, 2020) on biological relevance, weight of evidence and epidemiological evidence appraisal, and EFSA Panel (2022) on UL derivation. All documents are publicly available on the EFSA website.

Criteria		Y/N/partially met/?/NA	Notes
M	Was the work overseen by an expert advisory committee? Are potential conflicts of interest of committee members declared, managed and/or reported?	Y	Yes. The work was developed by the EFSA Panel and the Working Group on Upper Levels. The opinion explicitly states: 'If you wish to access the declaration of interests of any expert contributing to an EFSA scientific assessment, please contact interestmanagement@efsa.europa.eu.' EFSA operates a documented Independence Policy and routine COI screening for all panel members; declarations are publicly accessible on request.
M	Are funding sources declared for NRV development?	Y	Yes. The opinion was prepared at the request of the European Commission (Question number EFSA-Q-2021-00369). EFSA is identified as 'a European agency funded by the European Union'. The systematic review work was outsourced to the University of Copenhagen in collaboration with the University of Oslo and Karolinska Institute (Tetens et al., 2023) under an EFSA procurement procedure, which is acknowledged.
S	Was there public consultation on this work? if yes, is the public consultation documented and/or published?	Y	Yes. The draft opinion was released for public consultation from 13 January 2023 to 10 February 2023. The outcome of the public consultation is documented in a technical report published as Annex D to the Scientific Opinion.

Criteria		Y/N/partially met/?/NA	Notes
S	Is the advice peer reviewed? If so, is the peer review outcome documented and/or published?	P	Partially. The opinion underwent: (1) internal peer review within the EFSA NDA Panel (the Panel adopts the opinion collectively); (2) the literature search strategy was peer-reviewed by information specialists at the Karolinska Institute and EFSA; (3) public consultation served as an external review mechanism with the outcome published in Annex D. However, traditional external peer review of the final opinion (in the journal sense) is not described, as EFSA opinions are statements of an expert panel rather than peer-reviewed manuscripts. This is consistent with how EFSA outputs are typically produced and accepted as authoritative.
S	Was the guidance/advice developed or updated recently? Provide details.	Y	Yes. Adopted 29 March 2023; published in EFSA Journal 2023;21(5):8006 (May 2023).
	Evidence review parameters		
M	Are decisions about scope, definitions and evidence review parameters documented and publicly available?	Y	Yes. Section 1.3 (Interpretation of Terms of Reference), Section 2.1 (Problem formulation) and Table 2 (assessment sub questions sQ1–sQ6) document the scope. Definitions (e.g., adverse health effects per FAO/WHO 2009 and EFSA Scientific Committee 2017a) are explicit. The protocol is published as Annex A. The eligibility criteria for designs, populations, exposures and outcomes are described in Section 2.2.1.1.

Criteria		Y/N/partially met/?/NA	Notes
M	Is there a preference for data from studies that follow agreed international protocols or meet appropriate industry standards?	Y	Yes. The opinion follows EFSA's harmonised framework which prefers studies meeting recognised methodological standards. Risk of bias appraisal applies the OHAT-NTP (2015) tool, an internationally recognised standard. Eligibility excluded reviews, editorials, letters, abstracts, posters and theses 'not reporting on original data' (Section 2.2.1.1).
M	Were clinical/research questions articulated and PICO (or PECO) criteria outlined appropriate to the topic?	Y	Yes. Six assessment sub questions (sQ1–sQ6) are explicitly articulated in Table 2 (EFSA Panel 2023). Eligible designs (all human experimental and observational study designs including case reports), eligible populations (any age, healthy or with diseases unrelated to the exposure–outcome pathway; individuals with impaired vitamin B6 status excluded for sQ3a/sQ3b), eligible exposure measurements (vitamin B6 intake or biomarkers PN, PL, PLP and 4-PA) and outcomes (peripheral neuropathy for sQ3; developmental toxicity outcomes for sQ4) are all defined.

Criteria		Y/N/partially met/?/NA	Notes
M	Does the organisation use or undertake systematic literature review methods to identify and select data underpinning the advice? • are the methods used documented clearly? • are inclusion/exclusion criteria used to select or exclude certain studies from the review? If so, is justification provided? • is justification of inclusion/exclusion criteria provided?	Y	Yes. Systematic reviews were conducted for sQ3a, sQ3b and sQ4 (the priority adverse health effects). Methods are documented in Section 2.2.1.1, with full details in the outsourced project report (Tetens et al., 2023). Searches in MEDLINE, Embase and Cochrane Central; duplicate title/abstract and full-text screening in Distiller SR® with AI tool support; conflicts solved by a third reviewer; PRISMA flow diagrams provided in Appendix A of EFSA Panel 2023. For sQ3a/sQ3b: 3,793 unique references; 32 included publications. For sQ4: 4,941 unique references; 22 included publications. Reasons for exclusion at full-text level are reported in Tetens et al. (2023). Inclusion / exclusion justifications are provided (e.g., neural tube defects and oral clefts excluded from sQ4 because insufficient rather than excessive vitamin B6 is implicated).
M	If proprietary/confidential studies or data are considered by the agency, are these appropriately described/recorded?	NA	Not applicable. The opinion relies entirely on published literature (peer-reviewed studies, Member States' vigilance data which are publicly summarised, and EFSA's public food consumption databases). Member States' vigilance data informing the reference point (RP) are referenced in Section 3.6.1. No proprietary industry data are used.
M	Does the organisation use or adopt review findings or risk assessments from other organisations? What process was used to critically assess these external findings?	Y	Yes. Section 1.5 (Previous assessments by other bodies) explicitly compares the assessments of SCF (2000), IOM (1998), WHO/FAO (2004), and EVM (2003), discusses why these bodies reached different ULs (largely due to different choices of critical study), and explains the Panel's reasoning for revising the SCF (2000) RP downward. The opinion does not adopt external findings without critical appraisal.

Criteria		Y/N/partially met/?/NA	Notes
S	Can grey literature such as government reports and policy documents be included?	P	Partially. The opinion explicitly states (Section 2.2.1.1): 'Grey literature (i.e. literature not indexed in literature databases) was not searched' for the systematic review steps. However, grey-literature equivalents are used elsewhere: Member States' vigilance / pharmacovigilance data and national reports are used to support the RP (Section 3.6.1); national food consumption surveys and total diet studies are collected through competent authority contacts (Section 2.3.1). So grey literature is excluded from the systematic identification of health-effect studies but included for exposure assessment and as supportive evidence.
S	Is there documentation and justification on the selection of a toxicological endpoint for use as point of departure for health-based guidance derivation?	Y	Yes. Section 3.5 systematically reviews each candidate adverse endpoint (peripheral neuropathy, developmental toxicity including congenital anomalies / growth restriction / birth weight, photosensitisation / dermatological lesions, hip fracture, impaired memorisation, anti-lactogenic effect, testicular toxicity). Section 3.6.1 documents the selection of peripheral neuropathy as the critical effect, the choice of the Dalton & Dalton (1987) case–control study as the basis for the human RP of 50 mg/day, and the alternative animal-based RP from Phillips et al. (1978) in Beagle dogs (LOAEL 50 mg/kg bw/day). The reasoning for not using the Dalton & Dalton (1987) average intake of 100 mg/day (as SCF 2000 had done) is explicit.
	Evidence search		

Criteria		Y/N/partially met/?/NA	Notes
M	Are databases and other sources of evidence specified?	Y	Yes. MEDLINE (Ovid), Embase (Ovid) and Cochrane Central Register of Controlled Trials. Search strategy peer-reviewed by information specialists. EFSA Comprehensive European Food Consumption Database and EFSA food composition database for intake assessment. Mintel Global New Products Database for fortified food/supplement products. Competent authorities in 37 European countries for national survey data.
M	Does the literature search cover at least more than one scientific database as well as additional sources (which may include government reports and grey literature)?	Y	Yes. Three scientific databases (MEDLINE, Embase, Cochrane Central) plus hand-searching of relevant systematic reviews for additional pertinent studies.
M	Is it specified what date range the literature search covers? Is there a justification?	P	Partially. The opinion states 'No date limit was applied' for the systematic searches addressing health-effect questions, which is methodologically appropriate (no justification needed for an open start date). For the intake assessment, complementary searches covered surveys and reports 'published after 2016' (the cut-off of the previous dietary reference value (DRV) opinion) with justification. The Mintel GNPD search was limited to 'the past 5 years, from September 2017 to September 2022' for product information. The exact end date of the systematic literature searches for health effects is not explicitly stated in the main opinion text (it is detailed in Tetens et al., 2023, the outsourced report).
S	Are search terms and/or search strings specified?	Y	The main opinion states the search strategy 'was created by information specialists of the University of Oslo and peer reviewed by information specialists at the Karolinska Institute and EFSA. It is further detailed in the final report of the outsourcing project (Tetens et al., 2023).'

Criteria		Y/N/partially met/?/NA	Notes
-	Are there any other exclusion criteria for literature (e.g. publication language, publication dates)? If so, what are they and are they appropriate?	Y	Yes. Articles published in English only (Section 2.2.1.1). Reviews, expert opinions, editorials, letters to the editors, abstracts, posters and theses 'not reporting on original data' were excluded. Studies in individuals with impaired vitamin B6 status were excluded for sQ3a and sQ3b (appropriate, as the question concerns excess intake). Studies on neural tube defects and oral clefts were excluded from sQ4 with justification (these are deficiency-related outcomes).
	Critical appraisal methods and tools		
M	Is risk of bias of individual studies taken into consideration to assess internal validity? If so, what tools are used? If not, was any method used to assess study quality?	Y	Yes. RoB appraisal was applied to all eligible studies addressing sQ3a and sQ3b (peripheral neuropathy). Tool used: OHAT-NTP (2015) Risk of Bias tool, with criteria and rating instructions tailored for: (1) consideration of potential confounders, (2) confidence in exposure characterisation, (3) confidence in outcome assessment. Five-level rating (definitely low / probably low / not reported / probably high / definitely high). Performed in duplicate by independent experts at the University of Copenhagen with disagreements resolved by a third reviewer. Studies were tiered (tier 1 = low, tier 2 = moderate, tier 3 = high RoB) per OHAT-NTP (2019). Full RoB ratings for each included study are presented in Appendix B of the opinion of the EFSA document.

Criteria		Y/N/partially met/?/NA	Notes
S	Does the organisation use a systematic or some other methodological approach to synthesise the evidence (i.e. to assess and summarise the information provided in the studies)? If so, provide details.	P	Partially. Section 2.2.2.2 states: 'Owing to the heterogeneity of studies retrieved, the evidence was synthesised narratively, and no data analyses were conducted.' Narrative synthesis is appropriate given the heterogeneity (case reports, case–control studies, one HCT, vigilance data with varied exposure metrics and reporting). Evidence tables are provided in Appendix D (49 pages of detailed extraction tables) of EFSA Panel 2023. However, no quantitative pooling, no GRADE-style certainty rating, and no formal evidence integration framework beyond expert judgement is applied for the dose–response characterisation.
S	Does the organisation assess the overall certainty of the evidence and reach recommendations? If so, provide details.	P	Partially. The opinion does not apply a formal GRADE-style certainty-of-evidence framework. However, RoB tiers are reported per study (Appendix B of EFSA); the Panel notes 'The RoB of the overall body of evidence was moderate to high' for peripheral neuropathy evidence. Causality is described qualitatively as 'well-established' for vitamin B6 and peripheral neuropathy. The Panel applies the EFSA Scientific Committee (2017b) weight-of-evidence guidance and uses uncertainty factors to translate residual uncertainty into the UL derivation (UF of 4 on the human RP; UF of 300 on the animal LOAEL). Final recommendations are clear and quantitative.
	Derivation of nutrient reference values		

Criteria		Y/N/partially met/?/NA	Notes
M	Is there justification for the choice of uncertainty and safety factors?	Y	Yes. Uncertainty factor (UF) of 4 applied to the human RP (50 mg/day) is justified in Section 3.6.2.1: a factor of 2 to account for the inverse relationship between dose and time to onset of symptoms (covering uncertainty as to whether Dalton & Dalton 1987 exposure duration was sufficient), and an additional factor of 2 to account for limited available data (uncertainty about the level that would represent a true LOAEL and adequacy of representation of sensitive subgroups). The composite UF of 300 on the dog LOAEL is also fully justified: 2 × 2.5 × 10 × 2 × 3 (interspecies TK reduced from default 4 to 2 with rationale based on shared dog–human B6 metabolism per Scudi et al. 1942; default interspecies TD 2.5; default intra-human variability 10; subchronic-to-chronic 2; absence of NOAEL 3).
M	Are the assumptions and reference data (intake, body weights for age groups etc) used for the calculations clearly documented and explained?	Y	Yes. Default body weight for adults: 70 kg (EFSA Scientific Committee 2012). Reference body weights for age groups documented in Tables 12 and 13: 1–3 yr 11.9 kg, 4–6 yr 19.0 kg, 7–10 yr 28.7 kg, 11–14 yr 44.6 kg, 15–17 yr 60.3 kg, 4–6 mo 7.2 kg, 7–11 mo 8.6 kg. Sources: WHO Multicentre Growth Reference Study Group (2006) for ≤3 years, van Buuren et al. (2012) for 4–17 years. Recommended by EFSA NDA Panel (2022) guidance.

Criteria		Y/N/partially met/?/NA	Notes
M	Are the mathematical workings/algorithms clearly documented and explained?	Y	Yes. Section 3.6.2 sets out the calculations explicitly. Human-based UL: 50 mg/day ÷ 4 = 12.5 mg/day. Animal-based UL: (50 mg/kg bw/day ÷ 300) × 70 kg = 11.7 mg/day. The Panel proposes the midpoint, rounded down, giving UL = 12 mg/day for adults. For children/infants: allometric scaling using bw^0.75 with reference body weights from EFSA NDA Panel (2022). Worked tables (Tables 12, 13) show inputs and outputs.
M	Does the organisation take into consideration non-health related matters to account for feasibility of implementing the guidance values (e.g. measurement attainability)?	Y	Yes. Section 3.7 (Risk characterisation) compares the UL to actual EU intake distributions (Section 3.4) including from foods, fortified foods, and food supplements, and assesses feasibility: 'The Panel considers that it is unlikely that the UL for vitamin B6 is exceeded in European populations, except for regular users of food supplements containing high doses of vitamin B6.' Implementation context is therefore explicitly considered.
S	Is there documentation directing use of mechanistic, mode of action, or key events in adverse outcome pathways in deriving health-based guidance values?	Y	Yes. Section 3.5.1.3 (Mechanisms of toxicity) reviews four prevailing mechanistic theories for pyridoxine-induced neuropathy (drawing on Hadtstein & Vrolijk 2021): inhibition of PLP-dependent enzymes; disruption of axonal transport; direct neuronal toxicity; vitamer imbalance. The Panel concludes 'Several proposed mechanisms have been put forward by which vitamin B6 may cause neurotoxicity, but the causal mechanisms are still unknown.' Mechanistic data inform plausibility but the RP is based on observed dose–response, consistent with EFSA Scientific Committee (2017a, 2017b) guidance.

Criteria		Y/N/partially met/?/NA	Notes
M	What processes are used when expert judgement is required and applied? Is the process documented and published?	Y	Yes. Expert judgement is applied through the EFSA NDA Panel and the Working Group on ULs, drawing on EFSA Scientific Committee (2017b) guidance on the use of weight of evidence. Both groups have named members with declared interests managed by EFSA. Expert judgement is applied at: (1) RoB rating (in duplicate with third-reviewer adjudication), (2) selection of the critical effect, (3) selection of the RP, (4) decomposition and selection of UFs, (5) extrapolation across age groups. Processes are documented in Section 2.2 and the protocol (Annex A of EFSA 2023).
-	Is dose response modelling (e.g. BMDL) routinely used?	N	BMD modelling was not feasible due to data limitations (case reports and one case–control study with broad dose categories), not a methodological gap.
M	What is the organisation's policy for dealing with substances for which a non-threshold mode of action may be applicable in humans? Has the policy been articulated and recorded?	NA	Not applicable to this assessment. Vitamin B6 has an essential nutrient role with a clear threshold mode of action for neurotoxicity (peripheral neuropathy at high supplemental doses).
M	If applicable: For carcinogens, what is the level of cancer risk used by the organisation to set the health-based guidance value?	NA	Not applicable. Vitamin B6 is not a carcinogen.

Criteria		Y/N/partially met/?/NA	Notes
M	Is justification provided for any clinical/chronic endpoints selected as indicators/outcomes? (Details of endpoints to be provided in a supplementary table.)	Y	Yes. Peripheral neuropathy (sensory neuropathy, paraesthesia and related neurological signs/symptoms) is selected as the critical chronic endpoint with extensive justification in Section 3.5.1 (24 pages of evidence appraisal across human and animal studies and mechanisms). The decision rests on: causal plausibility (mechanistic theories), consistent observation across human case reports, case series and case–control evidence (Dalton & Dalton 1987), reproducibility in animal studies (Phillips et al. 1978 Beagle dogs; multiple rodent studies), and pharmacovigilance signals from Member States. Other endpoints (developmental toxicity, photosensitisation, hip fracture, impaired memorisation, anti-lactogenic effect, testicular toxicity) were systematically considered and rejected as bases for the UL with documented reasoning (Section 3.5.2 and 3.5.3).
M	Is justification provided for the value selected for the reference point^? (including mechanistic evidence, health outcome data, key events, balance studies) ^ reference point is usually the baseline value to which any scaling and uncertainty factors are applied.	Y	Yes. The 50 mg/day human RP is derived from Dalton & Dalton (1987): 'neuropathy was reported in 48% of all women having taken vitamin B6 supplements <50 mg/day for at least 6 months (i.e. the lowest dose group)'. The Panel notes this is supported by case reports (Dalton 1985; Dalton & Dalton 1987; Blackburn & Warren 2017) and Member States' vigilance data. The RP is identified as the lowest dose at which neuropathy is associated with certainty when consumed >6 months. The 50 mg/kg bw/day animal LOAEL from Phillips et al. (1978) is justified by the observation in 5/5 Beagle dogs of bilateral myelin loss in dorsal sensory nerve roots after ~100 days; mechanistic plausibility is provided in Section 3.5.1.3.

Criteria		Y/N/partially met/?/NA	Notes
M	Is the population group generalisable to the Australian and New Zealand population? • Where are the underlying studies from?	Y	Yes, broadly generalisable. The Dalton & Dalton (1987) study population was women in the United Kingdom attending a clinic for premenstrual syndrome treatment (genetically and dietetically comparable to AU/NZ populations). Case reports underpinning the supportive evidence are from a mix of European, US and Commonwealth settings (e.g. Schaumburg et al. US; Berger & Schaumburg US; Waterston & Gilligan; Friedman et al. US). Member States' vigilance data are EU-based but the underlying biological response is unlikely to differ between European and Australasian populations. The Phillips et al. (1978) Beagle dog study is interspecies-extrapolated, removing population-of-origin concerns. The Panel notes (Section 3.6.2.1) no indication that men would be more susceptible than women. Direct AU/NZ relevance is high.
M	If scaling was applied – was the method described, along with an appropriate rationale for the chosen method? • Is the method used appropriate for Australian and New Zealand populations?	Y	Yes. Allometric scaling was applied for: (1) interspecies extrapolation from dog to human (implicit in the UF of 2 for interspecies toxicokinetics), and (2) extrapolation from adult UL to child and infant ULs. Method is internationally accepted and equally appropriate for AU/NZ populations as for European populations.

Criteria		Y/N/partially met/?/NA	Notes
S	Is the Australian and New Zealand context (e.g. food system, dietary patterns, intakes, status) compatible with the jurisdiction in which the NRV under consideration was developed?	P	Partially. The intake assessment (Section 3.4) is specifically based on EU food consumption data and the EU food composition database, with EU-specific fortification practices and supplement market characterisation via Mintel GNPD (limited to ~25 EU Member States and Norway). The hazard characterisation (which underpins the UL itself) is largely population-independent given the use of allometric scaling and species-shared mechanisms. However, the intake portion may not be directly transferrable to AU/NZ — Australian and New Zealand fortification practices, supplement market and dietary patterns differ from the EU. The UL value (12 mg/day) is portable; the comparison to typical intakes would need to be re-done with Australian Bureau of Statistics nutrition survey data and FSANZ NUTTAB / AUSNUT data for AU/NZ application.

C.1.2 Credibility assessment – EFSA 2023

This assessment evaluates the methodological credibility and transparency of the EFSA Panel (2023) scientific opinion against the criteria set out in Appendix B of the NHMRC vitamin B6 UL research protocol. Where EFSA meets at least 80% of the combined 'must-have' and 'should-have' criteria, its findings (study selection, risk-of-bias assessments, evidence synthesis and the underlying point of departure) may be relied upon verbatim by the review team, with effort directed instead to synthesising new evidence published since EFSA's literature search cutoff date and integrating that new evidence with EFSA's findings.

The EFSA Panel (2023) opinion meets 21 of the 22 applicable 'must-have' criteria (with 1 partially met and 0 not met) and 5 of the 10 applicable 'should-have' criteria (with 5 partially met) (**Section C.1.1**). Combined, this gives a weighted score of 93.8% across applicable Must + Should Have items, which is above the 80% threshold defined in the NHMRC research protocol. The credibility threshold is therefore met, and the EFSA data extractions, RoB ratings, selection of the critical effect, reference point and uncertainty factors may be relied upon verbatim.

Summary of Credibility Assessment for EFSA Panel 2023

Criterion category	Total	Applicable	Met (Y)	Partial (P)	Not met (N)	Weighted score (%)(1)
Must-have (M)	25	22	21	1	0	97.7%
Should-have (S)	10	10	5	5	0	75%
Combined Must + Should	35	32	27	6	0	93.8%

Y = criterion met; P = criterion partially met; N = criterion not met; NA = not applicable. NA items are excluded from the denominator when calculating the percentage met. For the weighted score, Y counts as 1, P counts as 0.5, and N counts as 0.

(1) Weighted score was calculated using the following calculation:

$$Weighted\ score = \frac{Met\ (Y) + (0.5\ \times Partial\ (P))}{Applicabe} \times 100$$

Appendix D Data Extraction Tables – Health-based Guidance/Guideline

Evidence Evaluations for Vitamin B6 Upper Level (UL)

Vitamin B6 Upper Level (UL) Technical Report

National Health and Medical Research Council

SLR Project No.: 640.032359.00001

7 August 2026

D.1 Existing Health-based Guidance for vitamin B6

D.1.1 EFSA 2023

General Information

Parameter	Findings
Authors	EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA): Turck D, Bohn T, Castenmiller J, de Henauw S, Hirsch-Ernst K-I, Knutsen HK, Maciuk A, Mangelsdorf I, McArdle HJ, Pelaez C, Pentieva K, Siani A, Thies F, Tsabouri S, Vinceti M, Fairweather-Tait S, Vrolijk M, Fabiani L, Titz A, Naska A
Publication date	29 March 2023 (EFSA Journal 2023;21(5):8006)
Document/report title	Scientific opinion on the tolerable upper intake level for vitamin B6
Literature search timeframe	No date limit applied to systematic searches (MEDLINE (Ovid), Embase (Ovid), Cochrane Central Register of Controlled Trials); data collected from competent authorities September–November 2021; food supplement data August–October 2022; Mintel GNPD search limited to September 2017–September 2022
Literature search databases	MEDLINE (Ovid), Embase (Ovid), Cochrane Central Register of Controlled Trials; grey literature was not searched
Publication type	Scientific Opinion (regulatory/advisory document)
Peer reviewed?	Yes. The draft was released for public consultation from 13 January to 10 February 2023. The systematic review work was contracted to, and reviewed by, the University of Copenhagen, University of Oslo and Karolinska Institutet. The search strategy was also peer reviewed by information specialists.
Country of origin	European Union (EFSA, Parma, Italy)
Source of funding	European Commission (public funding); requested under Article 29(1)(a) of Regulation (EC) No 178/2002
Possible conflicts of interest	Declarations of interest available via interestmanagement@efsa.europa.eu; not detailed in the main document
Chemical/nutrient assessed	Vitamin B6 (all vitamers: pyridoxine (PN), pyridoxal (PL), pyridoxamine (PM) and their phosphate esters, including pyridoxal 5'-phosphate (PLP))
Regulatory context / purpose	Revision of UL for vitamin B6 to inform maximum amounts in fortified foods and food supplements under EC Regulation No 1925/2006 and Directive 2002/46/EC
Previous guidance value superseded	SCF (2000): UL of 25 mg/day for adults

Health considerations

Parameter	Findings
Exposure timeframe	Chronic/long-term exposure. The key case-control study, Dalton & Dalton (1987), involved vitamin B6 use for more than 6 months. Higher doses may cause effects over shorter periods.
Exposure route assessed	Oral exposure, including dietary and supplemental intake.

Parameter	Findings
Critical human health endpoint(s) – oral exposure	Peripheral sensory neuropathy, with symptoms such as paraesthesia, hyperaesthesia, bone pain, muscle weakness, fasciculation and numbness.
Justification provided by agency for critical endpoint	The link between high vitamin B6 intake and peripheral neuropathy is well established in humans and animals. It is dose-related, with higher doses causing symptoms after shorter exposure periods. Peripheral neuropathy was the only adverse effect with a suitable reference point for deriving the UL. Other effects, including hip fracture, photosensitivity, impaired memory, anti-lactogenic effects and testicular toxicity, were not considered sufficiently supported for UL derivation.
Other adverse health effects considered (not selected as critical)	Hip fracture risk, photosensitisation/dermatitis, impaired memory, anti-lactogenic effects and testicular toxicity in animals. These were not selected as critical effects due to limited or insufficient evidence.
Critical study(ies) underpinning point of departure	The main human study was Dalton & Dalton (1987), a case-control study of 172 women with PMS taking <50–500 mg/day supplemental vitamin B6 for more than 6 months. Symptoms of neuropathy were reported in 48% of the lowest dose group (<50 mg/day). Supporting evidence included Dalton (1985), Blackburn & Warren (2017), and Dutch and French nutrivigilance data. The main supporting animal study was Phillips et al. (1978), a subchronic Beagle dog study.
Species for critical study(ies)	Humans, specifically women with PMS, and Beagle dogs.
Point of departure type	For the human data, EFSA identified a reference point rather than a formal NOAEL or LOAEL. This represented the lowest intake clearly associated with neuropathy after more than 6 months. For the animal data, a LOAEL was identified.
Point of departure value (include units)	Human RP: 50 mg/day supplemental vitamin B6. Animal LOAEL: 50 mg/kg bw/day in Beagle dogs exposed for approximately 107 days.
Uncertainty factor(s) & rationale	For the human data, a total UF of 4 was applied: 2 for the inverse dose-time relationship and 2 for limited data and interindividual variability. EFSA considered this sufficient to also cover background dietary vitamin B6 intake. For the animal data, a total UF of 300 was applied to account for interspecies differences, intraspecies variability, subchronic-to-chronic extrapolation and the absence of a NOAEL.
The derivation (human)	RP (50 mg/day) ÷ UF (4) = 12.5 mg/day
The derivation (animal)	LOAEL (50 mg/kg bw/day) ÷ UF (300) = 0.17 mg/kg bw/day × default bw (70 kg) = 11.7 mg/day Midpoint of 12.5 and 11.7 = ~12.1; rounded down = 12 mg/day. The agreement between the human and animal approaches increased confidence in the UL.
Guidance value type	Tolerable Upper Intake Level (UL)
Guidance value (include units)	Adults, including pregnant and lactating women: 12 mg/day for total vitamin B6 intake from all dietary and supplemental sources. No specific increased susceptibility was identified during pregnancy or lactation. Anti-lactogenic effects occur at much higher intakes (450–600 mg/day). Children and adolescents: ULs were derived by allometric scaling from the adult UL: 3.2 mg/day (1–3 years); 4.5 mg/day (4–6 years); 6.1 mg/day (7–10 years); 8.6 mg/day (11–14 years); 10.7 mg/day (15–17 years).

Parameter	Findings
	Infants: 2.2 mg/day (4–6 months); 2.5 mg/day (7–11 months). No UL was set for infants under 4 months.
Mode of action for critical health endpoint	The exact mechanism is not known. The main hypotheses are that high pyridoxine intake may disrupt vitamin B6 metabolism, leading to accumulation of free pyridoxine or reduced PLP availability. This may affect GABA synthesis and increase excitability of dorsal root ganglia neurons, contributing to neuronal injury and peripheral neuropathy. Animal studies show damage involving axonal degeneration, myelin breakdown and cytoplasmic vacuolisation, with early lesions in the dorsal root ganglia.
Genotoxic oral carcinogen?	Not identified.
Identified sensitive sub-populations	Regular users of high-dose vitamin B6 supplements are the group most likely to exceed the UL. People with genetic differences affecting vitamin B6 metabolism may be more susceptible, although this is not well characterised. Women using high-dose vitamin B6 for PMS were the main population in the available human evidence. No specific increased susceptibility was identified for children, infants, pregnant or lactating women, older adults, or men.
Dose–response characterisation	Dalton & Dalton (1987) showed a dose-related increase in peripheral neuropathy. Human and animal data also suggest an inverse dose-time relationship, where higher doses cause symptoms sooner. A formal NOAEL or LOAEL could not be identified from the human data, and dose-response modelling was not possible due to differences between studies.
Recommendations for future research	Further research is needed on differences between vitamin B6 vitamers, toxicokinetics and toxicodynamics, genetic susceptibility, the influence of age, sex and epigenetics, and the possible role of high vitamin B6 intake in bone health.
Any non-health-based considerations?	None stated.

Appendix E Data Extraction Tables – Evidence Review for Recent (Health-based) Studies

Evidence Evaluations for Vitamin B6 Upper Level (UL)

Vitamin B6 Upper Level (UL) Technical Report

National Health and Medical Research Council

SLR Project No.: 640.032359.00001

7 August 2026

SLR

Recent Health-Based Studies for Vitamin B6

E.1 Health-based evidence review

E.1.1 Paluszny and Qiu., 2023

Study identification and design

Field	Extracted information
Citation	Paluszny, A., & Qiu, S. (2023). Vitamin B6 toxicity secondary to daily multivitamin use: A case report. Cureus, 15(11), e48792. https://doi.org/10.7759/cureus.48792
Publication status	Published, peer-reviewed (Cureus open-access journal). Review began 26 October 2023; review ended 8 November 2023; published 14 November 2023. Open access.
Country / setting	United States. Outpatient clinic at the University of Toledo Medical Center, Toledo, Ohio. Primary care follow-up of a single patient over an approximate three-year period.
Study design	Single-patient case report (descriptive observational, n = 1). No comparator group, no control, no statistical analysis. Retrospective description of one patient's clinical course, supplement history, laboratory findings and response to discontinuation of the suspected agent.
Funding / conflicts of interest	Authors declare no financial support was received for the submitted work and no financial relationships or other relationships that could appear to have influenced the work (ICMJE uniform disclosure form).

Population

Field	Extracted information
Sample size	n = 1
Patient characteristics	• 73-year-old male. • Reported a balanced diet with no recent dietary changes. • Denied use of additional vitamins (in addition to 6 mg/day multivitamin), energy drinks, workout supplements or other items with known high amounts of vitamin B6. • No relevant comorbidities reported in the available text. Preliminary work-up showed normal vitamin B12, thyroid function, HbA1C and antinuclear antibodies. Earlier (2020) peripheral neuropathy work-up was unremarkable.

Inclusion/exclusion of alternative causes	Common causes of peripheral neuropathy were investigated and excluded: B12 deficiency, thyroid dysfunction, diabetes (HbA1C normal), autoimmune disease (ANA negative). Electromyography confirmed bilateral sensory neuropathy with early progression to motor fibres, of unknown aetiology at that point. The authors note significant additional intake from unreported or unknown sources cannot be ruled out — a self-acknowledged residual confounder.

Exposure

Field	Extracted information
Exposure characterisation – source	Daily multivitamin containing 6 mg of vitamin B6, taken for more than 10 years. Vitamer form is reported as pyridoxine (PN). The exposure is self-reported by the patient retrospectively.
Exposure characterisation – dose	• Supplemental intake: 6 mg/day from the multivitamin (≈350% of the US adult Recommended Dietary Allowance (RDA) of 1.7 mg/day for men >50 years). • Background dietary intake: not directly measured; the authors cite a typical US dietary intake of approximately 2 mg/day for men. • Estimated total chronic intake: approximately 8 mg/day (6 mg supplement + ~2 mg estimated diet) for >10 years — i.e. below the EFSA Panel (2023) UL of 12 mg/day for adults.
Biomarker of exposure	Serum vitamin B6 concentration: 259.9 nmol/L (laboratory reference range 20–125 nmol/L), i.e. approximately 2.1 times the upper limit of normal. The specific vitamer measured (PN, PL, PLP or total) is not stated in the case report, which is a limitation for direct comparison with EFSA's biomarker framework (which references plasma PLP as the primary biomarker of B6 status).
Duration of exposure	More than 10 years of continuous daily multivitamin use, by self-report.

Outcomes

Field	Extracted information
Primary outcome	Peripheral neuropathy. The patient presented with a three-year history of progressive bilateral lower-limb numbness (initially nocturnal), later involving the fingertips. Supportive symptoms included new-onset light-headedness and dizziness at the third clinic visit.
Outcome assessment – clinical examination	• Initial visit: normal pulses, strength, reflexes, gait and mental status; decreased vibratory sense at the left ankle; decreased monofilament sensation bilaterally. • Eight-month follow-up: similar examination findings with bilaterally decreased vibratory sense.
Outcome assessment – objective testing	Electromyography (EMG): bilateral sensory neuropathy of unknown aetiology with early signs of progression to motor fibres. EMG is an objective electrophysiological measure with established validity for peripheral neuropathy.

Outcome assessment – tools used	Standard clinical neurological examination (vibration sense, monofilament testing, reflexes, gait, strength); EMG; serum vitamin B6 immunoassay (laboratory not specified). No validated patient-reported outcome instrument (e.g., Total Neuropathy Score) was used.
Response to withdrawal	One month after discontinuing the multivitamin, the patient reported resolution of dizziness and slight improvement in numbness and tingling. Repeat serum vitamin B6 was scheduled for four months.

Results and Conclusions

Field	Extracted information
Main results	• Documented peripheral neuropathy (clinically and on EMG) in a 73-year-old man with chronic low-dose pyridoxine supplementation (6 mg/day for >10 years) and elevated serum B6 (259.9 nmol/L). • Common alternative causes of peripheral neuropathy excluded by laboratory work-up. • Partial symptomatic improvement and resolution of dizziness within 1 month of stopping the multivitamin.
Authors' conclusions	The case suggests a need for more research into the effects of long-term, low-dose pyridoxine supplementation. Vitamin B6 toxicity should remain on the differential for peripheral neuropathy, especially when initial laboratory evaluations are inconclusive. The authors explicitly state that the patient's daily intake (estimated at ~8 mg/day) is below the newly established EFSA UL of 12 mg/day, raising a question about the protectiveness of that UL for some sensitive individuals.
Authors' acknowledged limitations	• Significant additional intake from unreported or unknown sources cannot be ruled out (recall bias and incomplete supplement history are acknowledged). • Retrospective dietary information over a 3-year span is difficult to collect accurately. • Single patient - no controls, no statistical inference possible.

Contextual information for the AU/NZ UL review

Generalisability to AU/NZ	The patient is from the US, a population genetically and dietetically broadly comparable to AU/NZ. US RDA values cited by the authors (1.3–1.7 mg/day for adults) are essentially aligned with the current AU/NZ NRVs. Multivitamin formulations containing 5–10 mg pyridoxine per daily dose are common in the AU/NZ over-the-counter market; the exposure scenario described is plausibly transferable to AU/NZ consumers.

E.1.2 Arai et al., 2023

Study identification and design

Field	Extracted information
Citation	Arai, Y., Okanishi, T., Kanai, S., Ohta, K., Sunada, H., Noma, H., & Maegaki, Y. (2023). Identifying risk factors for adverse events of pyridoxal phosphate in infantile epileptic spasms syndrome. Epilepsy & Behavior, 145, 109348.
Publication status	Published, peer-reviewed journal (Epilepsy & Behavior, Elsevier), available online 16 July 2023
Country / setting	Japan; Tottori University Hospital (retrospective hospital-based study).
Study design	Retrospective observational cohort study reviewing medical records of patients with IESS treated with PLP (n = 59).
Funding / conflicts of interest	No funding reported; authors declare no competing financial interests.

Population

Field	Extracted information
Sample size	n = 59
Patient characteristics	Infants/young children with infantile epileptic spasms syndrome (IESS); 32 males and 27 females. Age at IESS onset: 2–27 months (mean 8.0 months). Age at PLP treatment: 2–33 months (mean 9.6 months).
Inclusion/exclusion of alternative causes	Inclusion: diagnosed IESS (<36 months), treated with PLP, no prior ACTH or vigabatrin. Etiologies classified (structural, genetic, metabolic, infectious, unknown). No explicit systematic exclusion of all alternative causes of adverse events reported.

Exposure

Field	Extracted information
Exposure characterisation – source	Pyridoxal 5′-phosphate (PLP) administered as therapeutic treatment for IESS.
Exposure characterisation – dose	Initial dose: 10–20 mg/kg/day, increased to 30–50 mg/kg/day; maximum observed range 10–80 mg/kg/day (mean 33.8 mg/kg/day).

Field	Extracted information
Biomarker of exposure	NA (no direct biomarker of vitamin B6 status such as plasma PLP reported).
Duration of exposure	NA (duration varies; protocol includes initiation and escalation within one week, but total treatment duration not consistently reported).

Outcomes

Field	Extracted information
Primary outcome	Adverse events associated with PLP therapy (vomiting, elevated liver enzymes, rhabdomyolysis).
Outcome assessment – clinical examination	Monitoring for symptoms such as vomiting; adverse events defined as symptoms or lab abnormalities requiring dose reduction/discontinuation.
Outcome assessment – objective testing	Laboratory tests: AST, ALT, γ-GTP (liver enzymes), creatine kinase (CK). Rhabdomyolysis defined as CK >10× upper limit.
Outcome assessment – tools used	Routine blood tests; clinical observation; retrospective medical record review.
Response to withdrawal	Some adverse events (e.g., rhabdomyolysis cases) improved after management and/or dose reduction/discontinuation.

Results and Conclusions

Field	Extracted information
Main results	51.9% experienced adverse events. Vomiting: 59.3%; elevated liver enzymes: 55.6%; rhabdomyolysis: 3.4%. Risk factors for elevated liver enzymes: age <9 months and dose ≥40 mg/kg/day (RR 3.6 and 2.6 respectively).
Authors' conclusions	Adverse events are common with PLP therapy in IESS. Younger age and higher dose are risk factors for liver enzyme elevation; rhabdomyolysis may occur particularly in younger or higher-dose cases.
Authors' acknowledged limitations	Single-centre study; small sample size; no multivariate analysis; all participants Japanese; focus primarily on adverse events rather than efficacy.

Contextual information for the AU/NZ UL review

Generalisability to AU/NZ	Limited direct generalisability (Japanese infant population with epilepsy under hospital treatment). However, biological mechanisms (dose-dependent toxicity, liver immaturity in infants) likely applicable across populations. Clinical dosing context differs significantly from general population supplement use.

E.1.3 Bossard et al., 2022

Study identification and design

Field	Extracted information
Citation	Bossard, V., Bourmeyster, N., Pasini, S., Dupuis, P., El Balkhi, S., Richard, E., Alarcan, H., Hauet, T., & Thuillier, R. (2022). Problematic rise of vitamin B6 supplementation overuse and potential risk to bariatric surgery patients. Nutrition, 102, 111738.
Publication status	Published, peer-reviewed journal (Nutrition, Elsevier), 2022.
Country / setting	France; multicentre hospital-based study (Poitiers, Tours, Bordeaux, Limoges university hospitals).
Study design	Retrospective observational study of laboratory measurements (vitamin B6 blood levels).
Funding / conflicts of interest	Funded by CHU de Poitiers; no conflicts of interest stated.

Population

Field	Extracted information
Sample size	n = 40,311 samples (vitamin B6 measurements).
Patient characteristics	Mixed patient population undergoing vitamin B6 testing; 64% women, 36% men; most represented age group 41–60 years.
Inclusion/exclusion of alternative causes	All patients with available vitamin B6 measurements included; no explicit exclusion of alternative causes of elevated B6 levels (e.g., supplement use assumed but not directly measured).

Exposure

Field	Extracted information
Exposure characterisation – source	Vitamin B6 exposure inferred primarily from supplement use (particularly multivitamins), especially in bariatric surgery patients; not directly measured.
Exposure characterisation – dose	Not directly measured at individual level; multivitamin products commonly contain 1.5–12.6 mg vitamin B6 per tablet (up to ~900% of RDA).
Biomarker of exposure	Blood pyridoxal-5′-phosphate (PLP) measured using HPLC; categories: deficiency (<30 nmol/L), normal (30–100 nmol/L), overdose (>100 nmol/L).

Field	Extracted information
Duration of exposure	NA (not directly assessed; inferred chronic exposure due to supplement use trends over 2012–2020).

Outcomes

Field	Extracted information
Primary outcome	Prevalence of vitamin B6 deficiency and overdose (hypervitaminosis B6) based on blood levels.
Outcome assessment – clinical examination	NA (no direct clinical examination outcomes systematically reported).
Outcome assessment – objective testing	Laboratory measurement of PLP concentrations in whole blood via HPLC with fluorescence detection.
Outcome assessment – tools used	Chromsystems HPLC assay with fluorescence detection; defined biochemical thresholds for deficiency and overdose.
Response to withdrawal	NA (individual patient follow-up or withdrawal response not assessed in this study).

Results and Conclusions

Field	Extracted information
Main results	Marked increase in vitamin B6 testing and overdose over time (2012–2020). Overdose prevalence reached ~30–40% of samples across centres. Deficiencies decreased and became negligible by later years.
Dose-response / exposure-response	Higher blood PLP levels associated with likely increased supplement intake; no quantified intake–response relationship.
Additional findings	Overdose categories included moderate (101–200 nmol/L), high (201–500 nmol/L), and very high (>500 nmol/L), all increasing over time.
Authors' conclusions	Increasing vitamin B6 overdoses are likely driven by supplement use rather than diet. High B6 intake may lead to polyneuropathy. Clear guidelines on supplementation are needed, particularly for bariatric surgery patients.
Authors' acknowledged limitations	No direct measurement of supplement intake; observational design; inability to link individual exposure with clinical outcomes; reliance on laboratory data only.

Contextual information for the AU/NZ UL review

Generalisability to AU/NZ	Moderate. Population includes general clinical patients and bariatric populations; supplement use patterns likely comparable to AU/NZ. However, results are biomarker-based and not directly linked to intake levels.

E.1.4 Brands et al., 2026

Study identification and design

Field	Extracted information
Citation	Brands, M. M., de Puyraimond, C., Gospe, S. M., Schiff, M. M., Jaeger, B., Koot, B. G., Raphael, M. F., Lubout, C. M., Soto, B., Delanne, J., Imbard, A., Zempel, J., Kraal, K. C., Scheenstra, R., & Clayton, P. T. (2026). Hepatocellular carcinoma: A critical complication in patients treated with pyridoxal phosphate. *Neuropediatrics, 57*, 59–64.
Publication status	Published, peer-reviewed journal (Neuropediatrics), published January 2026.
Country / setting	Multinational case series (institutions in the Netherlands, France, USA, UK and others; tertiary hospital settings).
Study design	Case series of pediatric patients (n = 4) with vitamin B6-dependent epilepsy treated with long-term PLP.
Funding / conflicts of interest	No conflicts of interest declared; funding not clearly specified → NA

Population

Field	Extracted information
Sample size	n = 4
Patient characteristics	Pediatric patients with vitamin B6-dependent epilepsy; included PNPO deficiency (n = 2) and ALDH7A1 deficiency (n = 2); all required long-term PLP therapy
Inclusion/exclusion of alternative causes	Genetic diagnoses confirmed (PNPO or ALDH7A1 deficiency); authors considered underlying disease as alternative cause of liver pathology but concluded shared PLP exposure likely contributor

Exposure

Field	Extracted information
Exposure characterisation – source	Oral pyridoxal-5′-phosphate (PLP) used as therapeutic treatment for vitamin B6–dependent epilepsy
Exposure characterisation – dose	Approximately 30–50 mg/kg/day; highest reported doses up to 50 mg/kg/day; long-term exposure for ≥5 years prior to hepatocellular carcinoma in affected patients
Biomarker of exposure	NA (no direct plasma PLP concentrations systematically reported)
Duration of exposure	Several years (approximately 5–9 years before development of hepatocellular carcinoma)

Outcomes

Field	Extracted information
Primary outcome	Severe liver outcomes including hepatotoxicity, cirrhosis, and hepatocellular carcinoma (HCC)
Outcome assessment – clinical examination	Clinical monitoring for hepatomegaly, symptoms, and disease progression
Outcome assessment – objective testing	Liver enzyme monitoring (AST, ALT, γ-GT), imaging (ultrasound, MRI), alpha-fetoprotein (AFP), liver biopsy where applicable
Outcome assessment – tools used	Standard clinical biochemistry tests, imaging modalities, and tumour markers
Response to withdrawal	In one patient, liver dysfunction resolved after switching from PLP to pyridoxine; in others, dose reduction attempted but severe outcomes (HCC) still occurred

Results and Conclusions

Field	Extracted information
Main results	3/4 patients developed hepatocellular carcinoma after long-term PLP exposure; 1/4 developed severe but reversible hepatotoxicity; liver injury occurred after prolonged high-dose exposure and across different genetic conditions
Authors' conclusions	Long-term high-dose PLP therapy may pose significant hepatotoxic risk, including malignancy; careful monitoring and improved formulations are needed; PLP exposure is a likely contributing factor independent of underlying disease
Authors' acknowledged limitations	Small sample size (case series); difficulty separating effects of PLP from underlying metabolic disease; variable formulations and dosing; lack of controlled comparison

Contextual information for the AU/NZ UL review

Generalisability to AU/NZ	Limited; rare pediatric metabolic population on very high therapeutic doses; therapeutic level not relevant to the general population intake of vitamin B6.

E.1.5 Gdynia et al., 2025

Study identification and design

Field	Extracted information
Citation	Gdynia, N., Gratzer, A., & Gdynia, H.-J. (2025). Polyneuropathy due to vitamin B6 hypervitaminosis: A case series and call for more education. *Journal of Neurosciences in Rural Practice*.
Publication status	Published (article in press), peer-reviewed journal; accepted January 2025, early online publication February 2025.
Country / setting	Germany; outpatient neurology clinic (Clinic Enzensberg).
Study design	Case series of consecutively recruited patients with vitamin B6-associated polyneuropathy.
Funding / conflicts of interest	No financial support; no competing interests declared.

Population

Field	Extracted information
Sample size	n = 8
Patient characteristics	Older adults; mean age 80.1 years (range 70–86); 5 males, 3 females; all had suspected or confirmed polyneuropathy.
Inclusion/exclusion of alternative causes	Extensive diagnostic workup performed (laboratory, neurological, electrophysiological); no alternative causes identified in 7/8 patients; 1 patient had pre-existing neuropathy (uremia) with possible worsening due to B6.

Exposure

Field	Extracted information
Exposure characterisation – source	Vitamin B6 (pyridoxine) from supplements or multivitamin preparations (self-medication or prescribed).
Exposure characterisation – dose	Variable; examples include long-term intake of ~10 mg/day for 13 years and unspecified higher-dose polyvitamin use; some cases involved chronic high intake via multiple supplements
Biomarker of exposure	Serum vitamin B6 levels elevated in all patients; e.g. up to 373.6 µg/L (reference 3.6–18.0 µg/L)
Duration of exposure	Long-term exposure (years to >10 years in several cases)

Outcomes

Field	Extracted information
Primary outcome	Sensorimotor polyneuropathy associated with vitamin B6 hypervitaminosis
Outcome assessment – clinical examination	Neurological exam showing sensory deficits (loss of vibration sense, distal sensory loss, atactic gait in some patients)
Outcome assessment – objective testing	Nerve conduction studies (NCS), electromyography (EMG), laboratory testing including vitamin levels
Outcome assessment – tools used	Sensory and motor nerve conduction studies; EMG; blood tests including B6, B12, B1, methylmalonic acid
Response to withdrawal	In at least one patient, neurological improvement observed after discontinuation of vitamin B6; in others, symptoms persisted or only partially improved

Results and Conclusions

Field	Extracted information
Main results	7/8 patients developed sensorimotor polyneuropathy attributed to vitamin B6 hypervitaminosis; all patients had elevated serum B6; even modest elevations associated with motor nerve involvement
Authors' conclusions	Vitamin B6-induced polyneuropathy is a significant and under-recognised problem; often due to self-medication; even relatively low or “acceptable” supplement doses may be harmful; increased awareness and monitoring are needed
Authors' acknowledged limitations	Small sample size; case series design; reliance on observational data; limited ability to quantify exact doses and causality

Contextual information for the AU/NZ UL review

Generalisability to AU/NZ	Moderate; reflects real-world supplement use in general population; highlights risk from over-the-counter vitamin use at doses comparable to those available in AU/NZ

E.1.6 Gospe, 2022

Study identification and design

Field	Extracted information
Citation	Gospe, S. M., Jr. (2001, updated 2022). Pyridoxine-dependent epilepsy – ALDH7A1. In M. P. Adam, S. Bick, G. M. Mirzaa, et al. (Eds.), *GeneReviews*® [Internet]. University of Washington, Seattle.
Publication status	Published, peer-reviewed clinical reference (GeneReviews®), originally 2001, updated September 22, 2022
Country / setting	United States (University of Washington, Seattle; web-based clinical reference resource)
Study design	Narrative clinical review / reference monograph **(not original research study)**
Funding / conflicts of interest	NA (not explicitly reported in GeneReviews format)

Population

Field	Extracted information
Sample size	NA
Patient characteristics	Individuals with pyridoxine-dependent epilepsy (ALDH7A1 deficiency), typically presenting in neonates or early childhood; includes both classic and atypical phenotypes
Inclusion/exclusion of alternative causes	Diagnostic framework includes differentiation from PNPO deficiency, PLPBP deficiency, and other causes of vitamin B6-responsive seizures; relies on genetic confirmation (ALDH7A1 variants) and biochemical markers (α-AASA)

Exposure

Field	Extracted information
Exposure characterisation – source	Pharmacologic pyridoxine (vitamin B6) supplementation as lifelong therapy
Exposure characterisation – dose	Recommended doses: newborns ~100 mg/day; infants and beyond ~30 mg/kg/day (maximum 300–500 mg/day depending on age); temporary dose increases during illness
Biomarker of exposure	Indirect: biochemical markers of disease (e.g. α-aminoadipic semialdehyde [α-AASA], pipecolic acid); no direct biomarker of pyridoxine toxicity specified
Duration of exposure	Lifelong supplementation required

Outcomes

Field	Extracted information
Primary outcome	Seizure control in pyridoxine-dependent epilepsy
Outcome assessment – clinical examination	Neurological assessment including seizure response, developmental progress, signs of encephalopathy
Outcome assessment – objective testing	EEG monitoring, biochemical markers (α-AASA, neurotransmitter profiles), genetic testing
Outcome assessment – tools used	Clinical neurological exam, EEG, laboratory biochemical assays, molecular genetic testing
Response to withdrawal	Discontinuation of pyridoxine leads to recurrence of seizures and risk of status epilepticus

Results and Conclusions

Field	Extracted information
Main results	Lifelong pyridoxine supplementation effectively controls seizures in affected individuals; however, excessive doses (particularly >500 mg/day or megavitamin use) can cause reversible sensory neuropathy
Authors' conclusions	Pyridoxine is essential and life-saving therapy in this population; careful dosing and monitoring are required to avoid neurotoxicity
Authors' acknowledged limitations	Not a primary study; evidence based on case series, registries, and expert consensus rather than controlled trials

Contextual information for the AU/NZ UL review

Generalisability to AU/NZ	Limited for general population UL setting; represents a rare clinical population receiving very high therapeutic doses; Outside of the scope for general population.

E.1.7 He et al., 2025

Study identification and design

Field	Extracted information
Citation	He, L., Fan, Y., Hu, Y., Tian, C., Tian, Y., Zhang, J., Ren, Y., & Tan, J. (2025). The potential hazards of high doses of vitamin B6 in treating nausea and vomiting in pregnancy: A systematic review. *International Journal of Gynecology & Obstetrics, 169*, 38–50.
Publication status	Published, peer-reviewed journal article (International Journal of Gynecology & Obstetrics); published online November 2024, issue 2025
Country / setting	China; academic research institutions (Zunyi Medical University)
Study design	**Systematic review of literature (including case reports, RCTs, observational studies)**
Funding / conflicts of interest	Funded by Science and Technology Program of Guizhou Province and related grants; no conflicts of interest declared

Population

Field	Extracted information
Sample size	19 included studies (from 136 identified articles); includes data from multiple populations (e.g. 1226 individuals for neurological outcomes)
Patient characteristics	Pregnant women with nausea and vomiting of pregnancy (NVP) or hyperemesis gravidarum (HG); includes varied study populations from underlying included literature
Inclusion/exclusion of alternative causes	Review includes a range of study designs; underlying studies vary in control of confounding factors; not consistently standardised across included evidence

Exposure

Field	Extracted information
Exposure characterisation – source	Vitamin B6 (pyridoxine) supplementation for treatment of NVP/HG
Exposure characterisation – dose	Therapeutic doses typically 10–30 mg up to ~200 mg/day; adverse effects reported across a wide range including ≥30 mg/day and high-dose exposures (100–6000 mg/day in case reports)

Field	Extracted information
Biomarker of exposure	Plasma PLP (pyridoxal-5′-phosphate) used as biomarker of vitamin B6 status
Duration of exposure	Variable; includes short-term treatment in pregnancy and long-term/high-dose exposures in case reports

Outcomes

Field	Extracted information
Primary outcome	Adverse effects of high-dose vitamin B6, including neurological toxicity and pregnancy outcomes
Outcome assessment – clinical examination	Neurological symptoms (e.g. paresthesia, ataxia), pregnancy outcomes (miscarriage, fetal outcomes)
Outcome assessment – objective testing	Reported outcomes include biochemical markers, clinical diagnosis, and study-reported endpoints across included studies
Outcome assessment – tools used	Not standardised; varies across included studies (clinical assessment, observational reporting, RCT outcomes)
Response to withdrawal	Some included case reports indicate improvement in neurological symptoms following discontinuation of vitamin B6

Results and Conclusions

Field	Extracted information
Main results	Neurological symptoms reported in 164/1226 individuals (e.g. paresthesia, ataxia); evidence suggests association between high-dose vitamin B6 and neuropathy; some reports of miscarriage (4/245) and intrauterine death; evidence of possible congenital abnormalities but inconsistent findings
Authors' conclusions	High doses of vitamin B6 may pose risks including neurotoxicity and potential adverse pregnancy outcomes; caution is warranted when exceeding recommended intake levels, particularly in early pregnancy
Authors' acknowledged limitations	Limited high-quality evidence; reliance on case reports and heterogeneous studies; small sample sizes; lack of consistent follow-up and standardisation

Contextual information for the AU/NZ UL review

Generalisability to AU/NZ	Moderate; reflects clinical and supplement use contexts relevant to pregnancy; however, evidence is heterogeneous and based largely on secondary data rather than controlled trials

E.1.8 Kościńska-Shukla et al., 2025

Study identification and design

Field	Extracted information
Citation	Kościńska-Shukla, I., Jaskólska, M., Grochowalska, K., Okrój, M., & Chmielewski, M. (2025). Underestimated pyridoxine consumption and neurotoxicity: A novel manifestation with rheumatologic relevance – a case-based review. *Rheumatology International, 45*, 144.
Publication status	Published, peer-reviewed journal article (Rheumatology International); published online May 26, 2025
Country / setting	Poland; Medical University of Gdańsk (clinical rheumatology setting)
Study design	**Case-based review (3 clinical cases + narrative literature review component)**
Funding / conflicts of interest	No major conflicts reported (one author reported lecture sponsorship unrelated to results); no significant funding affecting interpretation

Population

Field	Extracted information
Sample size	3 clinical cases (plus ~50 studies included in literature component)
Patient characteristics	Adults (36-year-old female, 46-year-old male, 65-year-old female) presenting with neurological symptoms (peripheral neuropathy, cognitive symptoms), some with suspected or existing rheumatologic conditions
Inclusion/exclusion of alternative causes	Extensive diagnostic work-up performed (rheumatologic, neurological, imaging, biochemical); alternative causes largely excluded before attributing symptoms to vitamin B6 toxicity

Exposure

Field	Extracted information
Exposure characterisation – source	Excess vitamin B6 (pyridoxine) intake from supplements, diet (e.g. nuts), and/or prescribed formulations
Exposure characterisation – dose	Variable and often unquantified; includes high-dose supplementation (e.g. ≥200 mg/day prescribed product) and cumulative intake from diet + OTC sources
Biomarker of exposure	Serum vitamin B6 concentrations markedly elevated (e.g. 117 µg/L, 226.6 µg/L, 254.8 µg/L; reference range 5–30 µg/L)

Field	Extracted information
Duration of exposure	Chronic exposure (months to ~1 year of supplementation or dietary excess)

Outcomes

Field	Extracted information
Primary outcome	Neurological toxicity (primarily peripheral neuropathy; also cognitive/CNS symptoms)
Outcome assessment – clinical examination	Symptoms included paresthesia, neuropathic pain, cognitive impairment, memory deficits, and functional symptoms
Outcome assessment – objective testing	Neurophysiology, imaging (MRI), immunological tests, biochemical assays (vitamin levels, complement system)
Outcome assessment – tools used	Clinical neurological exam, neuropsychological assessment, laboratory biomarkers, imaging
Response to withdrawal	Strong: discontinuation of vitamin B6 led to normalisation of serum levels and resolution or marked improvement of symptoms in all cases

Results and Conclusions

Field	Extracted information
Main results	Excess vitamin B6 intake associated with peripheral neuropathy and possible CNS manifestations; symptoms improved after cessation; suggests both peripheral and potential central neurotoxicity
Authors' conclusions	Pyridoxine overdose can cause clinically significant neurotoxicity; clinicians should consider vitamin B6 toxicity in patients with unexplained neurological symptoms and routinely assess supplementation history
Authors' acknowledged limitations	Small sample size (case-based evidence); reliance on observational and case report data; lack of clear dose–response thresholds; heterogeneity in literature

Contextual information for the AU/NZ UL review

Generalisability to AU/NZ	Moderate; reflects real-world supplement use (including OTC products and fortified foods); supports evidence of neurotoxicity from excess intake, but limited by small sample size and case-report nature

E.1.9 Lee et al., 2025

Study identification and design

Field	Extracted information
Citation	Lee, J. Z. C., Chow, C. K., Fung, C.-W., Lui, S. T. Y., & Wong, S.-N. S. (2025). Hepatocellular carcinoma in a patient with pyridoxamine 5-phosphate oxidase (PNPO) deficiency undergoing pyridoxal 5-phosphate treatment. *Molecular Genetics and Metabolism Reports, 43*, 101224.
Publication status	Published, peer-reviewed journal article (Molecular Genetics and Metabolism Reports); published online May 9, 2025
Country / setting	Hong Kong; hospital-based clinical setting (United Christian Hospital / Hong Kong Children's Hospital)
Study design	Single case report
Funding / conflicts of interest	No competing financial interests reported

Population

Field	Extracted information
Sample size	1 patient
Patient characteristics	Male infant with pyridoxamine 5-phosphate oxidase (PNPO) deficiency (inborn error of metabolism); neonatal onset seizures resistant to standard anticonvulsants
Inclusion/exclusion of alternative causes	Extensive metabolic, imaging, infectious and immunological investigations performed; PNPO deficiency confirmed via genetic testing; other causes of liver disease (e.g. viral hepatitis) excluded

Exposure

Field	Extracted information
Exposure characterisation – source	Pyridoxal 5-phosphate (PLP) therapy (active form of vitamin B6)
Exposure characterisation – dose	Approximately 40 mg/kg/day (range used in literature 10–85 mg/kg/day)
Biomarker of exposure	Indirect: liver function tests (ALT, AST, GGT), alpha-fetoprotein (AFP) as tumour marker
Duration of exposure	Long-term treatment from early infancy through childhood

Outcomes

Field	Extracted information
Primary outcome	Liver toxicity and development of hepatocellular carcinoma (HCC)
Outcome assessment – clinical examination	Neurological status (seizure control), clinical deterioration with hepatic complications (encephalopathy, liver failure)
Outcome assessment – objective testing	Serial liver function tests, AFP levels, ultrasound, CT, MRI, PET imaging, liver biopsy
Outcome assessment – tools used	Biochemical assays, imaging modalities (ultrasound, CT, MRI, PET), histopathology (biopsy)
Response to withdrawal	Not fully assessable (treatment continued due to seizure control necessity); literature cited indicates liver dysfunction may improve with dose reduction

Results and Conclusions

Field	Extracted information
Main results	Progressive liver abnormalities observed (fatty liver → cirrhosis → hepatocellular carcinoma); marked rise in AFP over time (peaking >100,000 µg/L); confirmed HCC and eventual death due to liver failure
Authors' conclusions	Long-term PLP therapy may be associated with liver toxicity and potential development of HCC; recommends cautious dosing and regular liver monitoring in patients receiving PLP
Authors' acknowledged limitations	Single case report; association between PLP and HCC is hypothesis-generating and cannot establish causality

Contextual information for the AU/NZ UL review

Generalisability to AU/NZ	Very limited; represents a rare genetic disorder requiring extremely high therapeutic doses; however, provides evidence of potential hepatic toxicity of high-dose vitamin B6 (PLP) relevant for hazard identification

E.1.10 Modica et al., 2023

Study identification and design

Field	Extracted information
Citation	Modica, J. S., Déry, C., Canissario, R., Logigian, E., Bonno, D., Stanton, M., Dupré, N., McDermott, M. P., Bouchard, M., Lang, A. E., & Lizarraga, K. J. (2023). A systematic review of the potential consequences of abnormal serum levels of vitamin B6 in people living with Parkinson's disease. *Journal of the Neurological Sciences, 450*, 120690.
Publication status	Published, peer-reviewed systematic review (Elsevier); published May 18, 2023
Country / setting	International (USA, Canada, multiple centres); literature-based review
Study design	**Systematic review (PRISMA-compliant) including cohort, cross-sectional, case series, and case reports**
Funding / conflicts of interest	No major competing interests declared

Population

Field	Extracted information
Sample size	25 included studies; 145 patients with Parkinson's disease (PwPD) with serum B6 data for quantitative summary
Patient characteristics	Adults with Parkinson's disease; often receiving levodopa therapy (oral or intestinal gel)
Inclusion/exclusion of alternative causes	Excluded individuals with other causes of abnormal B6 (e.g. alcoholism, cancer, unrelated medications) and unrelated neuropathy/epilepsy

Exposure

Field	Extracted information
Exposure characterisation – source	Abnormal serum vitamin B6 levels (both low and high); influenced by levodopa therapy, supplementation, diet, and metabolism
Exposure characterisation – dose	Low: <20 nmol/L; Normal: 20–125 nmol/L; High: >125 nmol/L
Biomarker of exposure	Serum vitamin B6 (pyridoxal 5'-phosphate levels)
Prevelance of Exposure	41.4% abnormal B6 levels overall (35.9% low; 5.5% high)

Field	Extracted information
Exposure Modifiers	High levodopa doses (≥1000 mg/day), intestinal gel formulations (LCIG), diet, supplement use, age, gastrointestinal dysfunction

Outcomes

Field	Extracted information
Primary outcome	Polyneuropathy and epilepsy Associations reported - Polyneuropathy (low B6) in 14 cases - Polyneuropathy (high B6) in 4 cases - Epilepsy (low B6) in 4 cases
Outcome assessment – clinical examination	Neurological symptoms (sensory neuropathy, motor dysfunction, seizures, cognitive symptoms)
Outcome assessment – objective testing	Neurophysiology (NCS/EMG), EEG, laboratory biomarkers, clinical diagnosis
Outcome assessment – tools used	Mixed methods across studies (observational + clinical measures)
Response to withdrawal	NA

Results and Conclusions

Field	Extracted information
Main results	Abnormal vitamin B6 levels (both deficiency and excess) are associated with neurological outcomes; low B6 more common than high; possible dose–response relationship with levodopa exposure
Mechanistic Insights	Low B6 linked to homocysteine increase and neuropathy; high B6 associated with direct neurotoxicity (neuropathy)
Authors' conclusions	Abnormal vitamin B6 levels are common in PwPD and may contribute to preventable neurological complications; monitoring and management recommended
Authors' acknowledged limitations	Heterogeneous studies, small sample sizes, mostly observational data, limited ability to establish causality, outcome data incomplete

Contextual information for the AU/NZ UL review

Generalisability to AU/NZ	Moderate–low; specific to Parkinson's population with medication interactions; however, provides strong mechanistic and clinical evidence that both low and high B6 can cause neuropathy.

E.1.11 Morris et al., 2025

Study identification and design

Field	Extracted information
Citation	Morris, A. A. M., Sokolová, J., Pavlíková, M., Gleich, F., Kölker, S., Dionisi-Vici, C., Baumgartner, M. R., Hannibal, L., Blom, H. J., Huemer, M., Kožich, V., & E-HOD Consortium. (2025). Cystathionine β-synthase deficiency in the E-HOD Registry—Part II: Dietary and pharmacological treatment. *Journal of Inherited Metabolic Disease, 48*, e12844.
Publication status	Published, peer-reviewed article (open access, Wiley)
Country / setting	International registry (E-HOD consortium; ~70 centres worldwide)
Study design	Registry-based observational cohort study (retrospective analysis of prospective registry data)
Funding / conflicts of interest	Funded by Czech Ministry of Health and institutional support; some industry support but authors state independence

Population

Field	Extracted information
Sample size	311 patients (834 visits analysed)
Patient characteristics	Individuals with cystathionine β-synthase (CBS) deficiency (classical homocystinuria); includes varying phenotypes (non-responders, partial responders, responders to pyridoxine)
Inclusion/exclusion of alternative causes	Registry includes confirmed CBS deficiency; data cleaned and visits excluded if incomplete or not representative of treatment

Exposure

Field	Extracted information
Exposure characterisation – source	Pyridoxine (vitamin B6) treatment (as therapy), often combined with diet and/or betaine
Exposure characterisation – dose	Wide range; median ~3.8 mg/kg/day overall; some patients received very high doses (>500 mg/day or >10 mg/kg/day), with some >900 mg/day
Biomarker of exposure	Plasma total homocysteine (tHcy) used to assess treatment response; methionine levels also monitored

Field	Extracted information
Duration of exposure	Long-term treatment across multiple clinic visits (chronic exposure)

Outcomes

Field	Extracted information
Primary outcomes	• Treatment effectiveness (homocysteine reduction) and clinical outcomes (thromboembolism, lens dislocation) • Peripheral neuropathy risk from high-dose pyridoxine
Outcome assessment – clinical examination	Clinical complications (thrombosis, lens dislocation, neurological effects)
Outcome assessment – objective testing	Plasma homocysteine, methionine concentrations
Outcome assessment – tools used	Registry data, biochemical assays, clinical event tracking
Response to Withdrawal	NA

Results and Conclusions

Field	Extracted information
Main results (efficacy)	Pyridoxine responders achieved good biochemical control (tHcy <50 µmol/L); non-responders often required diet/betaine but many failed to reach targets
Main Results (clinical)	Early treatment reduced risk of thromboembolism (RR ~0.073) and lens dislocation (RR ~0.069)
Main Results (toxicity)	High-dose pyridoxine associated with risk of peripheral neuropathy, particularly:
Risk threshold	High risk above ~900 mg/day
Guideline safe upper range	≤500 mg/day or ≤10 mg/kg/day
Real-world finding	Some patients exceeded safe limits (including >900 mg/day)
Authors' conclusions	Treatment improves outcomes but excessive pyridoxine dosing occurs in practice and may cause harm (neuropathy risk); lowest effective dose should be used
Authors' acknowledged limitations	Registry data variability, incomplete data, inability to confirm compliance or causality

Contextual information for the AU/NZ UL review

Generalisability to AU/NZ	Limited for intake modelling (rare disease + therapeutic dosing), but highly relevant for upper limit hazard identification due to documented high-dose toxicity

E.1.12 Muhamad et al., 2023

Study identification and design

Field	Extracted information
Citation	Muhamad, R., Akrivaki, A., Papagiannopoulou, G., Zavridis, P., & Zis, P. (2023). The role of vitamin B6 in peripheral neuropathy: A systematic review. *Nutrients, 15*, 2823.
Publication status	Published, peer-reviewed systematic review (MDPI; open access)
Country / setting	International (literature-based review)
Study design	**Systematic review (PRISMA-based; 20 included studies)**
Funding / conflicts of interest	No external funding; no conflicts declared

Population

Field	Extracted information
Sample size	20 studies included (multiple populations; total participants vary across studies)
Patient characteristics	Mixed populations: general adults, Parkinson's disease, diabetes, dialysis patients, tuberculosis patients, and others with peripheral neuropathy (PN)
Inclusion/exclusion of alternative causes	Excluded non-human studies, case reports <5 participants, low-quality trials; attempted to isolate B6-related neuropathy but confounding often present

Exposure

Field	Extracted information
Exposure characterisation – source	Vitamin B6 (pyridoxine, pyridoxal, pyridoxamine); both deficiency and excess
Exposure characterisation – dose	Highly variable across studies:
Dietary intake	~1.6–2 mg/day recommended intake
Supplement doses	From ~25 mg/day up to grams per day (toxicity cases)
Biomarker of exposure	Plasma pyridoxal phosphate (PLP) levels
Exposure patterns identified	

Field	Extracted information
Low B6	observed in some PN populations
High B6	typically due to supplementation; associated with toxicity
Duration of Exposure	Lack of information- duration was generally a limitation of studies reviewed. Studies which had duration recorded ranged from 4 to 24 weeks

Outcomes

Field	Extracted information
Primary outcome	Peripheral neuropathy (PN)
Types of neuropathy	Predominantly sensory, axonal neuropathy with high B6 exposure
Outcome assessment – clinical examination	Symptoms (pain, paresthesia, weakness), neurological examination
Outcome assessment – objective testing	Nerve conduction studies (NCS), biopsies, questionnaires, sensory testing
Outcome assessment – tools used	Mixed tools, including the Brief Peripheral Neuropathy Screen, nerve conduction studies, quantitative sensory testing and the Neuropathy Total Symptom Score-6.
Response to withdrawal	Systematic Review did not focus on change of B6 exposure

Results and Conclusions

Field	Extracted information
Main results – high B6	Strong evidence that high vitamin B6 levels (usually from supplements) cause peripheral neuropathy, particularly sensory axonal neuropathy
Reversibility	Symptoms often improve after stopping B6 exposure
Main results – low B6	Low B6 commonly observed in PN patients, but no clear causal relationship established
Dose-response evidence	Higher doses associated with increased PN risk (e.g., higher supplementation results in higher risk in some studies)
Authors' conclusions	
High B6	neurotoxic and linked to neuropathy

Field	Extracted information
Low B6	association unclear, not proven causal
Supplementation	safe at recommended doses, but excessive intake harmful
Authors' acknowledged limitations	Heterogeneous data, small sample sizes, confounding factors, limited dose information

Contextual information for the AU/NZ UL review

Generalisability to AU/NZ	Moderate; includes general populations and supplement use, relevant for public health risk assessment

E.1.13 Sano et al. 2022

Study identification and design

Field	Extracted information
Citation	Sano T, Masuda Y, Yasuno H, Shinozawa T, Watanabe T, Kakehi M. Blood neurofilament light chain as a potential biomarker for central and peripheral nervous toxicity in rats. *Toxicological Sciences* 185(1):10–18, 2022. Advance Access 22 October 2021. https://doi.org/10.1093/toxsci/kfab122
Publication status	Published, peer-reviewed journal article (Open Access)
Country / setting	Japan; nonclinical (preclinical) animal laboratory study conducted at Shonan Health Innovation Park (animal work by Axcelead Drug Discovery Partners Inc.)
Study design	Controlled experimental animal study in Sprague Dawley rats using multiple neurotoxicant models (TMT, KA, MK-801 as CNS toxicants; pyridoxine as PNS toxicant), with sacrifice at multiple time points (days 2, 4, 8)
Funding / conflicts of interest	Funded internally by Takeda Pharmaceutical Company Limited. All authors are employees of Takeda Pharmaceutical Company. No external funding declared.

Population

Field	Extracted information
Sample size	48 male Sprague Dawley rats total; allocated to 12 groups of n=4 per group
Patient (test animal) characteristics	Male Sprague Dawley rats (Charles River Laboratories Japan), body weight 207–260 g at study start; selected using standardised normal values based on body weight

Inclusion/exclusion of alternative causes	Not applicable (controlled experimental design). Animals individually housed under standardised conditions (20–26°C, 40–70% humidity, 12-h light/dark cycle, ad libitum diet and water). Spontaneous focal necrosis noted in one pyridoxine animal (day 2) and noted as incidental finding.

Exposure

Field	Extracted information
Exposure characterisation – source	Four neurotoxicant compounds: (1) Trimethyltin (TMT; Tokyo Chemical Industry Co.); (2) Kainic acid (KA; FUJIFILM Wako Pure Chemical); (3) MK-801 (FUJIFILM Wako Pure Chemical); (4) Pyridoxine (Sigma-Aldrich Japan)
Exposure characterisation – dose	TMT: 10 mg/kg oral gavage, single dose; KA: 12 mg/kg subcutaneous, single dose; MK-801: 1 mg/kg subcutaneous, single dose; Pyridoxine: 1200 mg/kg/day (600 mg/kg BID) for 3 days
Biomarker of exposure	Not applicable (neurotoxicant exposure model, not an exposure biomarker study). Outcome biomarker measured: neurofilament light chain (NfL) in serum and erebrospinal fluid (CSF), measured by Simoa SR-X analyser (Quanterix, Simoa NF-light Advantage SR-X Kit)
Duration of exposure	TMT, KA, MK-801: single administration; Pyridoxine: 3 days (BID dosing). Observation/sacrifice at 1 day (day 2), 3 days (day 4), or 7 days (day 8) after first dose

Outcomes

Field	Extracted information
Primary outcome	Serum and CSF NfL levels as biomarkers of CNS and PNS neurotoxicity; correlation between NfL levels and histopathological evidence of neuronal damage
Outcome assessment	Daily clinical signs observation; body weight measured on days 2, 4, and 8; neurological signs recorded (convulsions, tremor, twitch, irritability, wet dog shake, locomotor activity, gait)
Outcome assessment – objective testing	Serum and CSF NfL measured by Simoa (single-molecule array technology); brain and spinal cord histopathology (H&E staining); Fluoro-Jade C staining (neuronal cell death marker); immunohistochemistry (anti-GFAP, anti-Iba1 antibodies for gliosis characterisation)

Outcome assessment – tools used	Simoa SR-X analyser with NF-light Advantage Kit; Leica Bond-Rx autostainer (IHC); H&E staining; FJ-C staining; SAS v9.3 for statistical analysis; Pearson's correlation coefficient for CSF-serum NfL correlation; Student's t-test or Aspin-Welch t-test for group comparisons
Response to withdrawal	Not assessed (no withdrawal phase; animals sacrificed at designated time points)

Results and Conclusions

Field	Extracted information
Main results	Neurofilament light chain levels increased in serum and cerebrospinal fluid after neurotoxic injury to the central and peripheral nervous systems. Pyridoxine caused damage to dorsal root ganglia and nerve fibres, with clear increases in neurofilament light chain, especially by day 4. Serum and cerebrospinal fluid levels were strongly correlated, and the biomarker performed similarly to histopathology in detecting nerve damage.
Authors' conclusions	Serum neurofilament light chain may be a useful blood biomarker for detecting neurotoxicity in rats. It reflected both brain and peripheral nerve injury and may help identify neurotoxicity risks during nonclinical drug development.
Authors' acknowledged limitations	The study used severe neurotoxicity models, so further work is needed with milder effects. It was not clear whether neurofilament light chain can detect damage before obvious tissue injury occurs. Some early increases were not fully explained, and group sizes were small, with four animals per group.

Contextual information for the AU/NZ UL review

Generalisability to AU/NZ	Animal study is relevant. However, the dose used was far above dietary or therapeutic exposure levels, and the acute/subacute animal model is not directly applicable to human AU/NZ UL risk assessment without dose conversion and careful extrapolation.

E.1.14 Schellack et al. 2025

Study identification and design

Field	Extracted information
Citation	Schellack N, Yotsombut K, Sabet A, Nafach J, Hiew FL, Kulkantrakorn K. Expert consensus on vitamin B6 therapeutic use for patients: guidance on safe dosage, duration and clinical management. *Drug, Healthcare and Patient Safety* 2025;17:97–108. https://doi.org/10.2147/DHPS.S499941
Publication status	Published, peer-reviewed open-access journal article (received October 2024, accepted March 2025, published April 2025)

Country / setting	International; expert panel from 5 countries (Australia, Malaysia, Thailand, UAE, South Africa). **Clinical guidance document, not a primary study**
Study design	Expert consensus statement using a modified two-round Delphi approach, including targeted literature review (58 articles), two anonymous online surveys, and a virtual expert roundtable. GRADE used to assess evidence quality
Funding / conflicts of interest	Funded by P&G Health, Singapore. No conflict of interest.

Population

Field	Extracted information
Sample size	No patient sample
Patient (test animal) characteristics	Guidance applies to adult patients indicated for vitamin B6 therapy. Explicitly excludes children, pregnant women, and lactating women.
Inclusion/exclusion of alternative causes	Not applicable (consensus/guidance document)

Exposure

Field	Extracted information
Exposure characterisation – source	Vitamin B6 (pyridoxine) - oral therapeutic supplementation and/or dietary intake
Exposure characterisation – dose	Consensus tolerable (maximum) doses for peripheral neuropathy patients: 50 mg/day (long-term possible); 100 mg/day (up to 5 years); 200 mg/day (up to 200 days); up to 600 mg/day (up to 18 weeks). RDA for adults: 1.3–1.7 mg/day. Note: PN risk reported even at 50–100 mg/day in susceptible individuals
Biomarker of exposure	Plasma pyridoxine, PLP (reference: 5–50 mcg/L), and pyridoxic acid (reference: 3–30 mcg/L); serum pyridoxine (reference: 51–183 nmol/L). Fasting ≥12 hours required before sampling
Duration of exposure	Varies by dose (see above); monitoring recommended for use >6 months at >50 mg/day

Outcomes

Field	Extracted information
Primary outcome	Peripheral neuropathy and other neurological adverse effects from high-dose/long-term vitamin B6; guidance on safe dosing and monitoring
Outcome assessment	Neurological examination (numbness, tingling, weakness in extremities); clinical signs of deficiency (seborrhoea, glossitis, anaemia)

Outcome assessment – objective testing	Blood tests for pyridoxine, PLP, pyridoxic acid levels; complete blood count; metabolic panels for haematological/hepatic monitoring
Outcome assessment – tools used	Clinical judgement, history-taking of B6 intake, periodic laboratory testing; GRADE framework for evidence assessment
Response to withdrawal	Adverse effects generally reversible on cessation when detected early. Recovery reported at 3 months to 2 years depending on dose and duration. Panel recommends washout of 20–40 days (3–6 weeks) before considering resuming; up to 3–6 months for prolonged symptoms. Calculated based on PLP half-life (36–95 hours) using 10× half-life approach

Results and Conclusions

Field	Extracted information
Main results	Five consensus statements endorsed: • vitamin B6 essential for neurotransmitter synthesis (strength of recommendation 9.8/10); • deficiency causes peripheral neuropathy, anaemia, seizures, etc. (strength of recommendation 9.2/10); • no clear dose/duration guidelines established; tolerable maximum doses proposed (strength of recommendation 8.3/10); • neurological adverse events rare but reported at high doses/long-term use, reversible if caught early (strength of recommendation 9.2/10); • monitoring recommended for >6 months/>50 mg/day use; washout of 20–40 days proposed (strength of recommendation 7.3/10)
Authors' conclusions	Vitamin B6 has important therapeutic uses but carries risk of neurological adverse effects at high doses with long-term use. Individualised dosing, monitoring, and early detection are key. A washout period of 20–40 days is recommended upon development of side effects. Further large-scale controlled trials are needed.
Authors' acknowledged limitations	Inconclusive data on well-tolerated dose/duration; limited post-marketing surveillance detail; guidance applies to adults only (not children, pregnant/lactating women); small expert panel size; evidence base largely low quality (lack of RCTs).

Contextual information for the AU/NZ UL review

Generalisability to AU/NZ	Directly relevant.

E.1.15 Stewart et al. 2022

Study identification and design

Field	Extracted information
Citation	Stewart SL, Thomas S, Höke E, Simpson D, Singleton JR, Höke A. Vitamin B6 levels do not correlate with severity of neuropathy in chronic idiopathic axonal polyneuropathy. *J Peripher Nerv Syst.* 2022;27(1):31–37. doi:10.1111/jns.12480
Publication status	Published, peer-reviewed journal article (received/revised/accepted December 2021)
Country / setting	USA; three academic neurology centres (Johns Hopkins, Mount Sinai, University of Utah). Cross-sectional analysis of a prospective registry
Study design	Cross-sectional observational study using data from the Peripheral Neuropathy Research Registry (PNRR), a multicentre prospective cohort
Funding / conflicts of interest	Funded by the Foundation for Peripheral Neuropathy (FPN). Senior author (A. Höke) chairs the FPN Scientific Advisory Board but FPN had no role in study conduct or writing. No other conflicts declared.

Population

Field	Extracted information
Sample size	261 Chronic idiopathic axonal polyneuropathy (CIAP) patients with complete dataset including plasma B6 value, enrolled prior to December 2020
Patient (test animal) characteristics	Mean age 61.2 years (±13.6); 56% male; 93% white; mean neuropathy duration 5.8 years; 74.7% had painful PN. Mean plasma B6 57.7 microgram/L. 67.8% had normal B6 (5–50 microgram /L), 32.2% elevated (>50 microgram /L)
Inclusion/exclusion of alternative causes	Inclusion: confirmed CIAP diagnosis; negative testing for other common PN aetiologies; plasma B6 value available within 3 years of enrolment. Exclusion: B6 deficiency (0–4.9 microgram/L); incomplete dataset

Exposure

Field	Extracted information
Exposure characterisation – source	Plasma vitamin B6 level (from dietary intake and/or supplementation: B6 supplements, B-complex, or multivitamins). Exact dose and duration of supplementation not recorded for all patients.

Field	Extracted information
Exposure characterisation – dose	Categorised as normal (5–50 microgram/L), mildly elevated (50–99.9 microgram/L), elevated (100–199.9 microgram/L), very elevated (200–299.9 microgram/L), extremely elevated (≥300 microgram/L; n=6, too small for analysis). Those taking B6 supplements had mean plasma level 115.4 microgram/L vs 54.7 microgram/L in non-supplement takers.
Biomarker of exposure	Plasma PLP (normal 5–50 mcg/L) or total pyridoxine (normal 3–30 mcg/L), per Mayo Clinic reference ranges.
Duration of exposure	Not systematically recorded; cross-sectional single plasma measurement used as proxy for cumulative exposure.

Outcomes

Field	Extracted information
Primary outcome	Relationship between elevated plasma B6 level and neuropathy severity in CIAP patients.
Outcome assessment	Neurological exam: muscle strength (finger, ankle, toe), deep tendon reflexes, vibration sense (Rydel fork), joint position sense, gait, Romberg test.
Outcome assessment – objective testing	Nerve conduction studies (peroneal motor, sural sensory - velocity and amplitude); intra-epidermal nerve fibre density (IENFD) by skin biopsy (Johns Hopkins patients only); TNSr score.
Outcome assessment – tools used	Total Neuropathy Score-reduced (TNSr); NCS; IENFD; patient-reported questionnaire (pain intensity 0–10, numbness, paresthesia type); logistic regression and chi-square analyses adjusted for age and neuropathy duration; STATA
Response to withdrawal	Not assessed (cross-sectional design; no intervention or withdrawal).

Results and Conclusions

Field	Extracted information
Main results	Elevated plasma vitamin B6 was not associated with worse neuropathy signs or symptoms. There were no meaningful differences in clinical scores, vibration sense, reflexes, strength, gait, skin biopsy findings, nerve conduction studies, pain, or numbness between patients with normal and elevated vitamin B6 levels. People taking vitamin B6 supplements had higher plasma levels, but not worse symptoms. Very high levels were uncommon, with only 2.3% of patients having plasma vitamin B6 ≥300 microgram/L.

Field	Extracted information
Authors' conclusions	Moderately elevated plasma vitamin B6, including levels of 100–200 microgram/L, was not linked to worse neuropathy in patients with chronic idiopathic axonal polyneuropathy. Standard vitamin B6 supplementation did not appear to have a major harmful effect, although the study could not assess whether stopping supplements would improve symptoms.
Authors' acknowledged limitations	The study could not assess symptoms before, during and after supplementation. Vitamin B6 results were only available for a subset of registry patients, which may have introduced bias. Supplement dose and duration were not available for all patients. Plasma vitamin B6 was used as a proxy for intake, and very high vitamin B6 levels were too uncommon for meaningful analysis.

Contextual information for the AU/NZ UL review

Generalisability to AU/NZ	US-based study; population were dominantly white (93%); findings are relevant to the Australian context regrading the supplement consumption and dose ranges.

E.1.16 Stolwijk et al 2025

Study identification and design

Field	Extracted information
Citation	Stolwijk NN, van Dussen L, Reijnhout ND, Brands MMMG, Jaeger B, Clayton PT, Hollak CEM, Bosch AM. Effectiveness of pyridoxal-5′-phosphate in PNPO deficiency: a systematic review. *J Inherit Metab Dis.* 2025;48:e70074. https://doi.org/10.1002/jimd.70074
Publication status	Published, peer-reviewed open-access journal article (received May 2025, accepted July 2025)
Country / setting	Netherlands/international; systematic review of published case reports and case series. PROSPERO registered (CRD42024542199). Search conducted April 2024
Study design	**Systematic review (PRISMA) with narrative synthesis; 30 included studies, all case reports or case series. Risk of bias assessed using Murad et al. tool**
Funding / conflicts of interest	Funded by Postcodeloterij (Dutch postcode lottery) via the Medicines for Society platform. Three authors are members of Medicines for Society, which advocates for PLP access. One author (CEMH) chairs that platform. One author (NDR) previously held a position at IQVIA. No other conflicts declared.

Population

Field	Extracted information
Sample size	49 patients with Pyridox(am)ine 5′-phosphate oxidase (PNPO) deficiency treated with pyridoxal-5′-phosphate (PLP) across 30 studies.
Patient (test animal) characteristics	Predominantly male (70.2%, n=33/47). Mostly neonatal onset: median seizure onset day 1 of life (range 0.5 hours to 17 months). Median age at last follow-up 3 years (range 48 days to 21 years). Mean PLP use duration 3 years (range 6 days to 11 years). 45/49 had biallelic PNPO variants confirmed.
Inclusion/exclusion of alternative causes	Included: PNPO deficiency patients treated with PLP with efficacy/safety data reported; single heterozygous PNPO variant cases included. Excluded: patients with B6-responsive epilepsy but negative PNPO sequencing; non-English publications; conference abstracts; studies published before 2005.

Exposure

Field	Extracted information
Exposure characterisation – source	Pyridoxal-5′-phosphate (PLP), the active form of vitamin B6, administered therapeutically for seizure control in PNPO deficiency. PLP is not authorised as a medicinal product; patients rely on food supplements
Exposure characterisation – dose	Median PLP dose in responsive patients: 35.5 mg/kg/day (range 10–74 mg/kg/day). Cirrhosis cases required 50–100 mg/kg/day. One PLP intoxication occurred at 74 mg/kg/day due to supplement mislabelling.
Biomarker of exposure	Plasma B6 vitamer profiles (LC-MS/MS) noted as a potential monitoring tool, but validated reference ranges not yet established for clinical use.
Duration of exposure	Mean 3 years (range 6 days to 11 years); most hepatotoxicity cases had >1 year of PLP therapy

Outcomes

Field	Extracted information
Primary outcome	Clinical seizure responsiveness to PLP therapy; survival; safety/adverse events.
Outcome assessment	Seizure frequency and type (neurological assessment); developmental outcomes (categorised by reporting authors as normal, minor/moderate delay, severe delay).
Outcome assessment – objective testing	EEG; liver function tests (transaminases); liver biopsy (for cirrhosis confirmation in 2 cases); Kaplan–Meier survival analysis comparing PLP-treated patients vs untreated siblings.
Outcome assessment – tools used	5-point seizure response scale (no response, complete cessation, improvement, stabilisation, worsening); CTCAE v5.0 for adverse event scoring; Kaplan–Meier/log-rank test for survival.

Response to withdrawal	Challenge–rechallenge documented in 7 patients: seizure recurrence following PLP withdrawal, with control regained on reintroduction. Seizure recurrence also noted at end of dosing intervals or after single missed doses.

Results and Conclusions

Field	Extracted information
Main results	Most patients with pyridoxamine 5'-phosphate oxidase deficiency responded to pyridoxal 5'-phosphate treatment, with improved seizure control and survival compared with untreated siblings. Pyridoxine was usually ineffective. Some patients had normal neurodevelopment, but developmental delay remained common. Adverse effects occurred in about one-third of patients, mainly liver toxicity after long-term treatment.
Authors' conclusions	Pyridoxal 5'-phosphate is the main effective treatment for most patients with this condition, but the safe dose range is narrow. Long-term or high-dose use may cause liver toxicity, so regular liver monitoring is recommended. The authors also noted the need for an authorised, high-quality pyridoxal 5'-phosphate medicine to improve dosing accuracy and safety monitoring.
Authors' acknowledged limitations	The evidence was based on small case reports and case series, with variable risk of bias. Dosing, treatment timing and follow-up were incomplete for some patients. Developmental outcomes may have been affected by prior seizures and birth complications. Follow-up may have been too short to detect long-term adverse effects, and serious adverse events may have been underreported.

Contextual information for the AU/NZ UL review

Generalisability to AU/NZ	Relevant – provides mechanistic context. it demonstrates that high-dose PLP (the active form of B6) can cause hepatotoxicity, and that the dose-toxicity relationship for B6 vitamers in a therapeutic context is real and clinically significant.

E.1.17 Sun et al. 2025

Study identification and design

Field	Extracted information
Citation	Sun Y, Yu X, Teng Y, Sun Y. Toxic effects of excess vitamins A, B6, and folic acid on the nervous system. *Behavioural Neurology.* 2025;2025:7888243. https://doi.org/10.1155/bn/7888243
Publication status	Published, peer-reviewed open-access journal article (received January 2025, accepted July 2025)
Country / setting	**China (Qingdao); narrative review article, no primary data**

Study design	Narrative review of the toxic neurological effects of excess vitamins A, B6, and folic acid. The B6 section summarises mechanistic hypotheses and clinical case literature
Funding / conflicts of interest	None.

Population

Field	Extracted information
Sample size	Not applicable — review article. Draws on multiple published case reports and studies (no systematic search reported).
Patient (test animal) characteristics	Various - review covers general healthy adults, pregnant/breastfeeding women, neonates, elderly, and animal models. Specific cases cited include neonates, a 54-year-old male, a 92-year-old female, and an adult multivitamin user.
Inclusion/exclusion of alternative causes	Not applicable - narrative review with no formal inclusion/exclusion criteria reported.

Exposure

Field	Extracted information
Exposure characterisation – source	Vitamin B6 (predominantly pyridoxine/PN) via dietary supplements; also food sources. Review notes pyridoxine (PN) is the inactive form most common in supplements.
Exposure characterisation – dose	Range discussed: as low as 6 mg/day (single case report of neuropathy after 10 years); IoM UL 100 mg/day; EFSA UL 12 mg/day (2023). Higher doses (>1000 mg/day) historically associated with sensory neuropathy; 960 mg/day associated with sensorimotor neuropathy.
Biomarker of exposure	Not discussed for B6 specifically.
Duration of exposure	Ranges from long-term chronic use (10 years at low dose) to shorter-term high-dose exposure; duration noted as a modifying factor alongside dose.

Outcomes

Field	Extracted information
Primary outcome	Neurological adverse effects of excessive vitamin B6 intake, particularly peripheral neuropathy.
Outcome assessment	Sensory neuropathy (ataxia, sensory dysfunction, stocking-glove paresthesia); motor neuropathy (first reported 1993); gait abnormalities; tremor in neonate; sensory ganglionopathy; autonomic neuropathy; demyelinating features.

Outcome assessment – objective testing	Electrophysiologic studies cited (nerve conduction) in individual cases; no systematic objective testing across the review.
Outcome assessment – tools used	Narrative synthesis of case reports and existing literature; no formal rating tools applied.
Response to withdrawal	Condition generally improves after stopping high-dose B6 but may continue to worsen for 2–3 weeks after cessation; some patients have persistent sensory deficits (possibly dose-related). Neonatal tremor and canine neuropathy noted as reversible.

Results and Conclusions

Field	Extracted information
Main results	Excess B6 (mainly as PN) causes peripheral neuropathy; sensory neuropathy predominates, with motor and autonomic involvement at higher doses. Two main mechanistic hypotheses: (1) PN accumulation competitively inhibits PLP-dependent enzymes, producing a functional B6 deficiency-like state; (2) PDXK inhibition disrupts GABA neurotransmission and peripheral sensory neurons. Accumulation of neurotoxic 3-hydroxykynurenine also proposed. Individual variation in B6 metabolism is significant - toxicity can occur at doses well below the IoM UL (e.g. 6 mg/day over 10 years).
Authors' conclusions	No clear consensus on the toxic exposure threshold for B6; EFSA's 12 mg/day UL is recommended for generally healthy adults. Particular care needed for pregnant/breastfeeding women and those with metabolic disorders. Long-term supplementation should be medically monitored; supplementation should cease if neurological symptoms emerge. More long-term, large-sample clinical studies needed to confirm precise safe intake thresholds.
Authors' acknowledged limitations	Narrative review only; no systematic search or quality assessment of included evidence. Mechanistic hypotheses for B6 toxicity remain unconfirmed. Dose–response relationship for individual susceptibility is unclear. No formal assessment of evidence quality.

Contextual information for the AU/NZ UL review

Generalisability to AU/NZ	Relevant as a narrative summary of the current mechanistic and clinical evidence base for B6 neurotoxicity.

E.1.18 Theil et al. 2023

Study identification and design

Field	Extracted information

Citation	Theil D, Kuhle J, Brees D, Tritto E, Pognan F, Frieauff W, Penraat K, Meseck E, Valdez R, Hartmann A. Neurofilament light chain: a translational safety biomarker for drug-induced peripheral neurotoxicity. *Toxicol Pathol.* 2023;51(3):135–147. https://doi.org/10.1177/01926233231180179
Publication status	Published, peer-reviewed journal article
Country / setting	Switzerland/USA; preclinical (non-clinical) animal study in juvenile beagle dogs conducted at Charles River Laboratories (Senneville, Canada)
Study design	Controlled 30-week investigative study in juvenile male beagle dogs. Three treatment groups (vehicle, pyridoxine positive control, branaplam) assessed for neuropathology, morphometry, electrophysiology, gene expression, and serum/CSF NfL levels
Funding / conflicts of interest	Funded by Novartis. Multiple authors are Novartis employees or former employees and hold/held stock options. Author Kuhle is a Novartis consultant. Novartis holds patent rights to branaplam.

Population

Field	Extracted information
Sample size	Juvenile male beagle dogs; n=16 per branaplam group, n=8 pyridoxine group, n=16 vehicle group (approximate, based on necropsy allocations of n=4 per time point).
Patient (test animal) characteristics	Male juvenile beagles, 14–17 weeks old at dosing start, weight 4.1–6.9 kg; acclimatised 5 weeks prior to dosing; group-housed.
Inclusion/exclusion of alternative causes	Controlled experimental design; vehicle group served as negative control. CSF not sampled at baseline to avoid lumbar puncture-induced artefactual NfL elevation

Exposure

Field	Extracted information
Exposure characterisation – source	Pyridoxine (positive control; Sigma-Aldrich) administered by daily oral gavage; branaplam (investigational drug, Novartis) by daily oral gavage
Exposure characterisation – dose	Pyridoxine: escalating doses up to 100–150 mg/kg/day for weeks 1–5, then 2-week drug-free period, then 50 mg/kg/day from week 8 to end of week 13, then discontinued. Branaplam: 2 mg/kg/day weeks 1–5, then reduced to 1 mg/kg/day weeks 8–30 (continuous) or intermittent cycles
Biomarker of exposure	Serum NfL and CSF NfL measured by Simoa platform (UmanDiagnostics NF-light assay). Elevated defined as >40 pg/mL (serum) and >650 pg/mL (CSF)
Duration of exposure	Pyridoxine: up to ~13 weeks total dosing (with interruptions); 17-week recovery period to week 30. Branaplam: up to 30 weeks. Necropsies at weeks 13, 17, 21, and 30

Outcomes

Field	Extracted information
Primary outcome	Utility of serum NfL as a biomarker for drug-induced peripheral neurotoxicity; correlation of NfL with histopathological and morphometric nerve damage.
Outcome assessment	Twice-daily health checks; neurological examinations at weeks 7, 15, 21, 30 (general attitude, motor function, postural reactions, cranial/spinal nerve function); body weight and food consumption.
Outcome assessment – objective testing	Nerve conduction velocity (NCV) and compound action potential amplitude (peroneal motor, sural sensory) at weeks 7, 15, 21; cauda equina latency; histopathology (H&E, toluidine blue on semi-thin sections); morphometry (g-ratio, axon size, myelin size, myelinated fibre density) of sural and ulnar nerves; gene expression profiling (GeneChip microarray, sciatic/sural nerves and DRG)
Outcome assessment – tools used	Simoa platform for NfL; Aperio scanner and ImageScope for morphometry; INHAND/STP nomenclature for histopathology severity grading; Pearson correlation for gene signature construction.
Response to withdrawal	Pyridoxine: neurological signs (ataxia) and NCV deficits reversed by weeks 21–30 after cessation at week 13. Serum NfL returned to normal by week 11 (after last high-dose week 5). Histopathological nerve fiber degeneration reduced at week 30 recovery compared with week 13.

Results and Conclusions

Field	Extracted information
Main results	Pyridoxine (100–150 mg/kg/day) produced DRG and peripheral nerve axonal degeneration, clinical ataxia, significant NCV slowing (sural sensory NCV ~38% decrease at week 7), and serum NfL 10- to 450-fold above vehicle at week 5. NfL normalised by week 11. Branaplam caused mild-to-moderate peripheral nerve fibre degeneration without clinical or electrophysiological signs, with serum NfL 2- to 20-fold above vehicle from week 11 onward. Moderate severity nerve fibre degeneration always correlated with elevated serum NfL; minimal degeneration did not consistently elevate NfL. CSF NfL was more sensitive for CNS/spinal cord lesions; serum NfL correlated better with peripheral nerve lesions. Gene expression profiling corroborated histopathological differences between the two compounds.
Authors' conclusions	Serum NfL is a sensitive, non-invasive biomarker capable of detecting PNS neurotoxicity including subclinical damage without clinical or electrophysiological signs in dogs. Pyridoxine served as an effective positive control. NfL monitoring has potential utility in both preclinical and clinical neurotoxicity assessment.

Field	Extracted information
Authors' acknowledged limitations	Small group sizes precluded formal statistical comparisons; CSF baseline samples not collected (to avoid puncture artefact); pyridoxine GEP analysis was likely too far from peak toxicity time point for full transcriptional characterisation; NfL elevation without histopathological correlate may reflect sampling limitations of thin-section microscopy rather than absence of lesion.

Contextual information for the AU/NZ UL review

Generalisability to AU/NZ	Preclinical dog study; not directly applicable to setting a population-level human dietary UL for vitamin B6. However, the pyridoxine arm provides useful mechanistic and dose–response context: 100–150 mg/kg/day in dogs produced rapid, marked axonal degeneration with clinical and electrophysiological signs, and serum NfL elevations up to 450-fold. The dose is far higher than human supplemental intake but the study characterises the neuropathological distribution pattern of pyridoxine toxicity (DRG-predominant, long myelinated fibre degeneration) consistent with the human sensory neuropathy/neuronopathy phenotype. The partial reversibility after cessation (improved NCV and histopathology at week 30) aligns with human clinical data on recovery.

E.1.19 vanHunsel et al. 2025

Study identification and design

Field	Extracted information
Citation	van Hunsel F, Scholl J, Vrolijk M, Ekhart C. Impact of regulatory action on dose maximalization for vitamin B6 dietary supplements on the reporting pattern for neuropathy. *Pharmacoepidemiol Drug Saf.* 2025;34:e70108. https://doi.org/10.1002/pds.70108
Publication status	Published, peer-reviewed open-access brief report (received March 2024, accepted January 2025)
Country / setting	Netherlands; pharmacovigilance analysis of the Dutch Spontaneous Reporting System (SRS) held by Lareb, covering August 2007 to December 2023.
Study design	Retrospective descriptive analysis of spontaneous adverse drug reaction (ADR) reports with changepoint analysis of reporting trends over time, before and after a 2018 regulatory dose restriction.
Funding / conflicts of interest	None.

Population

Field	Extracted information

Sample size	224 reports of neuropathy associated with vitamin B6 supplements
Patient (test animal) characteristics	75.4% female, 24.6% male. Mean age 52 years (median 53, range 3–92 years). Reporters included consumers/patients and healthcare professionals. Over 90 cases reported concomitant medication use. Potential alternative causes noted in a small number of cases (diabetes n=2, alcohol abuse n=1, Lyme disease n=1, radiotherapy n=1, pre-existing small fibre neuropathy n=1)
Inclusion/exclusion of alternative causes	Reports selected using MedDRA SMQ (Broad) "peripheral neuropathy" and vitamin B6 product coding. Full individual causality assessment was out of scope; alternative causes not systematically excluded.

Exposure

Field	Extracted information
Exposure characterisation – source	Dietary supplements containing vitamin B6, not registered medicines. Products varied in vitamer type (not always documented in reports).
Exposure characterisation – dose	Daily doses ranged widely; most pre-2018 reports involved higher doses. After the October 2018 regulatory action (max 21 mg/day in the Netherlands), only one report mentioned a dose substantially above this limit (200 mg/day, reported 2020).
Biomarker of exposure	Plasma vitamin B6 levels recorded in a subset of reports. Only 15% of variance in plasma levels explained by daily dose ($R^2 = 0.15$), indicating weak dose–plasma level correlation.
Duration of exposure	Duration of use not always recorded and not included in the trend analysis; noted as a limitation.

Outcomes

Field	Extracted information
Primary outcome	Reporting pattern of neuropathy adverse drug reactions (ADRs) associated with vitamin B6 supplements before and after the 2018 Dutch regulatory dose restriction.
Outcome assessment	Not applicable — spontaneous reports; neuropathy symptoms as reported by patients/HCPs, coded using MedDRA.
Outcome assessment – objective testing	Plasma vitamin B6 levels reported in a subset of cases (no standardised testing protocol).
Outcome assessment – tools used	Changepoint analysis (PELT method, cpt.mean, R v4.3.2); linear trend analysis; coefficient of determination (R^2) for dose–plasma level correlation; MedDRA coding
Response to withdrawal	Not formally assessed in this analysis.

Results and Conclusions

Field	Extracted information
Main results	224 reports included (2007–2023). After October 2018 dose restriction (max 21 mg/day), reported daily doses dropped markedly — only one post-2018 report mentioned a dose above the limit. Twelve changepoints identified in the reporting pattern, notably around 2018 (reflecting both the regulatory action and media attention). From the second half of 2019, report numbers per time period were lower with no further changepoints. Only 15% of plasma level variance explained by daily dose (weak correlation). Some cases of neuropathy at lower doses continued to be reported post-2018; this was raised with NVWA in November 2024.
Authors' conclusions	The regulatory dose restriction was associated with a clear reduction in high-dose vitamin B6 use in neuropathy reports. However, neuropathy cases at lower doses continue to be reported, which warrants further investigation. The weak dose–plasma level correlation suggests significant interindividual metabolic variability.
Authors' acknowledged limitations	SRS inherently prone to underreporting and notoriety bias (reporting spikes linked to media coverage); no denominator data so incidence rates cannot be calculated; vitamer type not recorded in many reports; declared supplement doses may be inaccurate; duration of use not always available; no individual causality assessment performed; overall increase in consumer reporting to Lareb over time not accounted for in trend analysis.

Contextual information for the AU/NZ UL review

Generalisability to AU/NZ	Directly relevant. The Dutch regulatory experience provides real-world evidence that lowering the permitted maximum daily dose of B6 in supplements (to 21 mg/day in 2018) was associated with a reduction in high-dose neuropathy reports.

E.1.20 Webster et al. 2026

Study identification and design

Field	Extracted information
Citation	Webster R, Parayil Sankaran B, Bandodkar S, Stormon M, Thomas G, Shun A, Bowen DG, Fielder T, Barclay P, Khalil Y, Mills P, Clayton P, Bhattacharya K. Liver transplantation in PNPO deficiency: management challenges and biological lessons. *JIMD Reports.* 2026;67:e70067. https://doi.org/10.1002/jmd2.70067
Publication status	Published, peer-reviewed open-access research report (received May 2025, accepted December 2025)
Country / setting	Australia (Children's Hospital at Westmead, Sydney); single patient case report with ethics approval (Sydney Children's Hospital Network, CCR2020/29)

Study design	Single case report with detailed longitudinal pharmacokinetic and clinical data spanning ~7 years (from diagnosis to 6 years post-transplant)
Funding / conflicts of interest	None.

Population

Field	Extracted information
Sample size	Single patient — a 15-year-old male at time of liver transplantation.
Patient (test animal) characteristics	Male; confirmed PNPO deficiency (heterozygous mutations PNPO c.98A>T, c.246delT); neonatal seizure onset treated with PLP from day 24 of life; cirrhosis diagnosed age 2 years; HCC confirmed age 13 years 8 months; cognitively normal with well-controlled epilepsy pre-transplant on PLP 50 mg/kg/day.
Inclusion/exclusion of alternative causes	Single case, no exclusion criteria applicable.

Exposure

Field	Extracted information
Exposure characterisation – source	Pyridoxal 5′-phosphate (PLP) administered therapeutically for PNPO deficiency, via oral, intravenous (continuous infusion and bolus), intranasal, and rectal routes. PLP sourced from TaiyoPharma (Japan) for IV; pharmaceutical grade powder (Medisca/PCCA Australia) for oral capsules.
Exposure characterisation – dose	Pre-transplant: 50 mg/kg/day oral PLP. Post-transplant acute phase: IV infusion 26.4 mg/kg/day, reduced to 7.8 mg/kg/day minimum before encephalopathy recurred. High-dose oral trial: escalated to 109 mg/kg/day, caused fulminant hepatotoxicity. Final stable post-transplant dose: 24 mg/kg/day oral PLP (3-hourly dosing). IV dose requirement approximately one third of oral dose.
Biomarker of exposure	Full plasma B6 vitamer profile (PL, PLP, PM, PN, PNP, PMP, 4-pyridoxic acid) by LC-MS/MS at multiple time points; CSF B6 vitamers measured once during IV infusion; liver function tests (AST, ALT, GGT, bilirubin); alpha-fetoprotein; liver biopsy (Ishak fibrosis staging).
Duration of exposure	PLP therapy from neonatal period (day 24) through to at least 6 years post-transplant (~20 years total); post-transplant management period reported spans ~22 months for dose stabilisation, with 6-year follow-up biopsy.

Outcomes

Field	Extracted information
Primary outcome	Feasibility and challenges of managing PNPO deficiency post liver transplantation; PLP-associated hepatotoxicity; pharmacokinetics of different PLP administration routes.

Outcome assessment	Neurological symptoms of PLP deficiency (visual disturbance, altered consciousness, seizures); liver function deterioration (nausea, vomiting, weight loss); general clinical status.
Outcome assessment – objective testing	Continuous EEG monitoring (4599 hours total); plasma B6 vitamer levels by LC-MS/MS; liver function tests (AST, ALT, GGT, bilirubin); serial liver biopsies (Ishak fibrosis staging); alpha-fetoprotein; hepatic MRI; CSF vitamer levels.
Outcome assessment – tools used	LC-MS/MS (Waters Acquity/TQ-XS) for vitamer quantification; Student's t-test for vitamer levels at deficiency vs non-deficiency timepoints; Ishak fibrosis and LAFSc scoring on biopsy.
Response to withdrawal	Hepatotoxicity reliably resolved upon cessation of oral PLP and re-initiation of IV PLP. Encephalopathy/seizures recurred promptly when PLP dose was reduced below threshold. Trials of pyridoxamine and pyridoxine (as alternatives to PLP) caused encephalopathy and were ceased.

Results and Conclusions

Field	Extracted information
Main results	Liver transplantation cured HCC but did not eliminate the need for supraphysiological PLP doses, indicating impaired neuronal (not hepatic) PLP salvage as the primary driver of PLP requirements. High-dose oral PLP (109 mg/kg/day) caused acute fulminant hepatotoxicity with extensive hepatocyte necrosis on biopsy; resolved with IV PLP at ~10-fold lower dose. IV PLP requirement was ~one third of oral dose. Chronic low-level hepatotoxicity persisted 6 years post-transplant (Ishak 2/6, LAFSc 3/9). Plasma PL level was the best predictor of encephalopathy (all episodes occurred with PL <2800 nmol/L), but high plasma PLP did not reliably prevent encephalopathy. Intranasal PLP was effective in aborting encephalopathy episodes. Pyridoxamine and pyridoxine could not substitute for PLP.
Authors' conclusions	PLP remains unavoidably hepatotoxic in PNPO deficiency even in a liver with normal PNPO function, confirming hepatotoxicity is a direct PLP effect rather than a consequence of PNPO deficiency per se. Supraphysiological PLP doses are required due to impaired neuronal PLP recycling, not hepatic PLP metabolism. Gradual dose changes, frequent dosing intervals, and IV PLP minimise hepatotoxicity. Liver transplantation may be needed in future PNPO patients with cirrhosis/HCC; this case provides management guidance.
Authors' acknowledged limitations	Single patient case; findings may not generalise to other PNPO deficiency phenotypes (especially PN-responsive patients); aggressive early PLP treatment prevented secondary epileptogenesis, complicating extrapolation; blood B6 vitamer levels imperfectly reflect intraneuronal PLP reserves; short duration of pyridoxamine/pyridoxine trials prevents definitive conclusions about their utility; B6 vitamer levels in this post-transplant patient unlikely to reflect those in non-transplanted PNPO patients.

Contextual information for the AU/NZ UL review

Generalisability to AU/NZ	Australian case (Children's Hospital at Westmead, Sydney) with direct AU/NZ institutional relevance. As with Stolwijk et al. 2025, this is a highly specialised ultra-rare disease context (PNPO deficiency) involving therapeutic PLP doses (24–109 mg/kg/day) far exceeding any dietary or supplemental intake relevant to a population-level UL. Therapeutic level not relevant to the general population intake of vitamin B6.

E.1.21 Whyte et al. 2024

Study identification and design

Field	Extracted information
Citation	Whyte MP, Zhang F, Mack KE, Wenkert D, Gottesman GS, Ericson KL, Cole JT, Coburn SP. Pyridoxine challenge reflects pediatric hypophosphatasia severity and thereby examines tissue-nonspecific alkaline phosphatase's role in vitamin B6 metabolism. *Bone.* 2024;181:117033. https://doi.org/10.1016/j.bone.2024.117033
Publication status	Published, peer-reviewed open-access full-length article (received August 2023, accepted January 2024)
Country / setting	USA; single tertiary metabolic bone disease centre (Shriners Hospitals for Children – St Louis / Washington University), participants enrolled 1986–2015.
Study design	Cross-sectional controlled challenge study; oral pyridoxine (PN·HCl) administered over 6 days to 116 children with HPP and comparison groups; pre- and post-challenge plasma B6 vitamer levels measured.
Funding / conflicts of interest	Funded by Shriners Hospitals for Children and The Clark and Mildred Cox Inherited Metabolic Bone Disease Research Endowed Fund. One author (DW) holds stock options in Inozyme Inc. No other conflicts declared.

Population

Field	Extracted information
Sample size	116 children/adolescents with HPP; 14 healthy adults (PN challenge controls); 19 children with other metabolic bone diseases (PN challenge controls); 38 historical healthy adult controls (baseline only); 21 healthy children/adolescents (baseline only). Primary analysis of PN challenge responses focused on 80 preteenage HPP patients and 19 preteenage controls.
Patient (test animal) characteristics	HPP patients: broad-ranging severity from odonto-HPP (mildest) to infantile HPP (most severe), classified using HPP clinical nosology. All preteenage patients had low serum ALP and elevated plasma PLP. Healthy adult

	controls: 7 men (ages 23–40) and 7 women (ages 31–54). Pediatric disease controls: mainly X-linked hypophosphataemia and osteogenesis imperfecta.
Inclusion/exclusion of alternative causes	Diagnosis of HPP confirmed by clinical nosology and ALPL genotyping. Perinatal (lethal) HPP excluded (rapidly fatal prior to study period). One severe childhood HPP outlier excluded from statistical analysis (extreme PLP response). Pubertal patients excluded from PN challenge analysis to minimise skeletal ALP confounding.

Exposure

Field	Extracted information
Exposure characterisation – source	Pyridoxine hydrochloride (PN·HCl) — same form used in over-the-counter B6 supplements — administered as oral challenge.
Exposure characterisation – dose	1/3 mg/kg/day orally once each morning for 6 consecutive days. Post-challenge blood drawn 24 hours after the final dose.
Biomarker of exposure	Plasma PLP, pyridoxal (PL), and pyridoxic acid (PA) measured by HPLC (Purdue University Fort Wayne); serum ALP activity.
Duration of exposure	6-day PN challenge; this is a short pharmacological loading protocol, not chronic supplementation.

Outcomes

Field	Extracted information
Primary outcome	Post-challenge plasma PLP level and PLP increment as reflectors of HPP severity; TNSALP's role in B6 metabolism.
Outcome assessment	HPP severity classification using validated clinical nosology (HPPSSC); height Z-scores.
Outcome assessment – objective testing	Plasma PLP, PA, and PL (HPLC); serum total ALP activity; paired pre/post comparisons; regression of post-challenge PLP against HPP severity score and height Z-score.
Outcome assessment – tools used	Cation-exchange HPLC for B6 vitamers; standard clinical ALP assay; SAS 9.4 for statistics; paired t-test; Spearman correlation (Rs).
Response to withdrawal	Not applicable.

Results and Conclusions

Field	Extracted information
Main results	PN challenge did not alter serum ALP activity in any group. In HPP, both post-challenge PLP level and PLP increment correlated significantly with HPP severity (HPPSSC Rs = +0.60, height Z-score Rs = −0.49; both p<0.0001), though imprecisely. PA and PL increments were progressively blunted with increasing HPP severity, becoming non-significant in infantile HPP (PA: p=0.30; PL: p=0.74). In healthy adults and non-HPP bone disease controls, PN challenge raised PLP, PA, and PL. Findings indicate cell-surface (extraskeletal) TNSALP - not circulating ALP - primarily controls plasma PLP levels, by hydrolysing PLP to PL for cellular uptake and subsequent PA production.
Authors' conclusions	PN challenge modestly reflects HPP severity via post-challenge PLP levels, but biochemical assessments remain of limited prognostic value for HPP. TNSALP's role in B6 metabolism is primarily extraskeletal and cell-surface mediated. Pharmacologic B6 supplementation in HPP is unlikely to be beneficial and may be counterproductive unless there is clear evidence of deficiency (e.g. B6-dependent seizures).
Authors' acknowledged limitations	Broad HPP severity range creates heterogeneity within groups; limited sample sizes precluded multiplicity correction for multi-group comparisons; pre-challenge PL values not determined in some healthy adult controls; HPP severity/genotype discordance means prognostication remains imprecise; data span nearly 30 years with potential assay variability.

Contextual information for the AU/NZ UL review

Generalisability to AU/NZ	Specialised disease context (HPP, an ultra-rare inborn error of metabolism) - Relevant to provides mechanistically important context. It demonstrates that TNSALP activity is the primary determinant of plasma PLP clearance, and that individuals with reduced TNSALP activity (including ~1/300 North Americans/Western Europeans who are heterozygous ALPL carriers) accumulate markedly elevated plasma PLP after PN loading. This supports the biological plausibility of individual susceptibility to B6 toxicity at lower doses due to variation in PLP metabolism, which is relevant to the rationale for a conservative population UL. The PN challenge dose used (1/3 mg/kg/day × 6 days ≈ ~20 mg/day for a 30 kg child) is within the range of common supplement doses, adding context for dose–response considerations. However, no neuropathy outcomes were assessed, limiting direct relevance to the peripheral neuropathy endpoint used in UL derivation.

E.1.22 Zervou et al. 2025

Study identification and design

Field	Extracted information
Citation	Zervou Z, van Velsen EFS, Zillikens MC. Hypophosphatasia and neuropathic pain: related to vitamin B6 metabolism? *JBMR Plus.* 2025;9:ziaf086. https://doi.org/10.1093/jbmrpl/ziaf086
Publication status	Published, peer-reviewed open-access case report (received December 2024, accepted May 2025, advance access June 2025)
Country / setting	Netherlands; single centre (Erasmus MC Bone Center, Rotterdam). Retrospective observational case series
Study design	Retrospective case series of 5 adult Hypophosphatasia (HPP) patients with neuropathic pain symptoms, selected from a clinic cohort of 43 HPP patients
Funding / conflicts of interest	No funding declared. Two authors (MCZ, EFSV) have received honoraria from Amgen, Kyowa Kirin, UCB unrelated to this work; MCZ also received research support from Kyowa Kirin

Population

Field	Extracted information
Sample size	5 adults with HPP and symptoms suggestive of neuropathic pain (from a total clinic cohort of 43 HPP patients)
Patient (test animal) characteristics	3 women, 2 men; ages 24–73 years; 2 with childhood-onset HPP, 3 with adult-onset HPP; 2 compound heterozygous and 3 heterozygous ALPL variants (ACMG class 4–5). Serum ALP 9–28 U/L (reference <98 U/L); serum vitamin B6 233–828 nmol/L (reference 35–110 nmol/L); urine PEA elevated in all. Duration of pain 3–7 years.
Inclusion/exclusion of alternative causes	Included based on symptoms of neuropathic pain (burning, pins and needles, tingling) and confirmed (likely) pathogenic ALPL variant. No standardised neuropathic pain questionnaire applied; not all referred to neurologist. Patient 3 had concomitant alcohol use (10 beers/week, reduced during follow-up). Patient 2 had nociceptive/nociplastic pain diagnosis. Alternative causes not systematically excluded across all cases.

Exposure

Field	Extracted information
Exposure characterisation – source	Endogenous accumulation of PLP due to TNSALP deficiency (HPP), not exogenous B6 supplementation. No patients were taking B6 supplements (confirmed for Patient 3).
Exposure characterisation – dose	Elevated plasma vitamin B6 levels ranging from 233 to 828 nmol/L (reference 35–110 nmol/L), representing 2- to 7-fold elevation above the upper reference limit.

Field	Extracted information
Biomarker of exposure	Serum vitamin B6 (PLP), serum ALP, urine phosphoethanolamine (PEA); serial measurements in some patients.
Duration of exposure	Lifelong in childhood-onset patients; from mid-adulthood in adult-onset patients. Duration of pain symptoms 3–7 years.

Outcomes

Field	Extracted information
Primary outcome	Neuropathic pain symptoms in adult HPP patients; proposed mechanistic link to disturbed B6 metabolism.
Outcome assessment	Neurological examination (where performed); pain characterisation (burning, tingling, numbness, location); functional impact (sleep disturbance, mobility); clinical response to treatment.
Outcome assessment – objective testing	EMG/nerve conduction studies (performed in patients 1, 3, 5); muscle biopsy (patient 5, showed mild myopathy); serum ALP; serum vitamin B6; urine PEA; serial B6 level monitoring.
Outcome assessment – tools used	Clinical assessment; EMG; no standardised neuropathic pain rating scale used.
Response to withdrawal	Not applicable in a supplementation sense.

Results and Conclusions

Field	Extracted information
Main results	All 5 patients had markedly elevated serum vitamin B6, reduced ALP, and elevated urine PEA consistent with HPP. Neuropathic pain (predominantly burning in lower extremities) was the common symptom. EMG confirmed peripheral neuropathy in patient 3 (mild axonal); patient 1 had small fibre neuropathy confirmed by neurologist but normal EMG. Asfotase alfa produced dramatic pain reduction in patient 5 (within 3 weeks), alongside normalisation of B6 levels. Nortriptyline + rehabilitation reduced pain in patient 1. Gabapentin partially helped patient 4. Patient 3 showed spontaneous fluctuating improvement correlated with B6 level changes. Patient 2 had poor pain control despite multiple analgesics.
Authors' conclusions	Neuropathic pain appears to be an underrecognised symptom of HPP. Disturbed B6 metabolism (either intracellular PLP deficiency in the brain or extracellular PLP excess) is the hypothesised mechanism. The dramatic response to asfotase alfa in one patient supports a causal role for B6 metabolic dysregulation. The mechanism may share features with sensory neuropathy seen in excessive B6 supplementation. Standardised neuropathic pain assessment in larger HPP cohorts and further mechanistic studies are needed.

Field	Extracted information
Authors' acknowledged limitations	Small case series (n=5) selected from a single centre; no standardised neuropathic pain questionnaire applied; not all patients referred to neurologist; cannot exclude alternative causes (e.g. alcohol in patient 3); mechanistic link to B6 metabolism remains speculative; no systematic measurement of B6 metabolite subfractions (PLP, PL, PA) in all patients.

Contextual information for the AU/NZ UL review

Generalisability to AU/NZ	This HPP-specific study has limited direct relevance for population-level AU/NZ UL derivation, as it does not provide data for healthy supplement users. However, it supports the biological plausibility of B6-related peripheral neuropathy by linking markedly elevated circulating PLP to neuropathic symptoms and showing symptom resolution after asfotase alfa normalised PLP metabolism.

E.1.23 Reddy 2022

Study identification and design

Field	Extracted information
Citation	Reddy, P. (2022). Preventing Vitamin B6–Related Neurotoxicity. American Journal of Therapeutics, 29(6), e637–e643.
Publication status	Published, peer-reviewed journal (American Journal of Therapeutics, Wolters Kluwer Health), published 2022.
Country / setting	USA; narrative review and therapeutic opinion article (no specific study setting).
Study design	Narrative review and therapeutic opinion based on a PubMed search of RCTs and meta-analyses. **Not a systematic review.**
Funding / conflicts of interest	No funding reported; author declares no conflicts of interest.

Population

Field	Extracted information
Sample size	NA (narrative review; no primary study population).
Patient (test animal) characteristics	NA; review covers general adult populations, elderly patients, patients with comorbidities, and specific clinical groups (e.g. patients with pyridoxine-dependent epilepsy, PNPO deficiency, HPP, homocystinuria, CBS deficiency).

Inclusion/exclusion of alternative causes	NA (not a primary study).

Exposure

Field	Extracted information
Exposure characterisation – source	Vitamin B6 from dietary sources, oral supplements (pyridoxine HCl and PLP), and intravenous formulations.
Exposure characterisation – dose	General population RDA: 1.5–2 mg/day. Supplements commonly available up to 100 mg/dose (PLP) or 500 mg/dose (pyridoxine). Therapeutic dosing for pyridoxine-dependent epilepsy/inborn errors: 30–50 mg/kg/day. Weekly PLP dosing of 50–100 mg suggested as safer alternative to daily use. Neuropathy risk reported at low doses of 25–50 mg/day for >6 months.
Biomarker of exposure	Plasma PLP: adequate >30 nmol/L; deficiency <20 nmol/L; toxicity typically at >100 nmol/L (25 µg/L). Plasma PLP half-life 12–48 hours; biological half-life 18–38 days. Delayed-release formulations prolong plasma PLP half-life to 80–120 hours.
Duration of exposure	Prolonged daily use associated with neurotoxicity risk; neuropathy reported at >6 months at low doses. Weekly dosing proposed to reduce toxicity risk due to long PLP biological half-life (18–38 days).

Outcomes

Field	Extracted information
Primary outcome	Peripheral neuropathy as the critical adverse effect of B6 excess. Secondary adverse effects include nausea, heartburn, dermatitis, photosensitivity, memory impairment, dizziness, autonomic dysfunction, and (at high therapeutic PLP doses) cirrhosis and platelet dysfunction.
Outcome assessment	Neurological symptoms: stocking-glove sensory loss, numbness, burning pain, bone pain, muscle weakness, fasciculation, ataxia, loss of balance.
Outcome assessment – objective testing	Not applicable (review); references plasma PLP concentration and prior case-series data (Dalton & Dalton 1987: elevated PLP >73 nmol/L in 172 women, 60% with neuropathy symptoms).
Outcome assessment – tools used	Not applicable (review).
Response to withdrawal	Plasma PLP rapidly normalises after cessation; clinical recovery slow (~6 months). Neuropathy symptoms may worsen 2–3 weeks after stopping before gradual recovery; only partial recovery in some patients after years of follow-up.

Results and Conclusions

Field	Extracted information
Main results	PLP may be less neurotoxic than pyridoxine, but neuropathy has still been reported with long-term vitamin B6 use, including at relatively low supplemental doses. Toxicity risk is difficult to predict because plasma vitamin B6 levels correlate poorly with symptoms and individual susceptibility varies widely.
Authors' conclusions	PLP-based supplements preferred over pyridoxine; weekly low-dose administration (50–100 mg/week) recommended to prevent B6 toxicity; plasma B6 levels should be routinely monitored; clearer clinical guidelines needed especially for high-risk groups.
Authors' acknowledged limitations	Narrative review only; further clinical trials needed to establish long-term safety of high-dose PLP supplements; association between elevated pyridoxine and neuropathy not well established.

Contextual information for the AU/NZ UL review

Generalisability to AU/NZ	The clinical and pharmacokinetic information is relevant to the AU/NZ context, particularly for supplement regulation and clinical guidance. However, the intake and exposure data are mainly from the US and EU and may not reflect AU/NZ supplement use or population patterns.

Appendix F Risk of Bias – Assessment Tables – Evidence Review for Recent Studies

Evidence Evaluations for Vitamin B6 Upper Level (UL)

Vitamin B6 Upper Level (UL) Technical Report

National Health and Medical Research Council

SLR Project No.: 640.032359.00001

7 August 2026

SLR

F.1 Risk of bias assessment summary – all new studies from evidence review

Summary of Risk of Bias Assessment

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

F.2 Risk of bias assessment for individual new study from evidence review

Tables below provide risk of bias assessment for each assessed study, showing the domain-level judgements applied to individual pieces of evidence. In addition, the overall confidence in the body of evidence for each relevant health outcome was conducted, taking into account the risk of bias findings, consistency, directness, precision and other relevant considerations.

F.2.1 Sano et al. 2022

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

Study Type:		Controlled animal experiment (in vivo rat study)
Study ID:		Sano et al. 2022
Health Outcome:		Neurotoxicity / neuronal damage; Neurofilament light chain (NfL) as a biomarker of CNS and PNS neurotoxicity in Sprague Dawley rats
Bias Domain	**Rate**	**Comment**
Selection		
Was administered dose or exposure level adequately randomized?	+	Group allocation appears to have been based on body-weight standardisation rather than explicit randomisation. This may have reduced baseline differences, but no formal randomisation method was reported.
Was allocation to study groups adequately concealed?	NR	Allocation concealment is not reported.
Were the comparison groups appropriate?	+	Small group size (n=4). Vehicle/untreated controls were included at all necropsy time points, and the use of multiple CNS and PNS neurotoxicant models provided a strong comparative framework.
Confounding – KEY DOMAIN		
Does the study design or analysis account for important confounding and modifying variables?	+	no formal confounder adjustment was reported, which is typical for this controlled animal design.
Performance		
Were experimental conditions identical across study groups?	++	Experimental conditions and sample collection procedures were well described and standardised across groups, supporting consistency in housing, husbandry, blood/CSF collection, and tissue processing.
Were the research personnel and human subjects blinded to the study group during the study?	NR	Blinding was not reported for in-life observations, sample collection, or study personnel, so performance bias cannot be ruled out.

Study Type:		Controlled animal experiment (in vivo rat study)
Attrition / Exclusion		
Were outcome data incomplete because of attrition or exclusion from analysis?	+	No attrition or exclusions were reported, with planned group sizes maintained. An incidental histopathology finding was noted and appropriately considered in interpretation.
Detection bias – KEY DOMAIN		
KEY - Can we be confident in the exposure characterisation?	++	Exposure characterisation was clearly reported, including dose, route, timing, dosing rationale, and chemical sources for all compounds.
KEY - Can we be confident in the outcome assessment?	-	Incomplete outcome data for the pyridoxine (excluded from the day 8 necropsy cohort unlike the trimethyltin (TMT) comparator).
Selective Reporting		
Were all measured outcomes reported?	+	All specified outcomes were reported across treatment groups and time points, with supplementary data referenced. However, lack of protocol registration prevents confirmation against a pre-specified analysis plan.
Other Sources of bias		
Were there any other potential threats to internal validity (e.g., inappropriate statistical methods)?	-	Key limitations include very small group sizes, limited statistical testing, no multiple-comparison correction, and mostly narrative reporting of NfL findings. All authors were Takeda employees, indicating a potential conflict of interest, although this does not necessarily imply bias. A full GLP study report with complete data may have warranted a lower risk of bias rating.
Overall risk of bias for the study (Low/Moderate/High)	**High**	**Very small group sizes (n=4), incomplete outcome data for the pyridoxine (excluded from the day 8 necropsy cohort 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.**

F.2.2 Stewart et al. 2022

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

Study Type:		Cross-sectional observational study (retrospective analysis of a prospective registry)
Study ID:		Stewart et al. 2022
Health Outcome:		Neuropathy severity (NCS, neurological examination, patient-reported symptoms) in chronic idiopathic axonal polyneuropathy (CIAP)
Bias Domain	**Rate**	**Comment**
Selection		
Was administered dose or exposure level adequately randomized?	NA	This was a cross-sectional observational study, so there was no experimental exposure allocation.
Was allocation to study groups adequately concealed?	NA	Not applicable; patients were grouped post hoc by observed plasma B6 level (normal vs elevated), not by investigator allocation.
Were the comparison groups appropriate?	+	Groups were defined by plasma B6 status within a CIAP registry cohort and were mostly comparable, except the elevated B6 group was older; age was adjusted for in analyses. However, exclusion of B6-deficient patients and inclusion only of complete PNRR records with B6 data may have introduced selection bias.
Confounding – KEY DOMAIN		
Does the study design or analysis account for important confounding and modifying variables?	-	Confounding was only partly addressed, with adjustment for age and neuropathy duration. Important factors such as comorbidities, medication use, supplement dose/duration, diet, and other nutritional deficiencies were not controlled, and the cross-sectional design prevents conclusions about temporality or causality.
Performance		
Were experimental conditions identical across study groups?	NA	This domain is not directly applicable to the observational registry design. Assessments used a standardised multicentre database, but inter-site variability across the three institutions may have affected examination consistency.
Were the research personnel and human subjects blinded to the study group during the study?	NR	Blinding is not described.
Attrition / Exclusion		
Were outcome data incomplete because of attrition or exclusion from analysis?	-	There is potential attrition/selection bias because inclusion required complete

Study Type:		Cross-sectional observational study (retrospective analysis of a prospective registry)
		registry data with plasma B6 results, and B6 testing may have been selectively ordered. Outcome data were also incomplete for some measures, with varying denominators and limited explanation of missingness.
Detection bias – KEY DOMAIN		
KEY - Can we be confident in the exposure characterisation?	-	Exposure assessment had important limitations, including use of two different B6 assays combined in analysis, reliance on a single plasma measurement, and limited supplement dose/duration data.
KEY - Can we be confident in the outcome assessment?	+	Outcome assessment used standardised and validated neuropathy measures, including NCS, neurological examination, and TNSr. However, subjective patient-reported symptoms may be prone to reporting bias, and blinding to B6 status was not indicated.
Selective Reporting		
Were all measured outcomes reported?	+	All stated outcomes were reported, including NCS, neurological examination, TNSr, symptoms, and IENFD. An unexpected significant finding was transparently reported and contextualised, but lack of protocol registration means full outcome pre-specification cannot be confirmed.
Other Sources of bias		
Were there any other potential threats to internal validity (e.g., inappropriate statistical methods)?	-	The cohort was predominantly White (93%), limiting generalisability to other populations. Additionally, the corresponding author serves as chair of the Scientific Advisory Board of the funding organisation (Foundation for Peripheral Neuropathy), representing a potential conflict of interest, though the authors state the FPN had no role in study conduct or reporting.
Overall risk of bias for the study (Low/Moderate/High)	**High**	

F.2.3 Theil et al. 2023

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

Study Type:		Controlled animal experiment
Study ID:		Theil et al. 2023
Health Outcome:		Serum neurofilament light chain (NfL) as a biomarker of drug-induced peripheral neurotoxicity
Bias Domain	**Rate**	**Comment**
Selection		
Was administered dose or exposure level adequately randomized?	+	Animals were randomised to groups by body weight; specific randomisation method not detailed.
Was allocation to study groups adequately concealed?	NR	Not reported; typical for nonclinical animal studies.
Were the comparison groups appropriate?	++	Vehicle (negative) and pyridoxine (positive) controls included alongside two branaplam regimens; age, weight, housing, and diet standardised.
Confounding – KEY DOMAIN		
Does the study design or analysis account for important confounding and modifying variables?	+	Controlled experimental conditions minimise confounding. Only males used. Variable dosing regimens (dose reductions and interruptions across groups) complicate attributing effects to specific exposure levels.
Performance		
Were experimental conditions identical across study groups?	+	Housing, diet, and administration route standardised. Dosing schedules and necropsy time points intentionally differed across groups, limiting direct temporal comparisons.
Were the research personnel and human subjects blinded to the study group during the study?	NR	Not reported for in-life monitoring or histopathological evaluation.
Attrition / Exclusion		
Were outcome data incomplete because of attrition or exclusion from analysis?	+	No unplanned animal losses. Some morphometry data missing due to poor sample quality, transparently reported. No baseline CSF collected (justified to avoid lumbar puncture artefact).
Detection bias – KEY DOMAIN		
KEY - Can we be confident in the exposure characterisation?	+	Dosing well-defined; compound sources identified. No toxicokinetic data included for pyridoxine, so actual systemic exposure for the positive control is unconfirmed.
KEY - Can we be confident in the outcome assessment?	+	Outcome assessment used multiple validated and complementary endpoints with pre-defined NfL thresholds. However, limited statistical testing and

Study Type:		Controlled animal experiment
		lack of reported histopathology blinding reduce confidence in the findings.
Selective Reporting		
Were all measured outcomes reported?	+	All stated outcomes reported including incidental vehicle-group findings. Supplementary data provided for individual animal NfL values. No protocol registration.
Other Sources of bias		
Were there any other potential threats to internal validity (e.g., inappropriate statistical methods)?	-	Use of juvenile male animals limits generalisability to adult or clinical populations. The strong Novartis funding/employment links and patent interest represent a substantial potential conflict of interest, although not necessarily evidence of bias.
Overall risk of bias for the study (Low/Moderate/High)	**Moderate**	

F.2.4 vanHunsel et al. 2025

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

Study Type:		Pharmacovigilance study (retrospective analysis of a spontaneous reporting system)
Study ID:		van Hunsel et al. 2025
Health Outcome:		Neuropathy reporting patterns
Bias Domain	**Rate**	**Comment**
Selection		
Was administered dose or exposure level adequately randomized?	NA	Observational study; no exposure was assigned.
Was allocation to study groups adequately concealed?	NA	Not applicable.
Were the comparison groups appropriate?	-	There are no formal comparison groups. Reports are split by time period (pre/post-2018), but there is no control group and no denominator data on how many people used B6 products in each period.
Confounding – KEY DOMAIN		
Does the study design or analysis account for important confounding and modifying variables?	--	Confounding is a major problem throughout. No adjustment was made for the steadily increasing volume of consumer reports in the Dutch SRS over time, concomitant medications,

Study Type:		Pharmacovigilance study (retrospective analysis of a spontaneous reporting system)
		underlying conditions, vitamer type, or duration of use. Notoriety bias (media attention driving reporting spikes around 2018) is acknowledged but not corrected for.
Performance		
Were experimental conditions identical across study groups?	NA	Not applicable to this study design.
Were the research personnel and human subjects blinded to the study group during the study?	NA	Not applicable.
Attrition / Exclusion		
Were outcome data incomplete because of attrition or exclusion from analysis?	-	Spontaneous reporting is inherently incomplete. Key data were missing in many reports - vitamer type, dosage accuracy, duration of use, timing of plasma testing, and dietary B6 intake and no imputation or sensitivity analysis was performed.
Detection bias – KEY DOMAIN		
KEY - Can we be confident in the exposure characterisation?	--	Exposure assessment was weak, relying on product labels and patient recall, with limited information on vitamer type. The poor relationship between reported dose and plasma B6 suggests substantial exposure misclassification.
KEY - Can we be confident in the outcome assessment?	-	Outcome assessment was limited by broad MedDRA SMQ coding, lack of clinical verification, and no individual causality assessment. Potential alternative causes of neuropathy, including comorbidities and concomitant medications, were not systematically addressed.
Selective Reporting		
Were all measured outcomes reported?	+	All stated analyses (report trends, dose over time, dose-plasma correlation, changepoint analysis) are reported. Limitations are transparently acknowledged.
Other Sources of bias		
Were there any other potential threats to internal validity (e.g., inappropriate statistical methods)?	-	No conflicts of interest and no external funding, which is a strength. However, the SRS is operated by one of the authors' institutions (Lareb), and the 2018 regulatory action itself was initiated by Lareb, creating a degree of institutional interest in demonstrating its

Study Type:		Pharmacovigilance study (retrospective analysis of a spontaneous reporting system)
		effectiveness though this is not necessarily a bias in the traditional sense.
Overall risk of bias for the study (Low/Moderate/High)	**High**	

F.2.5 Whyte et al. 2024 – not for dose – response health outcomes, for mechanistic information only

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

Study Type:		Controlled clinical challenge study (cross-sectional, single-centre, with historical and concurrent controls)
Study ID:		Whyte et al. 2024
Health Outcome:		Plasma B6 vitamer responses to oral pyridoxine challenge – mechanistic information only
Bias Domain	**Rate**	**Comment**
Selection		
Was administered dose or exposure level adequately randomized?	NA	All participants received the same weight-based PN challenge (1/3 mg/kg/day × 6 days); no randomisation to dose groups was relevant or attempted.
Was allocation to study groups adequately concealed?	NA	Groups were defined by clinical diagnosis, not by allocation.
Were the comparison groups appropriate?	+	Active control groups were appropriate, but some comparator limitations remain, including lack of PN challenge in healthy paediatric controls and use of historical adult reference samples, which may introduce temporal or methodological inconsistency.
Confounding – KEY DOMAIN		
Does the study design or analysis account for important confounding and modifying variables?	-	Confounding was not well controlled across the long study period, with limited reporting on diet, nutritional status, medications, and age-related factors. The change in PN formulation over time may also have affected absorption and B6 vitamer responses.
Performance		
Were experimental conditions identical across study groups?	-	Experimental conditions were not fully consistent due to differences in fasting

Study Type:		Controlled clinical challenge study (cross-sectional, single-centre, with historical and concurrent controls)
		status and PN formulation over time. However, post-challenge blood collection timing was standardised across groups.
Were the research personnel and human subjects blinded to the study group during the study?	NR	Blinding is not described. B6 vitamer assays were performed at a separate laboratory (Purdue University), which provides some separation, but blinding to diagnostic group is not stated.
Attrition / Exclusion		
Were outcome data incomplete because of attrition or exclusion from analysis?	-	Attrition/exclusion concerns include exclusion of one extreme outlier without a pre-specified rule, missing pre-challenge PL data for some healthy adults, and no multiplicity assessment due to small subgroup sizes.
Detection bias – KEY DOMAIN		
KEY - Can we be confident in the exposure characterisation?	+	The PN dose was weight-based and consistently administered, with PA increases used as a compliance check. The formulation change is a limitation but is acknowledged.
KEY - Can we be confident in the outcome assessment?	+	Exposure and clinical characterisation were generally robust, using validated HPLC B6 vitamer assays, established HPP severity classification, height Z-scores, and CLIA-certified ALP testing.
Selective Reporting		
Were all measured outcomes reported?	+	All stated biochemical outcomes were reported across groups and time points, including non-significant correlations with R and P values. The outlier exclusion was transparently disclosed.
Other Sources of bias		
Were there any other potential threats to internal validity (e.g., inappropriate statistical methods)?	-	Generalisability is limited by the single specialised referral-centre setting and long study period, likely enriching for more complex HPP cases. There is also potential circularity because the same group developed the clinical nosology used to assess PN challenge as a severity marker.
Overall risk of bias for the study (Low/Moderate/High)	**Moderate**	**Whyte et al. (2024) is assessed regarding the mechanistic rather than direct dose-response focus. Its finding of genotype-dependent impairment in PLP clearance is relevant to the intraspecies toxicokinetic variability component of**

Study Type:		Controlled clinical challenge study (cross-sectional, single-centre, with historical and concurrent controls)
		the uncertainty factor applied in UL derivation.

F.2.6 Paluszny and Qiu., 2023

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

Study Type:		Single case report
Study ID:		Paluszny and Qiu., 2023
Health Outcome:		Peripheral neuropathy
Bias Domain	**Rate**	**Comment**
Selection		
Was administered dose or exposure level adequately randomized?	NA	Single patient; not applicable.
Was allocation to study groups adequately concealed?	NA	Not applicable.
Were the comparison groups appropriate?	NA	No comparison group.
Confounding – KEY DOMAIN		
Does the study design or analysis account for important confounding and modifying variables?	--	Confounding could not be adequately controlled. Some alternative neuropathy causes were partly excluded, but dietary/supplement B6 exposure relied on self-report and additional unreported supplement sources could not be ruled out.
Performance		
Were experimental conditions identical across study groups?	NA	Not applicable.
Were the research personnel and human subjects blinded to the study group during the study?	NA	Not applicable.
Attrition / Exclusion		
Were outcome data incomplete because of attrition or exclusion from analysis?	-	Follow-up was short and based only on subjective symptom improvement. Repeat serum B6 and EMG were not available, so causality remains unconfirmed.
Detection bias – KEY DOMAIN		
KEY - Can we be confident in the exposure characterisation?	-	Exposure assessment was very limited, relying on self-reported long-term multivitamin use. Dietary B6 intake was not measured, and only total serum B6

Study Type:		Single case report
		was reported, limiting dose accuracy and mechanistic interpretation.
KEY - Can we be confident in the outcome assessment?	+	Peripheral neuropathy was objectively confirmed by EMG showing bilateral sensory neuropathy. Standard workup (B12, thyroid, HbA1c, ANA) was completed to exclude common alternative causes. Physical examination findings are documented across multiple visits.
Selective Reporting		
Were all measured outcomes reported?	+	The clinical course, laboratory results, and short-term treatment response are fully reported. No conflicts of interest and no external funding.
Other Sources of bias		
Were there any other potential threats to internal validity (e.g., inappropriate statistical methods)?	-	Causal attribution to B6 is uncertain because the patient is elderly, where idiopathic neuropathy is common, and the case lacks rechallenge or longer follow-up confirming resolution with normalised B6 levels.
Overall risk of bias for the study (Low/Moderate/High)	**High**	

F.2.7 Gdynia et al. 2025

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

Study Type:		Retrospective single-centre case series
Study ID:		Gdynia et al. 2025
Health Outcome:		Sensorimotor polyneuropathy (PN) associated with vitamin B6 hypervitaminosis
Bias Domain	**Rate**	**Comment**
Selection		
Was administered dose or exposure level adequately randomized?	NA	No intervention assigned; observational case series.
Was allocation to study groups adequately concealed?	NA	Not applicable.
Were the comparison groups appropriate?	NA	No comparison group. All eight patients were recruited from a single neurology outpatient clinic based on having elevated B6 and PN, which introduces bias.
Confounding – KEY DOMAIN		

Study Type:		Retrospective single-centre case series
Does the study design or analysis account for important confounding and modifying variables?	-	No confounding control. Most patients are elderly (mean age 80, range 70–86), an age group where idiopathic and age-related polyneuropathy is common. Patient 1 had established uremic PN. Several patients had co-elevated B12 and B1, raising the possibility of multi-vitamer toxicity.
Performance		
Were experimental conditions identical across study groups?	NA	Not applicable.
Were the research personnel and human subjects blinded to the study group during the study?	NA	Not applicable.
Attrition / Exclusion		
Were outcome data incomplete because of attrition or exclusion from analysis?	-	Follow-up data are available for only three of the eight patients (patients 1, 6, 8), with a 12-month interval reported. The remaining five patients have no reported follow-up, so symptom progression or recovery after B6 withdrawal is largely unknown.
Detection bias – KEY DOMAIN		
KEY - Can we be confident in the exposure characterisation?	-	Exposure relies entirely on patient self-report or proxy report of supplement use.
KEY - Can we be confident in the outcome assessment?	+	Polyneuropathy (PN) was assessed with a comprehensive and standardised workup including clinical neurological examination, nerve conduction studies (sensory and motor), EMG, and an extensive laboratory panel to exclude other causes. This is a strength of the series.
Selective Reporting		
Were all measured outcomes reported?	+	All eight patients are reported including one with a pre-existing cause (uremia). No conflicts of interest and no funding declared.
Other Sources of bias		
Were there any other potential threats to internal validity (e.g., inappropriate statistical methods)?	-	The study was conducted in a single specialist neurology rehabilitation clinic, which likely selected for more severe or complex cases and limits generalisability. The corresponding author had also co-authored an earlier paper describing motor involvement in vitamin B6-associated peripheral neuropathy, indicating a pre-existing research interest that may have

Study Type:		Retrospective single-centre case series
		influenced case selection or interpretation.
Overall risk of bias for the study (Low/Moderate/High)	**High**	

F.3 Confidence rating (intial and overall) – grouped based on health outcomes

The confidence in the body of evidence for each health outcome was assessed in two sequential steps. First, an initial confidence rating was assigned to each individual study based on its study design characteristics. Second, the initial ratings were adjusted upward or downward across the body of evidence within each health outcome category to arrive at a final overall confidence rating. The assessment framework applied differs by study type: for observational human studies, criteria focus on the presence of a comparison group, temporal sequence of exposure and outcome, and individual-level outcome assessment; for experimental animal studies, criteria focus on concurrent controls, sufficient group sizes, appropriate statistical analyses, and relevant adverse effect parameters. Studies for which a criterion is not applicable to their design are marked as NA.

F.3.1 Initial confidence rating

The initial confidence rating for each individual study was determined based on its study design characteristics, using a structured set of criteria adapted to the study type. For observational human studies (cross-sectional, cohort, case series, case reports, and pharmacovigilance), the applicable criteria included whether exposure was controlled, whether exposure preceded the outcome, whether outcomes were assessed at the individual level, and whether a comparison group was used. For experimental animal studies, the applicable criteria included the use of appropriate statistical analyses, concurrent control groups, sufficient numbers of animals per group, and appropriate parameters to assess adverse effects. Criteria not applicable to a given study design are marked as NA and do not penalise the rating. Individual study confidence ratings were then summarised into an overall initial confidence rating for each health outcome category and study type (human or animal), which served as the starting point for subsequent adjustments. Studies under the "Other" health outcome category were not assigned an overall group initial confidence rating at this stage (indicated by "–") due to the heterogeneity of outcomes and study designs within that category, which precluded a meaningful single group rating.

F.3.2 Adjustments to the Initial Confidence in the Body of Evidence

Following the assignment of initial confidence ratings, adjustments were applied at the level of the body of evidence within each health outcome category and study type, following a GRADE-informed approach. Downgrade factors considered included risk of bias across studies (e.g., observational designs, absence of comparison groups, small sample sizes), inconsistency in results across studies, indirectness or limited applicability of the evidence to the population and exposure of interest, imprecision, and potential publication bias. Upgrade factors considered included large magnitude of effect, presence of a dose–response gradient, and consistency across species or populations. The net result of these adjustments to the initial confidence rating yielded the final confidence rating for each body of evidence.

Initial Confidence Rating

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

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

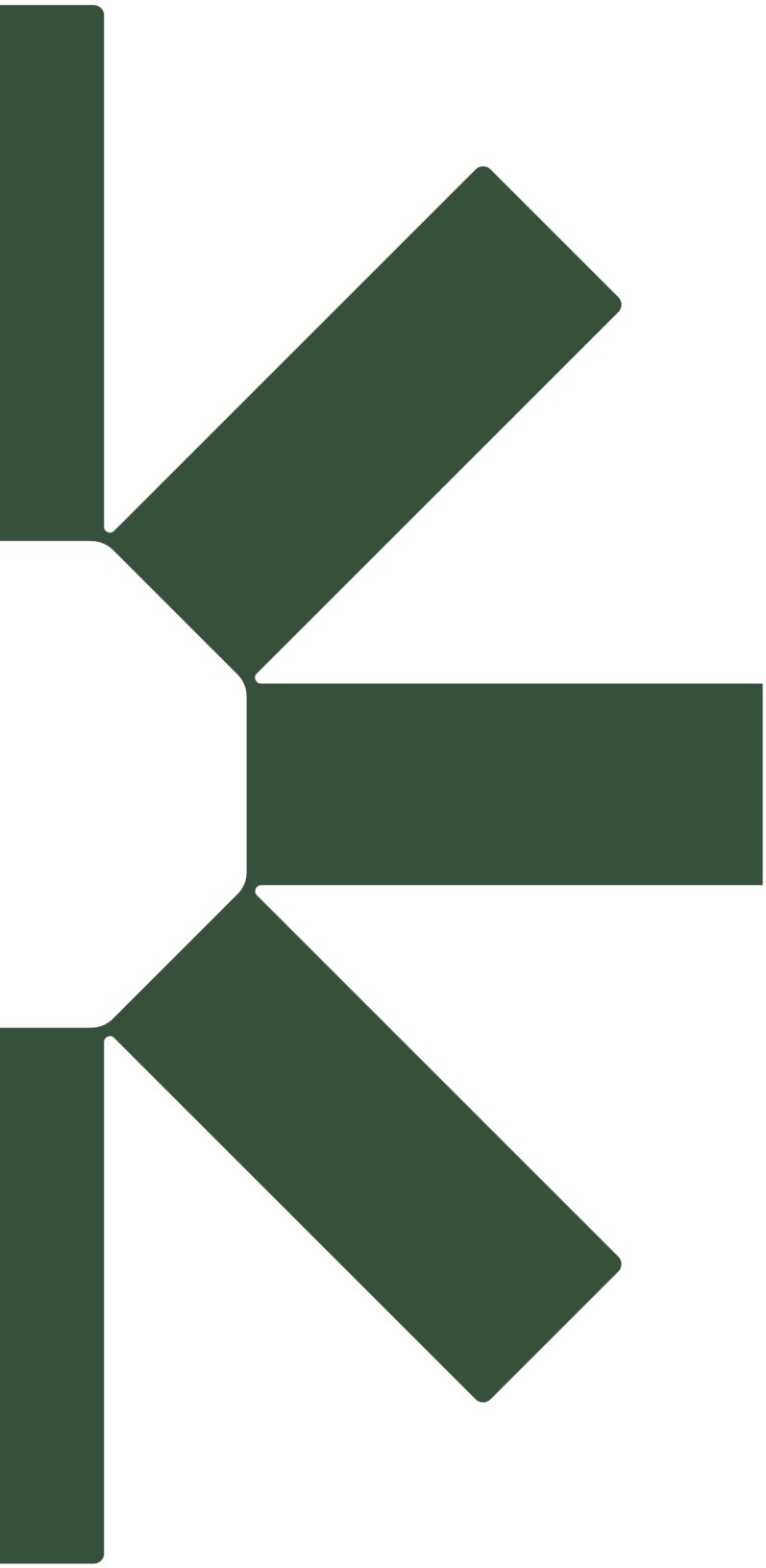
Health Outcome	Study Type and ID	Study design - controlled exposure	Study designs - Exposure prior to outcome	Study design - Outcome assessed on individual level	Study design - Use of comparison group	Study design - Appropriate statistical analyses	Study design - Concurrent control group	Study design - 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	
Neurological	Animal Sano et al. 2022	NA	NA	NA	NA	Yes	Yes	No	Yes	Moderate	Moderate
Neurological	Animal	NA	NA	NA	NA	Yes	Yes	Yes	Yes	High	

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**
	Theil et al. 2023										
Other	Human cross – sectional Whyte et al. 2024	No	No	Yes	Yes	NA	NA	NA	NA	Low	-

Adjustments to the Initial Confidence in the Body of Evidence

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



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