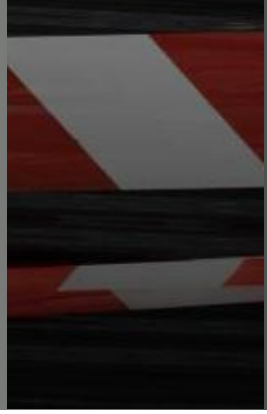
6.

MNZH MAKE NEW ZEALAND HEALTHY

Remove Pharmac/Medsafe Barriers to Recognised Safe Nutrients.



THE PROBLEM: New Zealand's regulatory system does not adequately recognise the biological necessity of nutrients and lacks effective mechanisms to signal their foundational role in human physiology. Its alignment with pharmaceutical toxicokinetic frameworks renders it relatively insensitive to nutrients as endogenous, biologically essential substances, resulting in regulatory settings that do not reflect their functional importance.

Current governance frameworks assess nutrients through models derived from deficiency prevention and chemical-style risk assessment, with emphasis on threshold-setting and avoidance of adverse effects. This approach does not adequately distinguish between adaptive physiological responses, nutrient interactions, and clinically meaningful toxicity. As a result, lower-order or context-dependent biological effects may be interpreted as safety risks, while the systemic roles of nutrients in metabolism, immune function, neurobiology, and long-term health are under-recognised.

A central issue concerns the overly broad 'therapeutic purpose' trigger in the Medicines Act 1981. Section 4 automatically categorises a nutrient formulation as a medicine if marketing and consumer information describes that formulation as influencing physiological processes, irrespective of dose or intrinsic risk. This blurs the line between the body's normal biology and drug treatment, bringing low-risk nutrients under medicine-style controls when they would be better managed through food and public health systems.

While different types of evidence - mechanistic, clinical, and observational, may be looked at, there's no clear process to bring them together into a coherent picture of how the biology actually works. This constrains decision-making and limits the ability to assess nutrients within complex, multi-factorial systems. At the same time, institutional processes tend toward precaution in the absence of demonstrated harm, rather than proportionate evaluation of risk.

These problems are made worse by how the system is set up economically. The approval process is built around pharmaceutical models that rely on commercial backing, which puts low-cost, non-patentable nutrients at a disadvantage and limits their access, funding, and use in practice.

The practical consequences are evident. Nutrients may be classified as medicines at relatively low thresholds, access pathways are fragmented, and regulatory decisions may default to established classification positions rather than iterative, evidence-led evaluation. The system is therefore weighted toward identifying theoretical risk rather than recognising biological necessity, functional sufficiency, and real-world exposure.

THE SOLUTION: Reform nutrient regulation so that biologically essential, low-risk nutrients are assessed through a proportionate, biologically informed framework.

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MNZH POLICY RECOMMENDATIONS

THE SOLUTION: Reform nutrient regulation so that biologically essential, low-risk nutrients are assessed through a proportionate nutrition and food-law lens, rather than being swept into medicines controls through overbroad functional triggers. Regulatory settings should be based on dose, exposure context, biological necessity, and demonstrated risk, not on the mere fact that a nutrient influences human physiology.

1. **Establish a Tiered, Risk-Proportionate Regulatory Framework.** Regulatory burden must scale with demonstrated risk, not biological activity. New Zealand should adopt a proportionate, biologically informed framework for nutrients that distinguishes essential nutrients from medicines and aligns regulatory control with dose, exposure, and demonstrated risk. Replace the current system, which can escalate substances into medicines regulation based on physiological effect alone, with a tiered model:
   i. Nutrients (food/supplement pathway)
   ii. Intermediate or higher-dose / novel substances (enhanced assessment pathway)
   iii. Medicines (high-risk, pharmacological)

   This approach reflects real-world biological and toxicological risk, establishes a continuum between food, supplements, and medicines, and ensures regulatory intensity increases only where there is credible evidence of pharmacological effect or harm.

   This intermediate pathway (ii) provides a proportionate regulatory route for substances where risk is low at proposed exposure levels, but where additional scientific characterisation is warranted. It enables controlled access under defined conditions, without default escalation into medicines regulation.

2. **Remove Automatic Medicines Classification Based on Physiological Function.** Nutrients that support, influence, or restore normal physiological function must not, in themselves, trigger medicines classification. Nutrients are endogenous and biologically essential, and their role in metabolic, immune, and physiological processes should be recognised as inherent rather than therapeutic.

3. **Use Upper Intake Levels as Scientific Risk Benchmarks Only.** Upper intake levels (ULs) should be treated strictly as scientific risk reference points, not regulatory thresholds. Exceeding a UL must not automatically trigger product reclassification. Legislation should make clear that ULs:

   - represent risk benchmarks rather than regulatory cut-offs; and
   - do not, in themselves, determine legal classification.

4. **Require Case-by-Case, Contextual Assessment.** Regulatory decisions should be made on a case-by-case basis, taking into account dose, chemical form, route of exposure, population context, and total cumulative intake. This replaces rigid classification rules with proportionate, context-sensitive judgement.

Assessment must explicitly distinguish between background (environmental or dietary) exposure and pharmacological exposure regimes, and evaluate risk within the appropriate biological context.

5. **Modernise and Implement Weight-of-Evidence Scientific Method.** A modernised evidential framework is required. Regulatory assessments must incorporate an assessment of:

    - Mechanistic biology
    - Clinical trials
    - Observational and cohort data
    - Case reports and real-world use
    - Biomarker and physiological data

Critically, this must involve expert synthesis into a coherent biological model, not mere parallel citation. Assessment must distinguish between adaptive physiological responses, nutrient interactions, and clinically meaningful toxicity.

In parallel, advanced analytical tools, including AI-assisted literature review, should be used to enable faster, deeper, and more comprehensive scientific evaluation.

6. **Recognise Biological Function as a Foundational Regulatory Principle.** Legislation should explicitly recognise that:
    - nutrients are endogenous and biologically essential; and
    - their physiological roles are expected and integral to normal human function.

    This ensures regulatory frameworks are aligned with biological reality.

7. **Enable Proportionate Decision-Making Under Uncertainty.** Introduce a statutory principle that absence of evidence of harm must not be treated as evidence of risk. Regulatory frameworks must distinguish between theoretical hazards, mechanistic plausibility, and demonstrated clinical harm.

    Where a substance is present in the diet or environment at measurable levels, this must be treated as relevant safety context in risk evaluation.

    This is particularly important for nutrients, where biological effects are context-dependent and often reflect normal physiological adaptation rather than toxicity, and addresses current precautionary overreach arising from failure to recognise biological necessity.

8. **Immediate Alignment of Clearly Outdated Thresholds.** Where existing thresholds are demonstrably conservative and not grounded in contemporary scientific risk assessment should be updated through secondary legislation without delay.

9. **Mandatory Scientific Transparency and Expertise Disclosure.** To restore confidence in decision-making, all nutrient-related decisions must include transparent disclosure of:

    - committee membership and relevant subject-matter expertise
    - conflicts of interest
    - external advice sought
    - how evidence has been weighted

Committees must include appropriate expertise in nutrition science, physiology, and nutritional toxicology, and must prioritise biological relevance in their assessments.

10. **Establish a Dedicated Nutrient Assessment Pathway**. A dedicated nutrient assessment pathway will operate independently of pharmaceutical approval models. This pathway should enable evaluation without reliance on commercial sponsorship, allow iterative evidence development, and provide a practical route for low-risk, non-patentable substances to be assessed and, where appropriate, made accessible. Key points:
    - Does not require a commercial sponsor
    - Allows public-interest or academic submissions
    - Supports iterative review (not one-shot rejection)
11. **Embed an 'Adequacy and Function' standard in law.** Legislation should move beyond a narrow deficiency–toxicity paradigm and require consideration of the full spectrum of nutritional status, including deficiency, insufficiency, adequacy, and functional sufficiency. While current science does not yet provide a complete framework for defining optimal intake, regulatory systems must at least be capable of recognising and supporting biologically adequate and functionally relevant levels of nutrient intake.
12. **Restore Independent, Evidence-Led Nutrient Standard Setting.** New Zealand should not automatically adopt or defer to external nutrient thresholds where those settings are based on legacy methodologies or do not reflect contemporary scientific evidence. Nutrient standards must be independently assessed against current evidence, including mechanistic, clinical, and population-level data, and calibrated to New Zealand's specific context, including baseline nutritional status, dietary patterns, and public health needs.

    Where existing thresholds have been derived from outdated frameworks or are not supported by current risk assessment, decision-makers should be required to:

    - undertake an independent, transparent scientific review;
    - explicitly justify continued reliance on external standards; or
    - depart from those standards where they are not scientifically proportionate.

    This approach ensures that regulatory settings are grounded in current evidence rather than institutional alignment, and that New Zealand retains sovereign capability to set proportionate, biologically relevant nutrient standards.

    Regulatory frameworks must not collapse materially distinct exposure regimes into a single classification where dose and biological effect differ by orders of magnitude.

BACKGROUND TO THIS POLICY

[1] A MULTILAYERED SYSTEM THAT PENALISES NUTRIENTS

New Zealand lacks a robust harm framework that coherently integrates clinical medicine, toxicology, and nutrition science in the evaluation of micronutrients.

Current governance frameworks for the regulation of nutrients lacks sufficient analytical sophistication to reflect the biological and clinical realities of micronutrients. It remains anchored in legacy approaches derived from deficiency prevention and chemical-style risk assessment, with a primary emphasis on threshold-setting and avoidance of adverse effects.

This interacting flaws create direct consequences for access, clinical practice, and population health

The system encourages regulatory hesitancy. Triggers built into the system signal harm when the nutrient itself does not present a toxicological risk, officials default to limit or deny increasing access to recognised safe levels of nutrients due to absence of evidence of harm.

The hesitancy of officials could be observed in recent decisions by Medsafe to decline Julia Rucklidge's application to increase permitted levels of vitamin D[1] and allow lithium[2] at environmentally relevant levels. [3]

The language used by the officials and their decisions, illustrate the practical consequences of the current regulatory framework. Rucklidge is a subject matter expert. Trials by Rucklidge and colleagues have consistently demonstrated a positive safety profile for nutrients where some are prescribed at higher levels than current New Zealand upper limits, that were established in 1984, permit.[4 5 6 7 8 9 10 11]

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[1] Medsafe. Submission for medicine reclassification for consideration by the Medicines Classification Committee. Agenda 74, 5.5 Vitamin D. https://www.medsafe.govt.nz/profs/class/Agendas/Agen74/5.5VitaminD.pdf

[2] Medsafe Agenda 74, 5.4 Lithium. Submission for medicine reclassification for consideration by the Medicines Classification Committee. https://medsafe.govt.nz/profs/class/Agendas/Agen74/5.4Lithium.pdf?

[3] Medsafe (Oct 30, 2025). Minutes for the 74th meeting of the Medicines Classification Committee held at 133 Molesworth Street, Wellington on 23 July 2025. 5.4 Lithium. 5.5 Vitamin D (Prof Julia Rucklidge). https://www.medsafe.govt.nz/profs/class/Minutes/2021-2025/74mccMin23July2025.htm#5.5

[4] Rucklidge JJ, Sherwin AH, Mulder RT, Manna L & Boden JM. (2026) Efficacy and Safety of Micronutrient Treatment for Irritability in Teenagers: 8-Week Double-Blinded Randomized Placebo-Controlled Trial (BEAM). Journal of the American Academy of Child & Adolescent Psychiatry.

[5] Rucklidge JJ, Eggleston MJF, Ealam B, Beaglehole B, Mulder RT. An Observational Preliminary Study on the Safety of Long-Term Consumption of Micronutrients for the Treatment of Psychiatric Symptoms. The Journal of Alternative and Complementary Medicine: Paradigm, Practice, and Policy Advancing Integrative Health. 2019;25(6):613-622. doi:10.1089/acm.2018.0352

[6] Rucklidge JJ, Frampton CM, Gorman B, Boggis A. Vitamin-mineral treatment of attention-deficit hyperactivity disorder in adults: double-blind randomised placebo-controlled trial. Br J Psychiatry. 2014;204:306-15. doi: 10.1192/bjp.bp.113.132126.

[7] Rucklidge, J. J., Eggleston, M. J. F., Johnstone, J. M., Darling, K., & Frampton, C. M. (2018). Vitamin-mineral treatment improves aggression and emotional regulation in children with ADHD: A fully blinded, randomized, placebo-controlled trial. Journal of Child Psychology and Psychiatry, 59(3), 232–246. https://doi.org/10.1111/jcpp.12817

[8] Bradley HA, Moltchanova E, Mulder RT, Dixon L, Henderson J, Rucklidge JJ. (2024) Efficacy and safety of a mineral and vitamin treatment on symptoms of antenatal depression: 12-week fully blinded randomised placebo-controlled trial (NUTRIMUM). BJPsych Open. 2024 Jun 3;10(4):e119. doi: 10.1192/bjo.2024.706.

[9] Mitchell, M., Bradley, H., Blampied, N.M., Mulder, R.T., Rucklidge, J.J. (2025). Protective effect of micronutrients used to treat antenatal depression on rates of postnatal depression at six months: A secondary analysis of NUTRIMUM. Journal of Affective Disorders 388 (2025) 119560. DOI: 10.1016/j.jad.2025.119560

[10] Blampied M, Bell C, Gilbert C & Rucklidge JJ (2020). Broad spectrum micronutrient formulas for the treatment of symptoms of depression, stress, and/or anxiety: a systematic review, Expert Review of Neurotherapeutics, 20:4, 351-371, DOI: 10.1080/14737175.2020.1740595

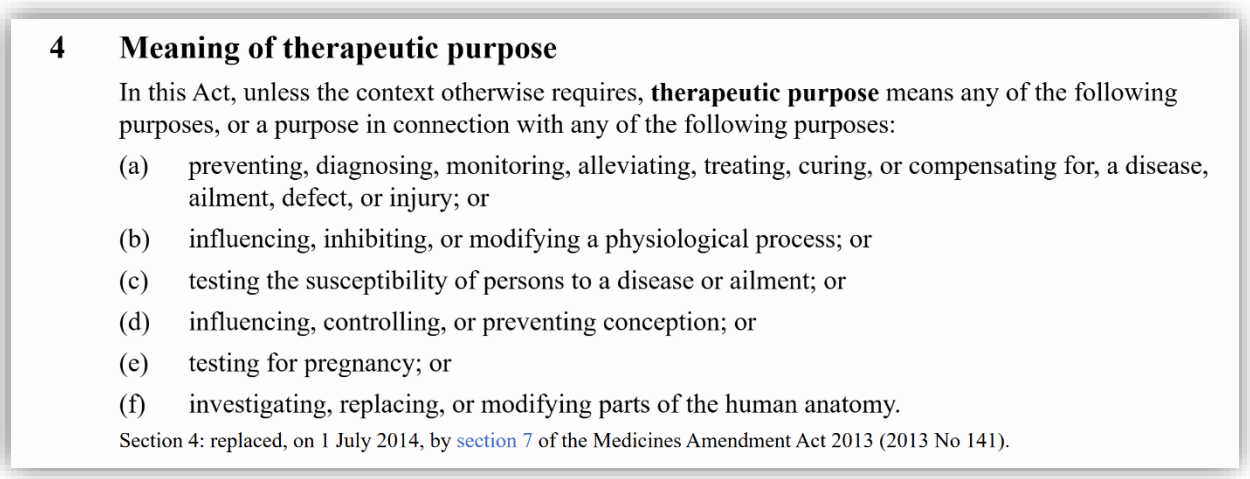
[11] Rucklidge, J. J., Johnstone, J. M., & Kaplan, B. J. (2021). Nutrition Provides the Essential Foundation for Optimizing Mental Health. Evidence-Based Practice in Child and Adolescent Mental Health, 6(1), 131–154. https://doi.org/10.1080/23794925.2021.1875342

Interlocking Barriers: Risk Framing that Suppresses Nutritional Function

As this paper discusses, from the NRV Methodological Framework and Nutrient Reference Values for Australia and New Zealand Including Recommended Dietary Intakes, to the Medicines Act 1981, Medicines Regulations 1984 and Dietary Supplements Regulations 1985, nutrients are assessed and governed through models that default to toxicological risk framing rather than biological function.

Upper intake levels are presented as 'safety' thresholds, yet are often derived from limited or indirect evidence, including nutrient-nutrient interactions (e.g. zinc-copper balance) or confounded trial contexts (e.g. calcium-vitamin D). In the absence of clear differentiation between adaptive physiological responses and clinically meaningful toxicity, these thresholds risk being interpreted as indicators of serious harm rather than context-dependent biological effects.

At the same time, the regulatory system permits nutrients to be classified as medicines where they are described as having metabolic, physiological, or immunological effects, irrespective of intrinsic risk or dose. The overbroad 'therapeutic purpose' trigger in Section 4 of the Medicines Act 1981 brings low-risk nutrients within medicines regulation, signalling to clinicians and patients that these substances are equivalent to pharmaceutical agents. This occurs despite the



4 Meaning of therapeutic purpose

In this Act, unless the context otherwise requires, **therapeutic purpose** means any of the following purposes, or a purpose in connection with any of the following purposes:

(a) preventing, diagnosing, monitoring, alleviating, treating, curing, or compensating for, a disease, ailment, defect, or injury; or

(b) influencing, inhibiting, or modifying a physiological process; or

(c) testing the susceptibility of persons to a disease or ailment; or

(d) influencing, controlling, or preventing conception; or

(e) testing for pregnancy; or

(f) investigating, replacing, or modifying parts of the human anatomy.

Section 4: replaced, on 1 July 2014, by section 7 of the Medicines Amendment Act 2013 (2013 No 141).

Figure 1 Medicines Act 1981, S.4. Meaning of therapeutic purpose.

fundamental distinction that micronutrients are involve in basic metabolic function, including enzymatic activity, cellular signalling, immune function, and metabolic regulation.

The medicines framework itself is based on a commercial cost-recovery model, in which regulatory and compliance costs are embedded in product pricing and supported by intellectual property protections. Pharmac funding mechanisms reflect this model, favouring patentable products backed by sponsors able to finance evidence generation and regulatory approval. Nutrients, by contrast, operate in a low-margin, non-excludable market, where such costs cannot be internalised. The result is systematic underinvestment in evidence and restricted access to regulatory and funding pathways, privileging high-cost interventions over low-cost, non-patentable alternatives.

Institutional preferences within the Ministry of Health and Medsafe reflect these pharmaceutical norms. This is particularly problematic in nutrition, where micronutrients do not behave like

conventional drugs. Their effects are context-dependent, non-linear, and shaped by baseline status, cofactor availability, and physiological demand. Phenomena such as cofactor displacement, redistribution, or increased metabolic utilisation are often features of normal physiological adaptation rather than toxicity. Current frameworks do not adequately capture these dynamics, nor do they provide tools to assess nutrients across the spectrum from deficiency through insufficiency to functional adequacy.

As a result, the system is weighted toward identifying potential risk rather than characterising biological necessity and functional sufficiency. This framing carries through into dietary guidance, regulatory settings, and clinical interpretation, shaping professional understanding and public messaging in ways that overstate risk while understating the essential, system-wide role of micronutrients in metabolic regulation, neurobiology, immune function, and long-term health.

These methodological, regulatory, and economic elements operate in concert to form a reinforcing system. A coordinated set of institutional conditions that limit availability, constrain clinical use, and reduce informed choice, while privileging intervention pathways aligned with pharmaceutical models.

The system lacks a coherent framework for classifying harm. Clinical medicine, toxicology, and nutrition each apply different lenses, severity-based, threshold-based, and adequacy-based respectively, without a unifying framework that distinguishes adaptive biological responses from true toxicological injury. In the absence of such a framework, there is a risk that mechanistically explicable and reversible nutrient effects are interpreted as safety signals, obscuring both deficiency-related harms and the legitimate role of nutrients in restoring optimal physiological function.

This limitation is compounded by the framework's insufficient integration of diverse evidence streams. Without an integrated method for synthesising mechanistic, clinical, and population data into a coherent biological model, decision-making tends to privilege discrete endpoints over systemic understanding. This constrains the ability of officials to recognise the role of micronutrients in complex, multi-factorial conditions and limits the development of guidance aligned with contemporary science.

A recent decision to reject an application to treat environmentally relevant levels of lithium as a nutrient, illustrates the operation of a regulatory model in which therapeutic purpose functions as the primary legal trigger, rather than dose, exposure, or demonstrated risk.

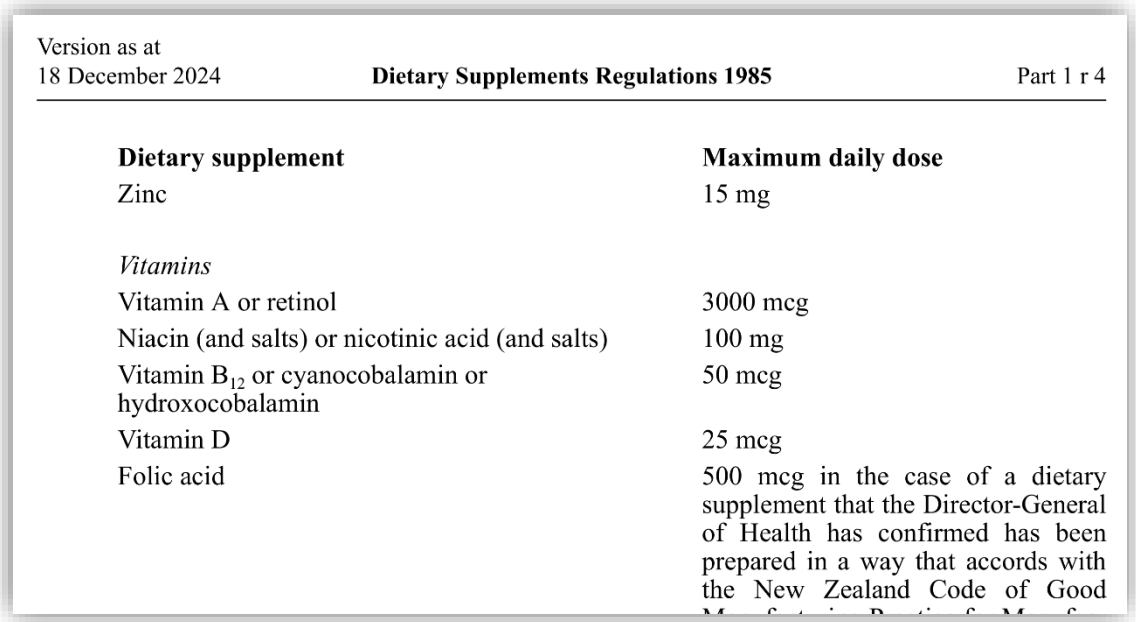
Officials currently operate within a rigid classification environment in which substances are treated as medicines or not, with limited capacity to recognise gradations based on biological context. Officials appear unable to discern the difference between trace nutritional exposure and pharmacological use, such that low-dose lithium is assessed within the same conceptual framework as high-dose therapeutic administration. Regulation must distinguish between pharmacological lithium and nutritionally relevant lithium, as these represent fundamentally different exposure regimes with different risk profiles, yet this is not currently the case.

From a public law perspective, this raises questions as to whether the framework and its application are fit for purpose. Where decision-making methodologies are incomplete or misaligned with the subject matter, there is a risk that relevant considerations are not fully taken into account, evidence is not properly weighted, and outcomes lack proportionality. In particular,

where the regulatory framework (across primary and secondary legislation) constrains the expression of scientific evidence, limits integration of relevant data, and defaults to precaution in the absence of demonstrated risk, this may indicate systematic under-recognition of relevant evidence. Such conditions give rise to concerns regarding fettering of discretion, failure to properly weigh relevant considerations (including dose–response and biological context), and the proportionality of resulting regulatory controls.

New Zealand vs European minimum standards

Examples of nutrients that are in common use as a nutrient in other countries, but which must go through a formal medicines pathway in New Zealand, once they are above a certain threshold, as listed on the Dietary Supplements Regulations 1985.



Version as at
18 December 2024 **Dietary Supplements Regulations 1985** Part 1 r 4

Dietary supplement	Maximum daily dose
Zinc	15 mg
Vitamins	
Vitamin A or retinol	3000 mcg
Niacin (and salts) or nicotinic acid (and salts)	100 mg
Vitamin B_{12} or cyanocobalamin or hydroxocobalamin	50 mcg
Vitamin D	25 mcg
Folic acid	500 mcg in the case of a dietary supplement that the Director-General of Health has confirmed has been prepared in a way that accords with the New Zealand Code of Good

Figure 2 Dietary Supplements Regulations 1985.

Folic Acid: Products such as Elevit, which contain folic acid at levels routinely recommended for pregnancy, are treated within European and United States frameworks as nutritional supplements despite their well-established physiological and preventive roles. In contrast, the New Zealand regulatory system applies a broader therapeutic purpose trigger, under which the same biological functions, such as prevention of neural tube defects, can bring nutrients within medicines classification. This reflects a fundamental difference in regulatory approach: nutrient function is treated as inherent and expected in European and US systems, but as a potential trigger for medicines regulation in New Zealand.

Hardys Essential Nutrients: Because the product is described as supporting brain function, Medsafe has categorised it as a medicine under the therapeutic purpose provisions. This occurs despite the product comprising micronutrients with a documented history of safe use, including evidence from clinical trials. The classification therefore reflects the regulatory emphasis on stated physiological effect, rather than an assessment of intrinsic risk or safety profile.

Vitamin D: In New Zealand, lower maximum doses for vitamin D within dietary supplement regulations (typically 1000 IU per daily dose) can result in higher cost and reduced convenience compared with Europe and the United States, where higher-dose vitamin D products are widely available within food or supplement frameworks, allowing more cost-efficient delivery at commonly used intake levels.

Higher Dose Iodine Formulations (E.g. Lugols): In the European Union, Lugol's iodine is typically available through pharmacy-based channels as a medicinal or compounded product, rather than as a standard dietary supplement.

Lugol's iodine is available in New Zealand, but only through fragmented pathways: as low-dose nutritional supplements, as externally labelled chemical solutions, or through limited practitioner channels.

[2] REGULATORY APPROACH: CONFLATING HARM FROM NUTRIENTS

(a) The GRADE Framework

The GRADE framework (Grading of Recommendations Assessment, Development and Evaluation) is widely used to assess the certainty of evidence, prioritising randomised controlled trials and ranking other forms of evidence accordingly. [12] [13] The GRADE framework is recommended as the preferred approach for assessing the evidence base for clinical, health and dietary guidelines, when reviewing nutrient reference values for Australia and New Zealand.[14]

While appropriate for evaluating discrete pharmaceutical interventions, this hierarchy is less suited to nutrients, which operate within complex, adaptive biological systems and are not easily reducible to single-variable interventions.

Nutrient effects are often context-dependent, influenced by baseline nutritional status, cofactor availability, dose, and physiological demand. As a result, meaningful evidence may arise from multiple domains, including mechanistic biology, biomarker studies, observational data, and clinical practice. These forms of evidence are frequently interdependent and collectively informative, rather than individually decisive.

The limitation is not simply that certain evidence types are ranked lower, but that the framework does not provide a method for integrating diverse forms of evidence into an integrated and scientifically robust biological understanding. Evidence may be appraised in isolation, without adequate synthesis across mechanistic, clinical, and population-level data, and without sufficient attention to how these lines of evidence interact.

This produces a regulatory framework that is poorly suited to the biological realities of nutrient function. Effects that are biologically plausible and supported across multiple domains (e.g. mechanistic, case and cohort data) may be discounted if not confirmed through conventional trial designs, while adaptive physiological responses or context-specific effects may be misinterpreted when assessed outside their biological context.

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[12] GRADE Handbook (2013). https://gdt.gradepro.org/app/handbook/handbook.html
[13] Cochrane Grade. https://www.cochrane.org/learn/courses-and-resources/cochrane-methodology/grade?
[14] Australian Government Department of Health (2022) Methodological framework for the review of Nutrient Reference Values 2015-2017. https://www.eatforhealth.gov.au/sites/default/files/2022-10/Final_NRV_Methodological_Framework_v2.0_0.pdf

In the context of nutrient regulation, reliance on hierarchical evidence frameworks without complementary integrative methods risks narrowing the evidential base, constraining interpretation, and reinforcing conservative regulatory positions that do not reflect the full scope of relevant science.

(b) Australia New Zealand updated NRV methodological framework (2022)

The updated nutrient reference values (NRV) methodological framework reflects the limitations described above.[15] The model is anchored in an historical approach, the population-level reference model, rather than a clinically grounded harm framework. It explicitly defines its purpose as deriving intake values to prevent deficiency, prevent harm (via ULs), and support chronic disease prevention.

The Australian NRV framework follows regulatory traditions and is oriented toward producing reference numbers (EAR, RDI, UL, SDT)[16]. It is not focussed on a biologically or clinically nuanced classification of harm. This means that while 'harm' is formally included, it is operationalised primarily as a threshold-setting exercise, not as a differentiated understanding of the nature, mechanism, or severity of adverse effects.

This leaves clinicians and health professionals without a sound basis to evaluate risk.

Although the framework adopts systematic review methods and draws on approaches such as GRADE to assess the quality of evidence, it reproduces the same limitation: evidence certainty is evaluated, but harm is not meaningfully stratified. The process requires identification of outcomes and synthesis of evidence across study types, but it does not support officials and researchers to distinguish between transient biochemical changes, nutrient–nutrient interactions, adaptive physiological responses, and clinically significant toxicity. It lacks nuance and sensitivity.

Even in the upper limit (UL) setting process, the emphasis is on identifying a point at which 'adverse effects' occur, using concepts such as no observed effect level (NOAEL) and lowest observed effect level (LOAEL), rather than classifying the clinical seriousness or reversibility of those effects.

As a result, the framework retains a threshold-based toxicology model, albeit modified for nutrients, without resolving the interpretive gap between different categories of harm.

The supporting material recognises that micronutrient risk assessment differs from standard chemical risk assessment and requires adaptation, noting that traditional approaches may be inappropriate for nutrients. However, this acknowledgement is not translated into a fully developed alternative framework.

There is no explicit taxonomy that separates adaptive or compensatory physiological responses (e.g. cofactor redistribution, increased metabolic demand) from true toxicological injury. Nor is there a consistent requirement to distinguish between subclinical, reversible effects and clinically meaningful outcomes such as organ dysfunction or hospitalisation. The framework therefore

[15] Aust Govt. Department of Health (2022) Methodological framework for the review of Nutrient Reference Values.
[16] EAR (Estimated Average Requirement); RDI (Recommended Dietary Intake); UL (Upper Limit); SDT (Suggested Dietary Target).

remains methodologically general but biologically under-specified, relying on expert judgement without providing the integrative, layered tools needed to ensure consistent interpretation.

The framework permits consideration of mechanistic, observational, and clinical evidence, but it does not establish a sufficiently rigorous or operational methodology for integrating these evidence streams. It does not set out a clear hierarchy or pathway to support evaluators to combine mechanistic, case, cohort, and trial data, to judge the weight of evidence, nor does it provide explicit guidance on how mechanistic evidence should inform conclusions where randomised trial evidence is limited or absent.

There is no requirement for the systematic synthesis of case reports or real-world clinical observations, despite their relevance for identifying patterns of response, adverse effects, and context-dependent outcomes in nutrition.

Concerningly, the framework does not articulate a method for constructing an integrative, biologically grounded model of nutrient function that integrates these diverse forms of evidence. As a result, while multiple evidence types may be included in principle, their interpretation remains variable and largely dependent on reviewer judgement, limiting the framework's capacity to capture the complexity of micronutrient biology and to support consistent, clinically meaningful conclusions.

The framework's inability to clearly articulate and classify harm is directly linked to its limited treatment of the evidence base. While it permits consideration of mechanistic, observational, and clinical data, it does not set out a clear hierarchy or integration method for combining mechanistic, case, cohort, and trial evidence, nor does it provide explicit guidance on how mechanistic evidence should inform conclusions where randomised trial evidence is limited.

It does not require officials to provide synthesise of case reports or real-world clinical observations, and it does not establish a framework for building a coherent, biologically grounded model of nutrient function across these evidence streams. As a result, the evidential base that would support a more nuanced understanding of micronutrients, their systemic roles, interactions, and context-dependent effects, is not consistently or systematically brought to bear in the assessment process.

In effect, the updated methodology reproduces historic institutional approaches seen across clinical medicine, toxicology, and nutrition science: it improves transparency and procedural consistency, but does not resolve how harms are defined, weighted, or communicated.

Without both a clinically anchored harm classification system and a nutritionally-relevant approach to integrating diverse forms of evidence, there remains a risk that lower-order, mechanistically explicable nutrient effects are interpreted as safety signals, while the distinction between adaptive physiological responses and true toxicity is obscured. The result is a system that is formally rigorous but substantively incomplete, and which continues to struggle to align evidential certainty with clinical significance in the evaluation of micronutrients.

(c) The Therapeutic Purpose Trigger

A related issue arises from the breadth of the 'therapeutic purpose' trigger within the Medicines Act 1981 legislative framework. Where a substance is presented as having a metabolic, immunological, or physiological effect, it may fall within the statutory definition of a medicine,

irrespective of its intrinsic risk profile. This expansive ‘catch-all’ captures nutrients and other low-risk substances within medicines regulation, irrespective of harm profile. It, as a blanket definition subjects nutrients to regulatory requirements designed for higher-risk pharmaceutical products.

In practice, this creates and supports a legal environment in which clinicians understand that recommending or utilising nutrients for therapeutic purposes may engage medicines legislation, even where there is no credible safety concern.

This overbroad trigger has resulted in medicines-level controls being extended into domains more appropriately governed by food and public health frameworks, since the enactment of the legislation, raising issues of proportionality, classification coherence, and alignment with biological reality

(d) Barriers to Pharmac Funding of Nutrients

There are significant institutional barriers to the funding of nutrients within the current health system. Funding pathways are largely designed around pharmaceutical drug application protocols, requiring a sponsoring entity, commercial backing, and trial protocols aligned with patentable products. Nutrients, by contrast, are typically low-cost, non-patentable, and lack a commercial sponsor capable of navigating these pathways.

As a result, even where there is an established safety profile and emerging clinical or mechanistic evidence, there is no clear or proportionate route into public funding. This creates a systematic exclusion of nutritional interventions from formal funding mechanisms, despite their potential relevance to prevention, adjunctive care, and population health outcomes.

[3] CASE STUDY: INTRAVENOUS VITAMIN C IN HOSPITALS

Intravenous vitamin C (IVC) remains a seriously investigated adjunctive therapy with heterogeneous evidence. For infectious indications, the most sustained hospital use has been in sepsis and septic shock, community-acquired or severe pneumonia, and viral pneumonia including COVID-19. The evidence suggests that, where patients request IVC, hospitals may reasonably consider a coordinated clinical response, which permits the use of IVC in a hospital environment, and potentially adds to the knowledge on the safety and efficacy of IVC as a therapeutic treatment.

IVC has been adopted in some countries, centres, and critical-care research programmes than others, and more likely to be used where clinicians are attentive to critical care nutrition, oxidative stress, endothelial injury, micronutrient depletion, or integrative adjunctive treatment than where sepsis or pneumonia care is tightly standardised around restrictive guideline pathways.

Vitamin C has a strong biological plausibility as a supportive intervention in both acute and chronic conditions due to its central role in multiple physiological systems. It contributes to redox balance through antioxidant activity, supports endothelial integrity and nitric oxide–mediated vascular function, and plays a role in maintaining microcirculatory flow and capillary stability. It is also involved in immune regulation, including leukocyte function and inflammatory signalling. In states of illness, particularly those characterised by inflammation or metabolic stress, vitamin C

levels are often depleted, and this depletion is associated with increased oxidative stress, endothelial injury, and microvascular dysfunction.

These processes are not confined to acute illness but are also features of many chronic conditions, including cardiometabolic and inflammatory disorders. In more severe states such as sepsis, acute respiratory distress syndrome (ARDS), pneumonia, and critical illness, these same pathways are amplified, providing a mechanistic rationale for higher-dose intravenous administration to restore plasma levels and support physiological function. While this biological framework supports investigation of vitamin C as an adjunct to reduce adverse outcomes, it does not in itself establish clinical efficacy, which remains dependent on dose, duration, timing, and patient context.

A 2023 meta-analysis of 12 randomised controlled trials including 1,712 critically ill patients, where intravenous vitamin C as a monotherapy found that, across the studies IVC reduced pooled mortality, durations of vasopressor use and mechanical ventilation.[17] The 2023 meta-analysis considered a low dose to be <100 mg/kg/day, and a high dose to be 10000 mg/kg/day. The classification of intravenous vitamin C dosing in the 2023 meta-analysis is methodologically imprecise, combining weight-based and absolute dosing thresholds into a single 'high-dose' category. This obscures substantial variation in actual administered doses and does not reflect a biologically validated toxicity or efficacy threshold. The available evidence suggests that both dose and duration may influence outcomes, but current analyses lack the granularity to distinguish between high-dose short-course regimens and moderate-dose longer-course approaches. As a result, conclusions regarding 'high' versus 'low' dose should be interpreted cautiously, as they may reflect artefacts of categorisation rather than true physiological effects.

Our subgroup analysis revealed that a low dosage of IVVC was associated with a reduced risk of mortality, while this benefit was not noted with a high dosage of IVVC. The current meta-analysis is the first to unveil this novel finding in the critically ill population.

The purposes for which IVC has been used in these systems are fairly consistent across countries, even where the outcomes differ. In sepsis and septic shock, the rationale has usually been mitigation of oxidative stress, support of endothelial and microcirculatory function, possible vasopressor reduction, correction of marked hypovitaminosis C, and modulation of inflammatory injury.

Sepsis

The pharmacological management of sepsis relies on multiple high-risk interventions, including broad-spectrum antibiotics[18], vasopressors, corticosteroids[19], and intensive supportive care. These therapies are associated with well-recognised adverse effects, including organ toxicity,

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[17] Hung K-C, Chuang M-H, Chen J-Y, Hsu C-W, Chiu C-C, Chang Y-J, Lee C-W, Chen I-W and Sun C-K (2023) Impact of intravenous vitamin C as a monotherapy on mortality risk in critically ill patients: A meta-analysis of randomized controlled trials with trial sequential analysis. Front. Nutr. 10:1094757. doi: 10.3389/fnut.2023.1094757

[18] Tang F, Yuan H, Li X, Qiao L. Effect of delayed antibiotic use on mortality outcomes in patients with sepsis or septic shock: A systematic review and meta-analysis. Int Immunopharmacol. 2024 Mar 10;129:111616. doi: 10.1016/j.intimp.2024.111616.

[19] Pitre T, Drover K, Chaudhuri D et al. (2024). Corticosteroids in Sepsis and Septic Shock: A Systematic Review, Pairwise, and Dose-Response Meta-Analysis. Critical Care Explorations 6(1):p e1000, January 2024. | DOI: 10.1097/CCE.0000000000001000

arrhythmias, immunosuppression, and ischemic complications. Their use reflects the severity of sepsis and the need for rapid physiological stabilisation.

In a South Korean study, 36,327 (9%) did and 347,955 did not receive vitamin C alone for ≥ 5 days or in combination with corticosteroids and/or thiamine. The hospital mortality was lower by - 0.9% in the treatment group. However, mortality decreased greater in patients who received vitamin C for ≥ 5 days (vs 1-2 or 3-4 days). Further, vitamin C was associated with a lower hospital mortality in patients with older age, multiple comorbidities, pneumonia, genitourinary infection, septic shock, and mechanical ventilation. [20] The large South Korean sepsis cohort identified a duration-dependent association (≥5 days) but did not report dosing, whereas smaller Korean ICU studies typically used moderate doses (~6 g/day).

That Korean finding contrasts with the large multinational LOVIT sepsis trial, which gave a very high dose for a shorter period: 50 mg/kg every 6 hours for 96 hours, i.e. 200 mg/kg/day for up to 4 days. LOVIT randomised 872 patients (435 vitamin C, 437 control) across 35 ICUs in Canada, France, and New Zealand. LOVIT found a worse composite outcome with vitamin C, which is one reason recent sepsis guidance moved against routine use.[21]

LOVIT trial:

- 50 mg per kilogram actual body wt mixed in a 50-ml solution of either dextrose 5% in water or normal saline
- Administered over 30 to 60 minutes every 6 hours for 96 hours (i.e., 200 mg per kilogram per day, with a maximum of 16 doses) as long as patients remained in the ICU

The contrast between 4 days in LOVIT and ≥5 days in the Korean cohort is therefore part of the current debate: some clinicians and authors argue that the negative sepsis trials may have used the wrong timing, duration, or patient selection, while guideline bodies treat the current randomised evidence as insufficient or unfavourable. That remains an open scientific question, primarily relating to dose and duration, not a settled one.

Chinese ICU COVID-19 pilot trial patients were randomised within 48 hours of ICU admission to 24 g/day of vitamin C, given as 12 g every 12 hours, for 7 days. The primary outcome was invasive mechanical ventilation-free days in 28 days, with a secondary outcomes based on 28-day mortality, organ failure. The trial enrolled 56 patients across three ICUs in Wuhan. IVC administration did not improve the primary endpoint, but it suggested a possible signal in oxygenation. [22] In India, the LOVIT-India pilot feasibility trial studied IVC in thirty adults with sepsis in ICUs, indicating ongoing interest within hospital critical care rather than settled clinical adoption.[23]

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[20] Jung SY, Lee MT, Baek MS, Kim WY. Vitamin C for ≥ 5 days is associated with decreased hospital mortality in sepsis subgroups: a nationwide cohort study. Crit Care. 2022 Jan 5;26(1):3. doi: 10.1186/s13054-021-03872-3.
[21] Lamontagne F, Masse MH, Menard J. et al. (2022). Intravenous Vitamin C in Adults with Sepsis in the Intensive Care Unit, NEJM, 386:2387-2398, DOI: 10.1056/NEJMoa2200644
[22] Zhang J, Rao X, Li Y, Zhu Y, Liu F, Guo G, Luo G, Meng Z, De Backer D, Xiang H, Peng Z. Pilot trial of high-dose vitamin C in critically ill COVID-19 patients. Ann Intensive Care. 2021 Jan 9;11(1):5. doi: 10.1186/s13613-020-00792-3.
[23] Vijayaraghavan BKT, Venkataraman R, Ramanathan Y, Margabandhu S, Jayakumar D, Ramachandran P, Adhikari NK, Lamontagne F, Pinto R, Masse MH, Ménard J, Sprague S, Ramakrishnan N. A Pilot Feasibility Randomized Controlled

Pneumonia

In severe pneumonia and viral pneumonia, including COVID-19, the rationale has typically been antioxidant support, attenuation of inflammatory lung injury, improved oxygenation, and correction of the low vitamin C concentrations commonly seen in hospitalised patients with acute infection.

In New Zealand community-acquired pneumonia work, patients admitted with CAP had low vitamin C status, and researchers reported a trend towards shorter duration of hospital stay and time to clinical stability in those who received supplemental vitamin C. The intervention was designed to restore saturating concentrations while testing feasibility for larger outcome trials. [24] [25]

In South Korean severe pneumonia studies, vitamin C was also used in combined protocols with hydrocortisone and thiamine, reflecting a broader 'metabolic resuscitation' or adjunctive critical-care approach rather than a stand-alone antimicrobial claim.[26] [27] A 2024 BMJ Open review protocol indicates that CAP remains an active research target for hospital vitamin C use. [28]

On side-effect reporting, the picture is mixed, but there is enough in the record to make several careful observations. The better-designed ICU trials did not ignore safety. The LOVIT programme explicitly tracked stage 3 acute kidney injury, hemolysis, and hypoglycemia, and the protocol provided for oversight of serious unexpected adverse events by an independent data and safety monitoring committee. The Chinese pilot trial in critically ill COVID-19 patients explicitly monitored adverse events and identified potential event categories including nausea/vomiting, electrolyte disturbance, and acute kidney injury, with follow-up under Chinese good clinical practice requirements.

The New Zealand CAP feasibility trial reported 31 adverse events within 30 days, including 8 serious adverse events, but noted that none of the serious events were considered related to the study drug and that only three adverse events were thought to be study-medication related; the doses were described as safe and well tolerated. The Indian LOVIT-India feasibility trial also predefined safety outcomes including stage 3 AKI, hemolysis, severe hemolysis, hypoglycemia, and serious adverse events.

Trial of Intravenous Vitamin C in Adults with Sepsis in the Intensive Care Unit: The Lessening Organ Dysfunction with Vitamin C-India (LOVIT-India) Trial. Indian J Crit Care Med. 2023 Dec;27(12):910-916. doi: 10.5005/jp-journals-10071-24587.

[24] Carr AC, Vlasiuk E, Zawari M, Scott-Thomas A, Storer M, Maze M, Chambers ST. Low Vitamin C Concentrations in Patients with Community-Acquired Pneumonia Resolved with Pragmatic Administration of Intravenous and Oral Vitamin C. Antioxidants (Basel). 2023 Aug 14;12(8):1610. doi: 10.3390/antiox12081610.

[25] Chambers ST, Storer M, Scott-Thomas A, Slow S, Williman J, Epton M, Murdoch DR, Metcalf S, Carr A, Isenman H, Maze M. Adjunctive intravenous then oral vitamin C for moderate and severe community-acquired pneumonia in hospitalized adults: feasibility of randomized controlled trial. Sci Rep. 2023 Jul 23;13(1):11879. doi: 10.1038/s41598-023-37934-z.

[26] Lee SI, Lim CM, Koh Y, Huh JW, Lee JS, Hong SB. The effectiveness of vitamin C for patients with severe viral pneumonia in respiratory failure. J Thorac Dis. 2021 Feb;13(2):632-641. doi: 10.21037/jtd-20-1306.

[27] Kim WY, Jo EJ, Eom JS et al (2018). Combined vitamin C, hydrocortisone, and thiamine therapy for patients with severe pneumonia who were admitted to the intensive care unit: Propensity score-based analysis of a before-after cohort study. Journal of Critical Care 47: 211-218

[28] Sharma Y, Sumanadasa S, Shahi R, et alRole of vitamin C in treatment of community-acquired pneumonia in adult patients requiring hospitalisation: a systematic review protocolBMJ Open 2024;14:e082257. doi: 10.1136/bmjopen-2023-082257

Side-effect reporting is not equally developed across all parts of the IVC literature. The more rigorous randomised trials and feasibility studies generally provide explicit safety monitoring frameworks, whereas some observational and before-after cohort studies are much more outcome-focused and less informative on adverse-event ascertainment. The literature is stronger on major monitored risks such as kidney injury, hemolysis, and hypoglycaemia in ICU trials than it is on systematic reporting of less serious or cumulative adverse effects across all settings.

Intravenous vitamin C (IVC) remains a seriously investigated adjunctive therapy in hospital care for infectious illness, particularly in settings where clinicians are focused on oxidative stress, micronutrient depletion, and the pathophysiology of critical illness. The current evidence base is heterogeneous and insufficient to support a consensus position, with variability in findings likely reflecting differences in dose, duration, timing, and patient selection. Within standard sepsis management, antibiotics demonstrate a clear benefit–risk profile and are indispensable, whereas other components of care (including corticosteroids and adjunctive therapies) show more variable outcomes alongside well-recognised and sometimes substantial adverse effect profiles.

In this context, IVC, particularly at moderate, clinically monitored doses below those associated with recognised toxicity, may present a comparatively different and potentially more manageable side-effect profile, although its clinical benefit remains uncertain.

This suggests that, where patients request IVC, hospitals may reasonably consider a structured clinical response rather than categorical refusal. Such an approach could include informed consent, clear communication of the current evidence and uncertainties, and use within a monitored clinical framework, with appropriate documentation and, where feasible, inclusion in prospective data collection or service-level evaluation.

This position is consistent with the current status of IVC as a continuing area of ICU and hospital investigation, where uptake varies across countries and centres and is influenced not only by the evidence base but also by local clinical practice, institutional norms, and the degree of adherence to guideline-based care.

[4] CASE STUDY: VITAMIN D – NEW ZEALAND VS EUROPE.

(a) Medsafe's Recent Decline of Lithium & Vitamin D applications by a Subject-Matter Expert

The expertise of the officials involved in decision-making remains undisclosed.

The application appears to have encountered the double bind that is imposed by the Medicine Act 1981, S.7 'trigger': the applicant could not fully articulate the biological and clinical effects of the nutrients without engaging the statutory 'therapeutic purpose' trigger, yet there was no substantive evidence of harm at the proposed levels.

In this context, the decision-making process appears to have defaulted to regulatory constraint rather than evidential evaluation. Despite a substantial body of published work, including randomised controlled trials and observational studies demonstrating safety and clinical relevance, there is little indication that Rucklidge's expertise was recognised, nor any evidence that there was a systematically approach to the assessment of either benefit or risk.

The reasoning described suggests difficulty within the framework in addressing situations where evidence of harm is absent but biological plausibility and evidence of benefit are present. Concerns raised regarding potential nutrient-drug interactions and lithium exposure appear to have been considered in a precautionary manner, without clear calibration to dose, context, or comparative exposure (including the well-established magnitude differences between environmental and pharmacological lithium use). This reflects a broader issue: the framework is not well equipped to distinguish between theoretical, low-order, or context-dependent risks and clinically meaningful harm. Nor does it appear to provide decision-makers with tools to appropriately weigh high-quality human evidence, mechanistic understanding, and real-world exposure data in a proportionate way.

The case also highlights a forward-looking concern. While vitamin D is reportedly under review, if that review proceeds within the same methodological and conceptual constraints, particularly reliance on NRV methodologies, limited integration of mechanistic and clinical evidence, and absence of a cohesive, integrative harm framework, there is a material risk that outcomes will remain conservatively bounded irrespective of the underlying evidence base. In this sense, the issue is not confined to a single decision but reflects a broader systemic limitation in how micronutrients are evaluated, classified, and regulated.

In the EU scientific system, EFSA's adult tolerable upper intake level for vitamin D is 100 micrograms/day (4,000 IU). That is a risk-assessment benchmark derived from toxicity review, not a medicine trigger. By contrast, in New Zealand, vitamin D for internal use is treated as a medicine once it exceeds 25 micrograms/day (1,000 IU), unless it falls within the limited exceptions in the Medicines Regulations 1984.

Prof Rucklidge's 2025 application sought to move the New Zealand cut-off from 25 micrograms/day (1,000 IU) to 75 micrograms/day (3,000 IU), which would still remain below EFSA's adult UL of 100 micrograms/day (4,000 IU).

In the EU, vitamin D is ordinarily governed within food supplement law, not automatically recategorised as a medicine merely because it has physiological effects. Directive 2002/46/EC provides the food-supplement pathway, and EU medicines law requires more than mere biological activity: the Court of Justice has held that a product is not a medicinal product 'by function' unless, having regard to its composition and intended use, it is capable of appreciably restoring, correcting, or modifying physiological functions by pharmacological, immunological, or metabolic action. In practice, that means going above an EFSA UL does not, by itself, create an automatic medicines classification; it raises a food-safety and risk-management question. New Zealand's framework is materially different: products with more than 25 micrograms/day of vitamin D are medicines by classification, and products making therapeutic claims are medicines even below that threshold.

On the published record, the Medsafe/MCC review of Prof Rucklidge's application was narrow and formalistic rather than exploratory. The *74th Medicines Classification Committee* minutes show that the Committee acknowledged vitamin D deficiency in New Zealand and the proposal to raise the general-sales limit from 25 micrograms to 75 micrograms, but focused on whether the submission contained sufficient information on New Zealand context, dose, overdose, and misuse

or abuse, and concluded that benefits were 'not clear' and that there were 'outstanding concerns'.[29]

The minutes also record Medsafe's advice that even if reclassification occurred, products between 25 and 75 micrograms would still likely be regarded as medicines if used to treat deficiency, and as medicines they would still require Medsafe approval. That is important: the published reasoning centres heavily on the existing statutory interface and its consequences, rather than on whether the current threshold is itself scientifically proportionate.

The same published record does not show any evident attempt by officials to develop the application further, despite New Zealand's acknowledged pathway problem. In other matters before the same Committee, the minutes expressly record deferral pending further information or consultation; for example, another reclassification item was deferred for more material. In the vitamin D and lithium matters, by contrast, the Committee noted perceived deficiencies in the submission, queried whether material was up to date, and then rejected the proposals on the information available, without any recorded request for supplementary evidence, external expert input, or structured follow-up. That does not prove no enquiry occurred outside the published record, but none is evident in the official minutes.

On names and expertise, the published minutes disclose the names of Committee members present and Medsafe staff in attendance: Alison Cossar, Dr Tim Hanlon, Dr Ben Hudson, Dr Marcia Walker, Megan Peters, Bronwen Shepherd, Holly Wilson, and Medsafe attendees including Matthew Spencer, with several observers also named. The minutes also record that no new conflicts of interest were declared. What they do not do is set out, in the decision itself, the primary authors of the decision and their expertise base, the specific subject-matter expertise each participant brought to micronutrient science, nutritional toxicology, endocrinology, or vitamin D metabolism, nor do they identify any external nutrient-specific expert advice sought for these applications.

The EU system treats vitamin D primarily as a nutrient within food law and uses the UL as a scientific risk benchmark; New Zealand uses a much lower product-classification trigger that shifts vitamin D into medicines law at 25 micrograms/day. Prof Rucklidge's proposal sat below EFSA's adult UL, but the New Zealand decision remained constrained by a legacy classification approaches in which the statutory trigger (section four of the Medicines Act 1981), not a mature nutrient risk assessment, appears to do much of the work. On the published record, that leaves open a serious question as to whether the framework is equipped to evaluate recognised safe nutrients on their own scientific terms.

[5] CASE STUDY: BARRIERS TO FUNDING NUTRIENT-BASED INTERVENTIONS

An application to Pharmac to fund a broad-spectrum micronutrient formulation (Hardy's Daily Essential Nutrients, DEN) exposes how the system creates barriers to evaluating and funding low-risk, non-patentable interventions. The application was led by Professor Julia Rucklidge alongside

[29] Medsafe (Oct 30, 2025). Minutes for the 74th meeting of the Medicines Classification Committee held at 133 Molesworth Street, Wellington on 23 July 2025. 5.5 Vitamin D (Prof Julia Rucklidge). https://www.medsafe.govt.nz/profs/class/Minutes/2021-2025/74mccMin23July2025.htm#5.5

psychiatrist Matt Eggleston and was supported by substantial patient and family correspondence. Families reported that, due to cost, they were unable to continue accessing the product and would revert to funded pharmaceutical treatments, often with poorer tolerability or outcomes from their perspective.

The application and Pharmac response had been on the Pharmac website, but is now unavailable.

Officials seemed unable to reconcile the application with the Government's stated objective of achieving equitable health outcomes. Low-income populations are more vulnerable to nutrient insufficiency due to cost and dietary constraints, while children and adolescents in these groups are simultaneously in critical developmental phases where nutrient availability is foundational to brain and physiological development. A system that restricts access to low-risk nutritional interventions while funding higher-risk pharmaceutical treatments risks entrenching inequities in both access and outcomes.

The outcome of the application reflects a deeper institutional problem. Pharmac's processes are designed around pharmaceutical development models that rely on commercial sponsorship, large-scale trials, and patentable products. Nutrient-based interventions do not fit this model. They are low-cost, non-patentable, and typically lack a sponsoring entity capable of funding regulatory-grade evidence. As a result, the absence of sponsor-driven evidence operates as a barrier to consideration, rather than prompting a proportionate or adaptive evaluation pathway.

This is particularly significant in mental health, where pharmaceutical treatments are variably effective and may be poorly tolerated. Despite emerging evidence base and a favourable safety profile for multinutrient approaches, there remains no viable pathway for such interventions to be assessed and funded. The result is a broadly inequitable system: access to nutritional interventions is determined by ability to pay, while funded options are restricted to those aligned with pharmaceutical pathways.

This case illustrates that current funding and regulatory systems directly impact which interventions are available, to whom, and on what terms. Where these systems are misaligned with biological, economic, and social realities, they constrain both clinical practice and the Government's stated objective of achieving equitable health outcomes.

[6] CASE STUDY: ENVIRONMENTALLY RELEVANT LITHIUM - NZ *VS* THE EU

Recent Medsafe Rejection of Environmentally Relevant Lithium

The application submitted by Julia Rucklidge to the Medicines Classification Committee sought a narrowly defined regulatory adjustment to permit lithium at trace, nutritionally relevant levels (≤3 mg/day) within products for internal use. The proposal explicitly distinguished these levels from pharmacological lithium use, where therapeutic dosing typically begins in the hundreds of milligrams, and instead positioned lithium at trace levels within a nutritional and physiological context, comparable to environmental exposure and inclusion within multinutrient formulations. The intent was not to reclassify lithium as a medicine, but to establish a proportionate pathway that would allow low-dose inclusion without triggering prescription-only status. In the lithium application, Rucklidge stated:

> *I ask the MCC to consider exercising more appropriate enforcement discretion by applying the methodology intended for nutritional components of diet to lithium. There is a large body of*

literature which clearly demonstrates that lithium intake exceeding 3 mg/day is within the normal dietary range. Given that some individuals have very low lithium intake due to the increasingly nutritionally depleted diets of the 21st century (due to the increasing consumption of ultra-processed foods, very low in essential nutrients), doses of supplemental lithium up to at least 3 mg/day should be viewed as nutritional rather than therapeutic.

Since it is neither justifiable from the scientific literature for lithium nor proportionate with the enforcement of other nutritional components of diet to transition to prescription status within the range of normal dietary intake, I ask that the use of an appropriate UL as a reference limit for dietary supplement categorization rather than the current 10 ppm concentration or any value within the range of normal dietary intake, including the provisional RDI of 1 mg/day. [30]

The Committee's consideration of the application, recognised Rucklidge's statements noting observational and preclinical evidence which suggested potential benefit. [31] However, the Committee then emphasised that lithium is historically classified as a prescription medicine and that any product intended for a therapeutic purpose is a medicine regardless of concentration. The scope of the assessment demonstrated no flexibility. Rather than evaluating whether trace-dose lithium represented a distinct category warranting differentiated treatment, the Committee assessed whether the submission justified departure from an established classification position. The reasoning recorded is high-level and precautionary, relying on conclusions that there was insufficient information regarding risk and that outstanding concerns remained, without detailed articulation of dose-specific toxicological thresholds or comparative exposure.

A notable feature of the decision-making process is the absence of evident iterative enquiry. The published record does not indicate any request for supplementary information, deferral pending further evidence, commissioning of independent expert advice, or expert engagement to clarify the evidential gaps identified. This is particularly significant given that the Committee itself recognised the complexity of the interface between the Medicines Act and the Dietary Supplements Regulations, describing it as difficult to navigate. Despite this acknowledgement, there is no indication that the process sought to provide recommendations that would address the current barriers, or to develop an evidential basis capable of supporting a more differentiated regulatory approach. The decision was made on the material as submitted, with perceived deficiencies operating as a basis for rejection rather than as triggers for further investigation.

This outcome must also be understood in the broader regulatory context. Official Ministry of Health documentation confirms that products containing lithium are treated as medicines under the Medicines Act, with access limited to prescription or unapproved medicine pathways. While work programmes are underway to review dose limits for certain vitamins and minerals, there is no clear indication of a corresponding pathway for lithium as a nutrient. The regulatory system therefore presents a recognised gap: substances such as lithium at trace levels do not sit

[30] Medsafe Agenda 74, 5.4 Lithium. Submission for medicine reclassification for consideration by the Medicines Classification Committee. https://medsafe.govt.nz/profs/class/Agendas/Agen74/5.4Lithium.pdf?
[31] Medsafe (Oct 30, 2025). Minutes for the 74th meeting of the Medicines Classification Committee held at 133 Molesworth Street, Wellington on 23 July 2025. 5.4 Lithium (Prof Julia Rucklidge). https://www.medsafe.govt.nz/profs/class/Minutes/2021-2025/74mccMin23July2025.htm#5.4

comfortably within either the medicines or food regulatory frameworks, yet there is no operational mechanism to assess or accommodate them outside existing classification doctrine.

Taken together, the lithium case demonstrates a system that is substantively constrained by its underlying legal architecture. The Committee identified evidential gaps but did not pursue iterative enquiry to resolve them, nor did it engage mechanisms to develop a more proportionate or scientifically differentiated assessment. In the absence of such mechanisms, decision-making defaults to established classification rules, limiting the system's ability to evaluate low-dose, biologically relevant substances outside a pharmaceutical paradigm.

European Regulatory Processes (Lithium).

In Europe, a nutrient product is not immediately designated a medicinal product simply because lithium is present at environmentally relevant levels, including where lithium is only present as a natural component of another ingredient. In Europe food supplements are regulated as foods, and the food-supplement regime is anchored in Directive 2002/46/EC and broader EU food law. EFSA's overview states that the responsibility for safety lies with the food business operator placing the product on the market.

Lithium is not one of the harmonised vitamins or minerals listed in Annex I to Directive 2002/46/EC, so it does not sit within the standard EU positive list for vitamin/mineral ingredients used in food supplements. A product intentionally adding lithium as a nutrient does not slot into the ordinary vitamins-and-minerals pathway. Instead, depending on the facts, it may fall under national rules for 'other substances', novel foods law if relevant, or other food-law controls. While lithium may face a food-law authorisation/classification problem, it will not automatically be classified as a medicine.

European law separates food law from medicines law more clearly than New Zealand does. Under the EU medicines code, a product may be classed as a medicinal product 'by function' only where it is capable of restoring, correcting, or modifying physiological functions by pharmacological, immunological, or metabolic action. The Court of Justice has made clear that this cannot be read so broadly that any product affecting physiology becomes a medicine: in Hecht-Pharma, the Court said the mere capacity to influence physiological functions is not enough; the product must be capable of doing so appreciably.

Therefore, if lithium is present only at trace or environmentally relevant levels as part of a food ingredient, that does not by itself point to medicinal classification under EU law. Regulatory questions may include: what exactly is the ingredient, is the lithium intentionally added or only naturally present, is there a history of safe food use, is the product being marketed as a food supplement, and what claims are being made? EU food law expressly allows supplements to contain not only vitamins and minerals but also 'other substances with a nutritional or physiological effect', and for ingredients other than vitamins and minerals EFSA notes that the rules may come from national law or other specific EU legislation.

Claims are also important. In the EU, a supplement can remain a food while making authorised nutrition or health claims under Regulation 1924/2006; that is different from presenting it as preventing, treating, or curing disease. EFSA explains that health claims on foods are handled within food law, and Directive 2002/46/EC requires that supplements' presentation and advertising must not attribute to them the property of preventing, treating, or curing human

disease. So the legal trigger is not 'any biological role', but a combination of classification, dose, effect, and presentation.

European regulation of lithium is not fully harmonised. As lithium is not part of the harmonised vitamin/mineral list for supplements, Member States may approach lithium-containing products differently under their own national rules for 'other substances' or borderline food/medicine cases. So the safest conclusion is: not automatically a medicinal product, but potentially a food-law or borderline-classification issue depending on dose, formulation, claims, and the Member State involved.

Case for Lithium as a Nutrient: An Upstream Modulator of Cellular Signalling Networks.

(2010 onward Review Literature)

Lithium may be described as an upstream modulator of cellular signalling Networks.

Synthetic formulations of lithium are primarily used for the treatment of bipolar psychiatry as a mood stabiliser with incompletely understood mechanisms. However, contemporary review literature supports a broader and more coherent interpretation: lithium functions as a small ionic modulator that perturbs upstream physicochemical constraints and signalling hubs, with downstream effects that propagate across neural, immune, endocrine, metabolic, and circadian systems.

Sakrajda and Rybakowski (2025) revisit both 'old' and 'new' findings and show that much of the apparent expansion of lithium biology converges upon a small number of foundational mechanistic nodes, particularly glycogen synthase kinase-3 (GSK-3) and the phosphatidylinositol (PI)/inositol signalling axis, while extending their implications into mitochondrial regulation, immune modulation, circadian timing, and genomic maintenance.

Taken together with Brown & Tracy (2013), Jakobsson (2017), Szklarska & Rzymski (2019), Strawbridge et al. (2023), Motoi et al. (2014), and foundational autophagy work (Sarkar 2005; Williams 2008), the literature supports a systems-biology model rather than a receptor-specific drug paradigm.

1. Ionic Competition and Membrane Transport

At the most upstream level, lithium acts as a monovalent cation capable of entering sodium transport pathways and partially occupying magnesium-dependent enzyme binding sites. Through partial substitution at Mg^{2+}-dependent catalytic sites, lithium alters enzyme conformation and reduces catalytic efficiency in specific kinases and phosphatases.

Sakrajda & Rybakowski revisit earlier work on electrolyte metabolism, lithium–sodium counter-transport, and Na^+/K^+-ATPase interactions, noting inter-individual differences in cellular lithium handling. These transport dynamics may influence intracellular lithium accumulation and biological responsiveness.

This node provides the biophysical substrate for downstream modulation.

2. Enzymatic Hubs: GSK-3 and the Inositol Cycle

GSK-3β as a Central Signalling Hub

GSK-3β remains one of the most consistently described molecular targets of lithium. Its inhibition influences:

- β-catenin/Wnt signalling
- neuronal polarity and neurogenesis
- cytoskeletal organisation and axonal growth
- inflammatory transcription pathways
- insulin and metabolic signalling
- circadian clock regulation

Sakrajda & Rybakowski emphasise that many newer mechanistic findings reinforce the centrality of GSK-3β. Downstream substrates include proteins involved in cytoskeletal stability (e.g., CRMP2), linking kinase modulation directly to structural plasticity.

Cytoskeletal growth and neurite extension therefore sit downstream of kinase modulation rather than constituting an independent mechanism.

Inositol Monophosphatase (IMPase) and the PI Cycle

Lithium inhibits IMPase and related phosphatases in the phosphatidylinositol cycle. This constrains regeneration of free inositol, reduces IP_3 production, alters DAG signalling, and modulates intracellular Ca^{2+} mobilisation.

Sakrajda & Rybakowski reaffirm that PI/inositol signalling remains a central mechanistic axis. By influencing membrane phospholipid composition and second messenger bandwidth, lithium alters signal amplification across diverse tissues.

3. Second Messenger Architecture

Lithium's modulation of cyclic nucleotide systems (e.g., cAMP pathways) and PI/IP_3/DAG/Ca^{2+} signalling places it at the level of intracellular signal amplification rather than receptor binding.

Second messengers convert local receptor events into cell-wide state shifts. Lithium's influence at this level allows distributed effects without targeting a specific neurotransmitter receptor.

4. Neurotrophic Signalling and Structural Plasticity

Lithium enhances neurotrophic signalling, including BDNF expression, partly via CREB activation and β-catenin pathways. Biologic effects include neurite outgrowth, dendritic spine modulation, and axonal remodelling.

Sakrajda & Rybakowski integrate cytoskeletal regulation with GSK-3 inhibition and genetic polymorphism findings (e.g., BDNF Val66Met), reinforcing that lithium's broader systemic effects are mechanistically coherent and modulated by biological variability.

These effects position lithium as a regulator of network architecture rather than solely neurotransmission.

5. Autophagy and Proteostasis

(mTOR-Independent Inositol Pathway)

Autophagy is a conserved cellular maintenance system responsible for the degradation and recycling of damaged proteins and organelles. It operates across neuronal, immune, endocrine, and metabolic tissues.

The mechanistic foundation of lithium-induced autophagy was demonstrated by Sarkar et al. (2005). Lithium induces autophagy via inhibition of IMPase, reducing intracellular inositol and lowering IP_3 signalling.

Williams et al., (2008) Clarified that lithium promotes autophagy through an mTOR-independent pathway. Motoi et al. (2014) synthesised these findings and positioned lithium as a mechanistic tool for studying inositol-linked autophagy in neurodegenerative models.

Mechanistic Sequence

Lithium

- IMPase inhibition
- reduced inositol
- decreased IP_3
- altered ER calcium signalling
- autophagy induction (mTOR-independent)

Autophagy sits downstream of PI signalling modulation and intersects with mitochondrial stress response and proteostasis.

Dose Consideration

Although robust autophagy induction has been demonstrated primarily at pharmacological lithium concentrations, the absence of funded research at environmentally relevant exposure levels should not be conflated with evidence of absence. Autophagy is a threshold-sensitive, metabolically integrated process governed by kinase activity, inositol signalling, calcium dynamics, and mitochondrial state.

Lithium's capacity to modulate upstream nodes such as IMPase and GSK-3 establishes a mechanistic pathway through which lower concentrations could plausibly exert low-amplitude regulatory effects on baseline autophagic tone or stress responsiveness. The fact that such dose–response relationships have not been systematically characterised reflects research prioritisation patterns rather than definitive biological impossibility. In systems biology, small upstream perturbations can produce distributed downstream shifts; the appropriate scientific response is rigorous investigation, not categorical dismissal on the basis of regulatory scope.

6. Mitochondrial Function and Oxidative Stress

Lithium influences mitochondrial regulation and oxidative stress signalling. GSK-3β interacts with mitochondrial proteins, modulating apoptosis and oxidative phosphorylation dynamics.

This node integrates neuronal energetics, immune activation, and metabolic resilience.

7. Immune and Inflammatory Modulation

Sakrajda & Rybakowski treat immunomodulation as a major modern extension of lithium biology. Lithium influences cytokine profiles and inflammasome-linked pathways, partly via GSK-3β.

Lithium's effects extend beyond neuroinflammation to include systemic immune phenomena, such as granulopoiesis and antiviral observations.

This positions immune modulation as a whole-body node rather than a psychiatric corollary.

8. Circadian Regulation

Lithium lengthens circadian period and shifts biological timing, plausibly via GSK-3β effects on clock gene phosphorylation.

Circadian systems coordinate endocrine pulses, immune trafficking, metabolic rhythms, and sleep architecture. Thus, circadian modulation represents a systems stabilisation mechanism.

9. Ageing and Genomic Maintenance

Emerging evidence links lithium exposure with telomere dynamics and markers of biological ageing, though findings remain heterogeneous. This node likely represents a downstream convergence of mitochondrial resilience and inflammatory modulation.

Hierarchical Integration

Lithium's biological action can be conceptualised across three tiers:

Tier 1 – Ionic Constraints: Ion transport and Mg^{2+}-dependent enzymatic modulation.

Tier 2 – Signalling Hubs: GSK-3 inhibition; PI/inositol pathway modulation; second messenger regulation.

Tier 3 – Systems Outcomes: Neuroplasticity, cytoskeletal stability, immune modulation, mitochondrial resilience, circadian regulation, endocrine interaction, and genomic maintenance.

This layered structure explains lithium's pleiotropic footprint.

Regulatory Implication: A Systems Modulator / Biologically Pleiotropic Ion

When regulatory frameworks classify lithium solely according to therapeutic purpose, they apply a single-indication pharmaceutical lens to a biologically pleiotropic ion. That model is appropriate for receptor-specific medicines but is less suited to substances whose biological activity is dose-dependent and operates across multiple interconnected systems.

At pharmacological doses, lithium's narrow therapeutic index justifies prescription control. However, environmentally relevant intake levels produce serum concentrations that are orders of magnitude lower and represent a biologically distinct exposure regime. The mechanistic literature demonstrates that lithium modulates convergent signalling hubs, including GSK-3 and the phosphatidylinositol cycle, with downstream implications for cytoskeletal regulation, immune signalling, mitochondrial function, and circadian timing. These effects are not confined to psychiatric pathways.

Failure to distinguish between pharmacological and trace exposure regimes risks collapsing materially different biological contexts into a single regulatory category. Such consolidation may

narrow evaluative scope and limit comprehensive assessment of potential public health implications.

Lithium's capacity to influence upstream signalling nodes establishes a plausible mechanistic pathway through which lower concentrations could exert low-amplitude regulatory effects. The absence of systematic characterisation of sub-therapeutic dose–response relationships reflects research prioritisation patterns rather than established biological irrelevance. In complex signalling systems, modest upstream modulation can produce distributed downstream consequences.

Proportional governance therefore requires integrated, cross-domain evidence assessment grounded in dose–response logic. This approach neither presumes benefit nor dismisses risk but ensures regulatory reasoning remains aligned with contemporary biological understanding.

Lithium Review: Conclusion

The post-2010 review literature, including Sakrajda & Rybakowski (2025), supports a coherent interpretation of lithium as a network-level ionic modulator acting at enzymatic and signalling hubs with distributed physiological consequences.

Lithium's mechanisms are not reducible to receptor binding nor confined to psychiatric pharmacology. They reflect perturbation of conserved cellular architectures: kinase regulation, phosphoinositide cycling, cytoskeletal dynamics, proteostasis, mitochondrial control, immune signalling, and biological timing.

Whether these mechanisms carry physiological relevance at environmentally encountered exposure levels remains an empirical question. What is clear is that lithium's biological role is broader than its historical pharmaceutical framing, and any mature evaluation must account for its systems-level character.

REFERENCES

Jakobsson, E., Argüello-Miranda, O., Chiu, SW. et al. Towards a Unified Understanding of Lithium Action in Basic Biology and its Significance for Applied Biology. J Membrane Biol 250, 587–604 (2017). https://doi.org/10.1007/s00232-017-9998-2

Brown KM, Tracy DK. Lithium: the pharmacodynamic actions of the amazing ion. Ther Adv Psychopharmacol. 2013 Jun;3(3):163-76. doi: 10.1177/2045125312471963. PMID: 24167688; PMCID: PMC3805456.

Bortolozzi *et al.* 2024. New Advances in the Pharmacology and Toxicology of Lithium: A Neurobiologically Oriented Overview. Pharmacological Reviews Volume 76, Issue 3, May 2024, Pages 323-357, doi: 10.1124/pharmrev.120.000007

Jakobsson, E., Argüello-Miranda, O., Chiu, SW. et al. Towards a Unified Understanding of Lithium Action in Basic Biology and its Significance for Applied Biology. J Membrane Biol 250, 587–604 (2017). https://doi.org/10.1007/s00232-017-9998-2

Motoi *et al.* 2014 Lithium and Autophagy. *ACS Chem. Neurosci*. 2014, 5, 6, 434–442. Doi: 10.1021/cn500056q

Sakrajda and Rybakowski 2025. The Mechanisms of Lithium Action: The Old and New Findings. Pharmaceuticals. 2025; 18(4):467. https://doi.org/10.3390/ph18040467

Sarkar R. Floto A, Berger Z, *et al.* Lithium induces autophagy by inhibiting inositol monophosphatase . *J Cell Biol* 26 September 2005; 170 (7): 1101–1111. doi:10.1083/jcb.200504035

Strawbridge et al 2023. Identifying the neuropsychiatric health effects of low-dose lithium interventions: A systematic review. *Neuroscience & Biobehavioral Reviews,* 144:104975. Doi: 10.1016/j.neubiorev.2022.104975

Szklarska and Rzymski 2018. Is Lithium a Micronutrient? From Biological Activity and Epidemiological Observation to Food Fortification. *Biol Trace Elem Res*. 2019 May;189(1):18-27. doi: 10.1007/s12011-018-1455-2. Epub 2018 Jul 31. PMID: 30066063; PMCID: PMC6443601.

Sarkar, R. Andres Floto, Zdenek Berger, Sara Imarisio, Axelle Cordenier, Matthieu Pasco, Lynnette J. Cook, David C. Rubinsztein; Lithium induces autophagy by inhibiting inositol monophosphatase . J Cell Biol 26 September 2005; 170 (7): 1101–1111. doi: https://doi.org/10.1083/jcb.200504035

[7] CASE STUDY: IODINE - SUPPORTING CONSUMER CHOICE IN IODINE NUTRITION

In Europe and the United States, iodine, including higher-dose preparations such as Lugol's (iodine and potassium iodide), is primarily regulated within food or dietary supplement frameworks, with classification determined by dose, presentation, and pharmacological effect. In the European Union (EU), Lugol's iodine is typically available through pharmacy-based channels as a medicinal or compounded product, rather than as a standard dietary supplement.

Lugol's iodine is available in New Zealand, but only through fragmented pathways: as low-dose nutritional supplements, as externally labelled chemical solutions, or through limited practitioner channels. Full-strength preparations are typically not marketed for ingestion, reflecting regulatory constraints rather than absence of supply. This results in a system where the substance is accessible in principle, but not readily available in a clear, consumer-facing form aligned with its traditional use.

European classification is determined on a case-by-case basis according to dose, presentation, and pharmacological effect, allowing controlled access without outright exclusion. By contrast, the New Zealand system applies a broader therapeutic purpose trigger, whereby substances that influence physiological function, such as iodine's effects on the thyroid, are more readily captured within medicines regulation. This results in more limited availability of higher-dose iodine products, including Lugol's solution.

Jurisdiction	**Classification Approach**	**Practical Access to Lugol's**	**Regulatory Mechanism**
Germany	Contextual (not automatically medicinal)	High - widely available via retail,	Claims restricted; often sold as reagent or general iodine solution

Jurisdiction	Classification Approach	Practical Access to Lugol's	Regulatory Mechanism
		online, and lab suppliers	
United Kingdom	Contextual, claim-sensitive	Moderate–high – available online and via niche suppliers	"Not for internal use" labelling used to avoid medicines classification
France	Pharmacy-mediated for higher doses	Controlled – primarily via pharmacies	Pharmacist oversight; medicinal framing at higher doses
European Union (general)	Dose + claims + pharmacological effect	Permitted but variable across Member States	Layered system: food, medicine, or general product depending on context
New Zealand	Therapeutic purpose trigger (function-based)	Restricted- limited general retail availability	Early classification as a medicine constrains access

Iodine deficiency remains a recognised public health issue globally, although its severity varies by region. While iodised salt programmes have reduced severe deficiency, mild-to-moderate iodine insufficiency persists, particularly in populations with changing dietary patterns and reduced salt intake. Pregnant women are consistently identified as a high-risk group, as iodine requirements increase during pregnancy and deficiency is associated with adverse neurodevelopmental outcomes.

The link between iodine and thyroid health was first clearly recognised in the early 19th century, shortly after iodine itself was discovered in 1811 by Bernard Courtois. By the 1820s, clinicians, including Jean Guillaume Auguste Lugol, had observed that iodine could reduce goitre, establishing one of the earliest examples of a nutrient correcting a specific disease. Over time, this observation evolved into a broader public health understanding: that endemic goitre and cretinism in inland and mountainous regions were caused by environmental iodine deficiency.

Lugol's contribution was to develop a practical, standardised formulation of iodine for clinical use, combining elemental iodine with potassium iodide in aqueous solution. This formulation addressed a key chemical limitation: elemental iodine is poorly soluble in water, making it difficult to administer consistently. The addition of potassium iodide increases solubility by forming triiodide ions in solution, allowing iodine to be delivered in a stable, bioavailable form. Clinically, this enabled more reliable dosing and broader therapeutic application. Over time, Lugol's solution became widely used not only for goitre and iodine deficiency, but also in thyroid disorders,

antisepsis, and later radiation protection, illustrating how a chemically simple modification facilitated the transition from empirical observation to practical medical and public health use.

In New Zealand, iodine deficiency re-emerged in the late 20th century and has been partially addressed through mandatory iodisation of bread and supplementation guidance.

Although population iodine status has improved, pregnant and breastfeeding women remain at risk of insufficient intake, and mild insufficiency may persist in segments of the general population. This indicates that, from a public health perspective, the dominant risk in New Zealand remains insufficient iodine intake rather than excess, particularly when compared with historical and global patterns of deficiency.

In this context, the current regulatory approach, approached primarily through a pharmacological and risk-based lens, does not fully reflect the biological necessity of iodine or the ongoing risk of insufficiency. Nor does it readily accommodate informed consumer choice in relation to different iodine sources and dosing strategies. Preparations such as Lugol's iodine, which have a long history of use when taken according to established guidance, fall outside accessible pathways despite representing one of several approaches to iodine intake. As medicines registration is costly and commercially unattractive for low-cost, non-patentable products, there is limited incentive for sponsors to bring such products through the approval pathway, contributing to their absence from the market. This highlights a broader misalignment between regulatory classification, population nutritional risk, and the practical ways in which individuals may seek to achieve adequate iodine status.

Overall, while iodine deficiency disorders have been reduced, maintaining adequate iodine nutrition remains an active public health requirement, and regulatory settings that emphasise risk without proportionate consideration of deficiency and biological function limit both clinical flexibility and informed choice.

[8] WHERE SHOULD NZ LOOK TO FOR BEST PRACTICE NUTRIENTS REGULATION?

Australia similarly treats nutrients primarily as medicines rather than foods once therapeutic intent is implied. Many vitamin products therefore fall under the complementary medicines framework administered by the Australian Therapeutic Goods Administration (TGA).

In Ministry of Health policies in support of a Medical Products Bill currently in draft stage, the review documents focus on the Australian model. They do not consider wider regulatory examples, and what might be considered best practice, or most appropriate for the regulation of nutrient compounds.

As MNZH discussed in Policy (4), policy development for primary legislation should be grounded in comparative best practice, drawing on multiple competent regulatory systems and assessing their strengths, limitations, and relevance to New Zealand's context. In the absence of evidence that such comparative analysis has been undertaken, it is difficult for the public to have confidence that the proposed legislation will be fit for purpose and aligned with current scientific, legal, and regulatory standards.

The EU framework provides a more differentiated and proportionate regulatory model for nutrients and natural health products, which is directly relevant to reducing current barriers within Pharmac and Medsafe systems.

The European system has reached its current nutrient reference positions through a more strategic, integrated and expansive scientific review process than that underpinning the Australia and New Zealand NRVs. Reviews undertaken by the European Food Safety Authority and earlier by the Scientific Committee on Food typically involve comprehensive, purpose-built evaluations of individual nutrients, drawing on toxicology, human clinical data, observational studies, mechanistic evidence, and biomarker analysis. These assessments are conducted as discrete scientific opinions with transparent documentation of endpoints, uncertainty factors, and biological mechanisms.

By contrast, the Australia-New Zealand NRV framework, while incorporating systematic review methods, is more constrained in how evidence is integrated and applied. It places greater emphasis on generalised methodological consistency and population reference setting, but provides a relatively insensitive framework for synthesising mechanistic, clinical, and real-world evidence into a coherent biological model. As a result, European reviews tend to demonstrate greater depth at the level of individual nutrients, even though both systems ultimately remain anchored to deficiency prevention and risk avoidance rather than optimisation.

A further distinction lies in regulatory classification. Within the European framework, nutrients are not automatically categorised as medicines once intake exceeds upper levels or when physiological effects are described. The European approach therefore provides a more proportionate, risk-based pathway, whereas the Australia-New Zealand system tends toward functional classification based on claimed effect, contributing to regulatory escalation and reduced accessibility for otherwise low-risk, biologically essential nutrients.

Rather than relying on an overbroad ‘therapeutic purpose’ trigger, the EU maintains a clear legal and functional distinction between food, supplements, and medicines, with each governed under separate statutory pathways aligned to risk, dose, and intended use. Nutrients are primarily regulated under food law, where safety is assessed through toxicological thresholds, exposure modelling, and population-level risk, rather than being defaulted into medicines regulation based on biological activity alone.

A central feature of the EU approach is its tiered, risk-proportionate structure. Low-risk substances, including vitamins and minerals, are managed through safety, composition, and labelling requirements, while traditional herbal products are accommodated through simplified registration pathways based on long-standing human use. Medicines-level regulation is reserved for substances demonstrating significant pharmacological effect at relevant doses. This ensures that regulatory burden is aligned with demonstrable risk, avoiding unnecessary escalation of low-risk nutrients into pharmaceutical regulatory regimes.

The EU framework also adopts a weight-of-evidence approach, integrating mechanistic, clinical, observational, and real-world safety data into a coherent biological and regulatory assessment. Importantly, it recognises long-standing human use and physiological function as valid components of evidence, enabling decision-making even where conventional trial data are

limited. This contrasts with sponsor-driven, trial-centric models that disadvantage nutrients within current New Zealand funding and approval systems.[32]

The European model demonstrates that it is both feasible and operationally effective to maintain access to recognised safe nutrients while applying proportionate safeguards, without defaulting to medicines regulation. It provides a practical template for reform: establishing clear classification boundaries, aligning regulatory intensity with toxicological risk and dose, enabling non-sponsor-driven evaluation pathways, and supporting integration of nutrients into health systems on a public-health basis.

Bracketed, Aus-NZ, Maximum Daily Dose as described in the Dietary Supplements Regulations 1985, Part 1, General Requirements, Section 3.

Copper (NZ and EFSA 5 mg). The European scientific basis for copper derives from the Scientific Committee on Food (SCF) opinion (2003), which established a tolerable upper intake level (UL) of 5 mg/day for adults. This value aligns directly with the level cited, representing one of the few cases where regulatory reference values closely reflect the underlying scientific assessment of risk.

Iron (NZ 24 mg). For iron, the European Food Safety Authority (EFSA) has not established a formal UL, most recently reaffirmed in its 2024 review. Instead, EFSA identifies a level of intake unlikely to pose risk for the general population (approximately 40 mg/day in adults, including pregnant and lactating women).[33] The commonly cited value of 24 mg does not derive from an EU scientific UL, but rather reflects a more conservative policy or national-level regulatory position.

Selenium (NZ 150 mcg). EFSA updated its assessment of selenium in 2023, establishing an adult UL of 255 mcg/day (with earlier SCF guidance at 300 mcg/day).[34] The value of 150 mcg is therefore substantially below the scientific UL and represents a precautionary regulatory level rather than a toxicological threshold derived from European risk assessment.

Zinc (NZ 15 mg). The SCF established a UL for zinc of 25 mg/day in 2003. A value of 15 mg, as commonly applied in some regulatory contexts, does not correspond to this scientific threshold and instead reflects a lower, policy-driven limit. The scientific UL itself is based on considerations of copper status interaction at higher intakes, rather than direct toxicity.

Vitamin A (NZ and EFSA 3000 mcg). EFSA's most recent assessment (2024) confirms an adult UL of 3000 mcg/day (retinol equivalents). This aligns directly with the value cited and represents a clear case where regulatory reference levels correspond closely with the established toxicological threshold, based primarily on liver toxicity risk at sustained high intakes.

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[32] EFSA (Nov 14, 2024). Webinar PDF. EFSA's Activities on Tolerable Upper Intake Levels for Vitamins and Essential Minerals. https://www.efsa.europa.eu/sites/default/files/2024-11/UL%20Webinar_14%20Nov%2024.pdf?

[33] EFSA NDA Panel (EFSA Panel on Nutrition, Novel Foods and Food Allergens), Turck, D., Bohn, T., Castenmiller, J., de Henauw, S., Hirsch-Ernst, K.-I., Knutsen, H. K., Maciuk, A., Mangelsdorf, I., McArdle, H. J., Pentieva, K., Siani, A., Thies, F., Tsabouri, S., Vinceti, M., Aggett, P., Fairweather-Tait, S., de Sesmaisons Lecarré, A., Fabiani, L., … Naska, A. (2024). Scientific opinion on the tolerable upper intake level for iron. EFSA Journal, 22(6), e8819. https://doi.org/10.2903/j.efsa.2024.8819

[34] EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA); Turck D, Bohn T, Castenmiller J, de Henauw S, Hirsch-Ernst KI, Knutsen HK, Maciuk A, Mangelsdorf I, McArdle HJ, Peláez C, Pentieva K, Siani A, Thies F, Tsabouri S, Vinceti M, Aggett P, Crous Bou M, Cubadda F, Ciccolallo L, de Sesmaisons Lecarré A, Fabiani L, Titz A, Naska A. Scientific opinion on the tolerable upper intake level for selenium. EFSA J. 2023 Jan 20;21(1):e07704. doi: 10.2903/j.efsa.2023.7704.

Niacin (NZ 100 mg). The SCF (2002) established different ULs depending on form: 10 mg/day for nicotinic acid (based on flushing) and 900 mg/day for nicotinamide. The value of 100 mg does not reflect a formal EU UL but appears to be a policy compromise level. This illustrates how regulatory limits may diverge from scientific thresholds, particularly where different biochemical forms have markedly different safety profiles.

Vitamin B12 (NZ 50 mcg). For vitamin B12, both SCF and EFSA have concluded that no UL can be established due to the absence of evidence for toxicity. The value of 50 mcg is therefore not grounded in a toxicological limit but represents a pragmatic or administrative reference point, rather than a scientifically defined upper boundary.

Vitamin D (NZ 25 mcg). EFSA established an adult UL for vitamin D of 100 mcg/day (2012, reaffirmed subsequently). The value of 25 mcg is well below this threshold and is commonly used as a conservative regulatory or guidance level. It does not reflect the level at which adverse effects are expected to occur, but rather a lower policy setting.[35]

Folic Acid (NZ 500 mcg). The SCF (2000) and EFSA have established a UL of 1000 mcg/day for folic acid, based on the potential to mask vitamin B12 deficiency. A value of 500 mcg sits below this threshold and represents a precautionary regulatory level rather than a direct expression of toxicological risk.[36]

Across these nutrients, only a two values, (copper and vitamin A) align directly with European scientific ULs. In most cases, the levels applied in regulatory or policy contexts are more conservative than the underlying toxicological assessments. This reflects a distinction within the European system between scientific risk assessment (ULs) and risk management decisions, where operational limits may be set below levels associated with demonstrated harm.

It must be noted that whilst European nutrient assessments extend beyond deficiency in a limited way through consideration of functional biomarkers and adequacy, but they do not establish or operationalise 'optimal intake' levels. The framework remains anchored to deficiency prevention and risk avoidance, with no systematic methodology for identifying intake levels that support optimal physiological function.

[35] EFSA NDA Panel (EFSA Panel on Nutrition, Novel Foods and Food Allergens), Turck, D., Bohn, T., Castenmiller, J., de Henauw, S., Hirsch-Ernst, K.-I., Knutsen, H. K., Maciuk, A., Mangelsdorf, I., McArdle, H. J., Pentieva, K., Siani, A., Thies, F., Tsabouri, S., Vinceti, M., Lanham-New, S., Passeri, G., Craciun, I., Fabiani, L., … Naska, A. (2023). Scientific opinion on the tolerable upper intake level for vitamin D, including the derivation of a conversion factor for calcidiol monohydrate. EFSA Journal, 21(8), 1–219 pp. http://doi.org/10.2903/j.efsa.2023.8145

[36] EFSA NDA Panel (EFSA Panel on Nutrition, Novel Foods and Food Allergens), Turck, D., Bohn, T., Castenmiller, J., de Henauw, S., Hirsch-Ernst, K.-I., Knutsen, H. K., Maciuk, A., Mangelsdorf, I., McArdle, H. J., Pentieva, K., Siani, A., Thies, F., Tsabouri, S., Vinceti, M., Crous-Bou, M., Molloy, A., Ciccolallo, L., de Sesmaisons Lecarré, A., Fabiani, L. … Naska, A. (2023). Scientific opinion on the tolerable upper intake level for folate. EFSA Journal, 21(11), 1–119. https://doi.org/10.2903/j.efsa.2023.8353