RESPONSE BY:

The Alliance for Natural Health Europe

TO:

EFSA Draft scientific opinion on the Tolerable Upper Intake Level for vitamin B6 by EFSA NDA Panel

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The following comments refer to the draft opinion that was subject to open consultation: https://connect.efsa.europa.eu/RM/sfc/servlet.shepherd/document/download/0690900000HryrRAAR

Note: The headings below refer to the headings given in the consultation document, and bracketed line numbers in our comments refer to the line numbers in the left margin of the consultation document.

1. Introduction

1. Section 1.1 (lines 123-124) indicates the review of the Scientific Committee on Food (SCF) of the NDA Panel's previous ULs on vitamin B6 (vitB6) is justified in order "to take into account recent scientific developments and evidence".

2. This remit should specifically include consideration of the increasing evidence that different forms of the same vitamin (or mineral) may have quite different safety profiles.

3. This phenomenon is already well recognised formally by EFSA in relation to the 90-fold difference TULs set for two forms of vitamin B3, namely nicotinic acid (adult TUL = 10 mg/d) and niacinamide (adult TUL = 900 mg/d). However, while such profound

differences in risk profile are far from unique and are well known in the cases of several other vitamins and minerals (e.g. iron sulphate vs iron bisglycinate, magnesium oxide vs magnesium malate, glycinate, gluconate, etc.), it is a major oversight in EFSA's scientific advice to the European regulatory process that, in such cases, different TULs for different forms of the same nutrient have yet to be proposed.

4. This is issue has been well described in the peer review literature, especially by Verkerk & Hickey (2010), Verkerk (2010) and Krul et al (2017). None of these reviews are cited in the document, presumably because they do not mention vitamin B6 and so were 'missed'.

5. This omission of information on new and relevant methodologies appears to relate to a serious failure in the AI methodology used for article selection (described on pp. 20-21 of the external scientific report prepared by the University of Copenhagen as part of the preparatory work by Tetens et al, 2023), which excluded research articles that did not include vitamin B6.

6. If the methodology is flawed, so, obviously, are the results, which is why a TUL based on pyridoxine (PN) and then applied to the bioactive form of vitamin B6, pyridoxal 5'-phosphate (PLP), is entirely spurious. The invalidity of a TUL applied to PLP can be readily confirmed by expert clinicians with years of clinical experience in the fields of clinical nutrition or orthomolecular medicine. This clinical experience is one of the foundation stones of an evidence-based medicine approach (Sackett et al, 1996). Such outcome-based experience is, in effect, also the basis for clinical epidemiology (Sackett, 2002) which remains one of the benchmarks for assessing real-world effects of health-impacting interventions, including high dose vitamin therapies that have long been administered by clinical nutritionists, orthomolecular doctors, functional medicine practitioners, naturopaths and other nutrition specialists.

7. Ignoring such expert views and relying only on desk-based research is a further major failing of the approach used in this draft revision.

2. Data and Methodologies

8. Another major weakness of the draft proposal is that there is no attempt to determine if the available evidence flags any differences in risk profile between any of the 6 different vitB6 vitamers. We are aware that the narrative review conducted as part of the preparatory work (Tetens et al, 2023) considered absorption, distribution, metabolism and excretion (ADME) studies (sQ1a), yet most experienced clinicians who have had long-term experience prescribing high dose vitB6 are well aware that peripheral neuropathy never occurs when the bioactive form PLP is used. Peripheral neuropathy case reports are limited to high dose pyridoxine (PN), not the phosphorylated or non-phosphorylated forms of pyridoxal (PL) or pyridoxamine (PM), and generally PN's long-term use in excess of 1000 mg/day (Bender, 1999).

9. While sQ3c included a narrative review on "the potential mechanisms/mode(s) of action underlying the relationships between vitamin B6 intake and peripheral neuropathy in humans?", this failed to signal this well known clinical fact, a stark reminder of the severe limitations of desk-based research as used for the draft vitB6 TUL proposal. While the report indicates "a causal relationship between 'high' vitamin B6 intake and peripheral neuropathy is well-established" (lines 356-357) this should be corrected to indicate that the causal relationship is established only for one vitamer, namely PN.

10. Only one study (a cohort study as shown by Tetens et al [2023]) was found to have no risk of bias across the three key areas of exposure, outcome and confounding (as well as another two areas), implying this study has the lowest risk of bias (= "definitely low risk of bias" using the Office of Health Assessment and Translation (OHAT) RoB tool) of any of the studies considered. The study in question was by Stewart et al (2022) and was based on 261 patients enrolled on the Peripheral Neuropathy Research Registry, and was funded by the Foundation for Peripheral Neuropathy (PNRR; https://www.foundationforpn.org/research/research-registry/). It investigated the relationship between vitB6 plasma values and nerve conduction

study results, neurological examination findings and reported symptoms, and yet found no relationship between plasma levels and any of the parameters for peripheral neuropathy. The study suggested that "moderately elevated plasma B6 levels, even in the 100 to 200 µg/L range, are not associated with significantly worse neuropathy signs or symptoms."

11. This is a further indication of the futility of the classic toxicological approach that ignores both clinical epidemiology and evidence of benefit, as used in the EFSA draft report. The proposed value (12.5 mg/d, adults) is just one-eighth of that set (100 mg/d, adults) by the National Academy of Medicine (formerly the Institute of Medicine) in the USA (IoM, 1998) that for scientific reason, discounted the discredited Dalton and Dalton (1987) study.

12. The failure to address any of the reasons for why individuals supplement with high doses (e.g. to reduce premenstrual symptoms, reduce cognitive decline – see comments in Conclusions, and associated references), or to consider risk-benefit analysis over risk-only analysis, will lead to unnecessary restrictions of the amounts of vitB6 in food supplements. This in turn thwarts freedom of choice among those aiming to derive health benefits.

13. Methods for risk-benefit analysis of micronutrients (more specifically to determine maximum safe dosages of supplements to particular population groups using ULs) were proposed originally by Renwick et al (2004) and subsequently considered by EFSA itself in 2007 (EFSA, 2007). Many of these concepts could be usefully applied to determinations of ULs, especially the consideration of different ULs for different forms with different safety profiles and the consideration of benefit.

14. The risk/benefit approach was further picked up and translated into a practical model by Krul et al (2017) and then clarified as an open source model by Hanekamp et al (2021) (the latter work forming the basis of an article that is currently in preparation for peer review submission). It is particularly pertinent that this latter work also includes vitamin B6. The effective dose for risk (Risk ED_{50}) is based on PN

and EFSA's estimated average requirement (EAR) which ignores benefits achieved at higher doses (e.g. premenstrual syndrome, Wyatt et al, 1999; prevention of cognitive decline, Douaud et al, 2013; Wang et al, 2022) and is in the range of 37 – 74 mg at a scientifically justifiable (Renwick et al, 2004) predefined incidence risk based on a 45% coefficient of variation.

15. There is a clear 'zone of overlap' between risks and benefits in the case of many micronutrients (Verkerk 2010), including vitB6, therefore a risk-only approach to determining a TUL (or maximum permitted level) will tend to deny benefit for which benefit can only be derived through higher intakes. Such considerations are pivotal in the face of the spiralling burden of preventable diseases on EU populations.

16. The methodology has entirely ignored what appears to be a clear vitamin B6 paradox, the mechanism of which was explained through in vitro experimentation by Vrolijk et al (2017), in which high doses of PN mediate symptoms of peripheral neuropathy equivalent to those caused by vitB6 deficiency. This putative mechanism appears to be associated with PN-mediated competitive inhibition of the bioactive, coenzyme PL 5'-phosphate form of vitB6.

3. Assessment

17. Figure 1 (lines 428-429) omits pyridoxine glucoside (mentioned in line 431) that is an important vitamer of B6 in plant-based foods.

18. These comments are focused exclusively on the work in relation to the endpoint of peripheral neuropathy, and accordingly do not relate to developmental toxicity (for which no overt concerns were noted in the preparatory work by Tetens et al [2023]).

19. Minor differences in bioavailability between different forms of vitamin B6 in foods and supplements were noted, whether in their phosphorylated and non-phosphorylated forms, with the exception being for PN glucoside, which has been

found to be much less bioavailable, but only represents a minor component (~15%) of vitB6 intake in the diet and is not authorised in food supplements.

20. However, the ADME section (lines 431-532) did not adequately distinguish between the three forms of vitB6 authorised for use in food supplements in the EU (under Directive 2002/46/EC, as amended), two of which are PN forms (hydrochloride and 5'-phosphate), the other being the bioactive PLP form.

21. The ADME section also makes no mention that it has been estimated that the majority, probably around 80%, of the body's vitB6 stores are in muscles, the predominant form being PLP bound to phosphorylase (Coburn et al, 1988), suggesting that plasma levels of PLP will be buffered and tightly regulated, so limiting the risk of neurotoxic levels. This perhaps explains why the high-quality, unbiased Stewart et al (2022) study found no trend for a dose response, and why the paradoxical mechanism for neuropathic 'toxicity' proposed by Vrolijk et al (2017) is so plausible.

22. The biomarkers section (lines 503-553) fails to make any mention of muscle stores as a biomarker of status, although it is recognised that biopsy is significantly more challenging for research or routine monitoring than blood draws for plasma PLP. However, just because the method of assessment is more challenging is not sufficient scientific reason to omit considering its physiological importance.

23. The keyrole of vitB6-producing microbiota is mentioned in passing (lines 551-553), in the context of it contributing to inter-individual differences, but no references are given.

24. The intake assessment work appears to usefully draw together available data and provides a reminder, from the few available population studies, of the importance of supplemental intakes (summarised in lines 806-841). However, no attempt has been made to determine how much of the high intake (> 25 mg/d, that was found by Mintel to represent less than 1% of the survey sample) contained PLP, and in what

proportion, or if it was or was not present together with one or both of the other EU authorised forms, PN HCl and PN 5'-phosphate.

25. The reliance on the flawed case report of Dalton and Dalton (1987) that EFSA (2006), Institute of Medicine (1998) and others regarded as of dubious quality, flawed or discredited, does not meet the remit given by the European Commission for this revision of the UL which required that recent scientific methods and developments were taken into account. Not only that, using a case report of a single subject, Blackburn and Warren (2017), along with the flawed Dalton and Dalton (1987) study (lines 1606-1612), to justify that levels of "50 mg and below" may induce neuropathy represents a very low calibre of scientific approach. Especially given the weight of evidence pertaining to consumption of higher doses of B6 while showing no neuropathic symptoms. Also, the Blackburn and Warren (2017) case report involved an energy drink with only 5.1 mg of PN (i.e. one that would not be banned by any new maximum limits induced by a lowering of the UL to 12.5 mg), and it was quite possible that the reported neuropathy attributed to the 6 cans consumed daily (31 mg PN/d total) was caused by other factors or interactions.

26. Therefore the statement (lines 1613-14), "The value of 50 mg/day represents the lowest level of vitamin B6 intake that is associated with certainty with the development of neuropathy when consumed for more than 6 months" is incorrect as certainty cannot be attributed to studies that are recognised by the NDA panel as having significant limitations or biases in key areas (see Tetens et al [2023]).

27. The reliance on a 45-year-old study on five Beagle dogs (Phillips et al, 1978) to justify a Lowest Observable Adverse Effect Level (LOAEL) in order to support the lowering of the UL, including use of an excessive uncertainty factor of 300, is nothing short of outrageous – and certainly does not take account of "recent scientific developments" as required by the terms of reference given to EFSA's NDA panel.

28. In order to meet these terms of reference, the NDA panel should have considered much more recent developments in the field of human and micronutrient risk

assessment, rather than dig out old, indirectly relevant animal studies. This revision should have included consideration of risk/benefit approaches (Krul et al, 2017) as well as a totality and weight of evidence approaches, and not have re-implemented a scientifically defunct toxicological approach that should only be applicable to substances for which no benefits can be derived (Verkerk & Hickey, 2010; Verkerk, 2010).

Conclusions

29. No clear scientific justification of the methodology used was made in relation to a critical effect (peripheral neuropathy caused by high intakes of vitB6) for which there are known to be limited data. A large amount of data relevant to totality of evidence (ToE) (Venkatakrishnan & Cook, 2018) and evidenced-based approaches (Sackett et al, 1996), especially clinical experience, known benefits at high doses, and data showing differences between vitB6 vitamers, have been ignored.

30. Given that all evidence points to the fact that only PN vitamers of vitB6 are capable of inducing peripheral neurotoxicity, the entire premise of reducing the UL of all vitB6 vitamers, regardless of their form, is flawed scientifically. If lowered maximum limits of PLP in food supplements, based on a revised 12.5 mg UL, are passed in EU or national law, this would likely be able to be demonstrated in court to be legally disproportionate.

31. Owing to EFSA's continued use of classical toxicological methods to substances for which risk and benefit overlap (Verkerk, 2010), the role of higher dosage intakes, such as those that relate to homocysteine lowering, especially when taken in combination with folate and vitamin B12, have been ignored entirely.

32. The tight terms of reference given to EFSA mean that the reasons (e.g. satisfaction of need states, reducing disease risk, improving wellbeing) for members of the public taking, or practitioners recommending, higher doses of vitB6 have simply not been considered. There has, for example, been long standing recognition, supported by

extensive clinical experience and, albeit, generally poor quality studies (e.g review by Wyatt et al, 1999), of the role of higher vitB6 intakes in relieving symptoms of premenstrual syndrome. This recommendation is even made by some medical authorities, including the UK's National Institute for Health and Care Excellence (NICE) (https://bnf.nice.org.uk/drugs/pyridoxine-hydrochloride/). However, because vitB6 is unlicensed for this purpose, supplemental use remains the only method of ingestion.

33. More recently, substantial evidence has emerged on the role of high dose vitamin B6, in combination with folate, vitamin B12 and omega-3 fatty acids, in slowing age-related cognitive decline and brain shrinkage, so reducing the risk of dementia, most notably Alzheimer's disease in almost half of those who supplement (Douaud et al, 2013).

34. The overall evidence is comprehensively considered in the recent systematic review and meta-analysis conducted by Wang et al (2022). Supplemental doses delivered (e.g. Douaud et al 2023) are typically 20 mg vitB6 daily, this being 160% over the proposed new TUL.

35. Therefore setting a revised TUL below this level would have a catastrophic impact on the ability of individuals in the EU to self care with the aim of preventing cognitive decline and dementia, which remain among the greatest burdens on health and care systems.

36. As indicated by Morris (2008), it is apparent that daily intakes of vitB6 in the region of 3- 5 mg/d will cause "substantial proportions of some population subgroups [to] not meet accepted criteria for adequate vitamin B-6 status."

37. Yet such restricted levels will be even more likely if national regulators, or the EU as a single market, mandates restrictions on maximum permitted levels based on a revised UL of 12.5 mg. Such restriction of daily intakes of PLP, based on zero

evidence of neuropathy for this form, would be unnecessary, a great injustice to public health, as well as likely being *ultra vires*.

38. At the very least, the final version of the NDA opinion should include a recommendation that PLP should not be subject to a UL that is based on a critical effect that is not applicable to this form.

39. Furthermore, the UL should be revised following exclusion of low grade, discredited or biased case reports such as Dalton and Dalton (1987) and Blackburn and Warren (2017). Additionally, because risks and benefits overlap, risk should not be considered in the absence of evaluating benefits (see Krul et al, 2017 and Hanekamp et al, 2021), and the totality of available published and clinical evidence.

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