Dear Sasha Barclay,

I write to you regarding the "Therapeutic Goods (Declared Goods) Order 2019" as part of the open consultation process you have currently engaged in. As a research fellow employed at an Australian university with degrees in psychology and neuroscience, including a PhD from the leading institute of research into neuroscience and mental health in Australia, I find this proposal highly concerning and problematic on several accounts.

Foremost, the proposed declaration is bizarrely specific for the composition of food targeted, with no justification for the specificity being provided. Simultaneously the proposed declaration unreasonably broad in its application. The proposed declaration targets any goods that contain any form of folate, including derivatives, represented as a Food for Special Medical Purpose (FSMP) or similar and may be used or considered likely to be used for therapeutic use. The latter potential use where a product may be considered likely to be taken for therapeutic use is a largely subjective notion that is virtually impossible to address meaningfully and creates instability for future products. The most concerning part of the proposed wording is the inclusion of alleviating folate deficiency, a perfectly reasonable use for a FSMP, directly in line with the intention of Standard 2.9.5 of the Food Standard Code which defines the area. There are numerous metabolic disorders which FSMPs are intended to address. It is difficult to understand why the TGA has identified folates in FSMPs as an area to target with the proposed declaration, based on the available evidence or even on general principle. Indeed, the background provided about the proposed declaration fails to provide any justification for the actual wording of the proposed declaration. If a product is suitable to be presented as a food and is targeted to address a dietary requirement related to a disease or disorder, it would appropriately be considered a FSMP. If a product is intended to treat a disease or disorder or advertised for therapeutic use, then the existing legislation defined in the *Therapeutic Goods Act 1989* ('the Act') should be sufficient for regulation. The idea of making an order under subsection 7(1) of the Act appears unnecessary and suggests an inappropriately heavy-handed approach when logically the current framework should be sufficient. In essence, it suggests that the TGA is unable to use either legal or scientific facts to support a decision reached internally and rather than either find supporting evidence or acknowledge that the initial decision was made in error, the department has chosen to use extraordinary measures to bypass these requirements. This seems like a fundamental breach of trust of the Australian public who do rely upon the TGA to protect them, but also to allow them access to products where suitable. While this perception may be faulty, the incredibly short timeframe of this consultation (less than half that of the next shortest consultation period that I could find) makes this possibility appear more likely, especially given the limited information provided as background.

Secondly and related to this, it is entirely possible that a product can be specially formulated as a good for the dietary management of individuals with a disease or disorder. This is directly compliant with FSMP legislation and in-line with comparable legislation internationally. The proposed declaration appears to target links between folate, and depression, folate deficiencies, or metabolic errors in processing folate. The notion that a FSMP cannot target a dietary requirement for a vitamin, even when it is due to an in-born error of metabolism is in direct conflict with Standard 2.9.5 of the Food Standards Code. The decision also directly conflicts with the use of comparable (in the case of the EU, near identical) legislation defining FSMPs in

their relevant jurisdictions. This will limit the Australian public's access to products previously available and virtually eliminate any Australian business from competing in this field on an international stage. Furthermore, the very act of implementing the proposed declaration, instead of relying on existing legislation if suitable, will create uncertainty for future products intended to be regulated under the FSMP standards. If the TGA is seen as willing to pass legislation with no justification, both local and global industry will invariably become wary about the Australian marketplace for FSMPs. This would show the TGA is unwilling to work within currently defined boundaries and is willing, without any obvious justification, to change legislation to achieve objectives. It has also been shown that supplementation with 15mg L-5-MTHF is effective at addressing a dietary need for folate in those deficient and that those with genetic mutations which impair folate metabolism, such as the C677T polymorphism, require more intense dietary management that could only be regulated as a FSMP (Ambrosino et al., 2015; Girelli et al., 2003).

It is acknowledged that the specific reference to depression and folate does not present the same logical barrier as linking folate based FSMPs with disorders of folate metabolism or deficiencies. However, there is significant evidence supporting the appropriateness of this relationship. Numerous studies looking at populations of individuals diagnosed with depression have observed a significant deficit in folate levels in red blood cell and serum levels (Abou-Saleh & Coppen, 1989; Astorg et al., 2008; Morris, Fava, Jacques, Selhub, & Rosenberg, 2003; Ng, Feng, Niti, Kua, & Yap, 2009; Sánchez-Villegas et al., 2009). Approximately 30.4% to 64% of patients suffering from Major depressive disorder (MDD) display a red blood cell folate deficiency, with about 36% of depressed patients showing cerebral 5-MTHF deficiency (where serum folate levels are normal but cerebral spinal fluid 5-MTHF is low) (Bottiglieri et al., 2000; Farah & Farah, 2009; L. A. Pan et al., 2017). This relationship has been confirmed through multiple robust meta-analyses (the most reliable form of evidence) which have concluded a significant relationship between folate status and depression, even after adjusting for potential confounds (Bender, Hagan, & Kingston, 2017; Gilbody, Lightfoot, & Sheldon, 2007). However, there is no indication that folate can be considered a therapeutic treatment for depression. Only that many of those with depression have a need for dietary management that involves foods containing folate. Furthermore, evidence shows that up to 70% of depressed patients are carriers of the MTHFR C677T allele, showing either a C677T heterogeneous or homogenous polymorphism (Arinami, Yamada, Yamakawa-Kobayashi, Hamaguchi, & Toru, 1997; Bjelland, Tell, Vollset, Refsum, & Ueland, 2003; Farah & Farah, 2009; Ginsberg, Oubre, & Daoud, 2011; Kelly et al., 2004; Shelton, Manning, Barrentine, & Tipa, 2013). These patients show a markedly reduced ability to convert folate to L-5-Methylfolate (L-5-MTHF), a feature not able to be remedied by intake of normal food. The failure of normal dietary folate has also been empirically demonstrated (Girelli et al., 2003). Therefore, this relatively common mutation can lead to a functional alteration of the metabolic processing of folate to L-5-MTHF, resulting in a deficiency of L-5-MTHF in the cerebrospinal fluid (CSF). This specific polymorphism results in an inborn error of metabolism and has been found to be associated with depression in several studies (Almeida et al., 2005; Bjelland et al., 2003; Chen et al., 2005; Kelly et al., 2004; Naumovski et al., 2010; Tan et al., 2004). Finally, again this association has been confirmed across multiple meta-analyses, supporting a significant association with the MTHFR C677T polymorphism and a clinical diagnosis of major depressive disorder (Chen; et al., 2005; C.-C. Pan et al., 2009; Rai, 2017). Again, this does not mean that folate can be used as a treatment for depression, only that

many of those diagnosed with depression have a unique need for bioactive forms of folate that would most suitably be regulated as a FSMP.

Numerous clinical studies in humans have found that 15mg/day of L-5-MTHF, was effective in addressing an underlying dietary deficiency in patients with SSRI-resistant MDD (Ginsberg et al., 2011; Papakostas et al., 2014, 2012; Passeri et al., 1993; Shelton et al., 2013). This dietary management only resulted in significant improvements when combined with standard SSRI treatment, when compared with outcomes relative to SSRI treatment alone. As such, not only is dietary management not intended for therapeutic use, it would be inappropriate to use folate or derivatives of folate as a therapeutic for depression. Depression is an intractable disease that directly or indirectly impacts millions of Australians every year. Any products that may assist the Australian public who are battling this disease should of course be verified for efficacy and safety. However, in the absence of concerns about efficacy or safety and where suitable regulatory structures already exist, placing unnecessary and wholly inappropriate hurdles specifically for products that aim to assist those with the management of dietary aspects related to their disease (without providing any evidence as justification) is ethically wrong.

Finally, as a matter of full disclosure, I have been involved as a consultant with some regulatory work in the EU and Australia for products that will be severely affected should the proposed declaration be implemented. It is this involvement that allowed me to see the call for consultation despite the short timeframe. Despite this, I believe there is little conflict of interest from my end as I hold no shares in any company that produces products that may be affected and have received no payment of any kind for submitting this letter. However, this insight means that I know, as you are likely also aware, that should the proposed declaration be implemented, numerous patients will no longer be able to access any FSMP products related to the dietary management of folate deficiencies whether related to depression or otherwise. The notion that patients may maintain access through special schemes or authorized prescribers is faulty, as the manufacturers will no longer be able to financially justify production and distribution of these products in Australia in the current form. Furthermore, as an additional disclosure, I have both a close friend and a family member who have taken FSMPs (or FSMP like products which are not in Australia) that assist with the dietary management of folate disorder specifically related to depression in conjunction with prescribed medication. I personally believe both benefited from this approach. The struggles those with chronic depression experience are heartbreaking. These difficulties certainly contribute towards Australia's frightening statistics on suicide, the *Black Dog Institute* estimates that in 2017 more than 3000 Australians died by suicide and over 65,000 attempted suicide. It was the leading cause of death for Australians between 15 and 44 years of age. While it may seem odd that something as simple as a medical food can help, given the supporting evidence, it is difficult to argue against it. To invoke unusual legislation to block and limit access, especially when it goes against both wording and principle of existing legislation and conflicts with the balance of the scientific literature would be a mistake. For these reasons I sincerely hope you reconsider implementing the proposed declaration.

Yours sincerely,

Dr Brett J. Kagan, *B.*

Soc. Sci(Psych)(Hons), M. Neurosci, PhD.