COMMENTS ON THE BACKGROUND DISCUSSION PAPER (TOX/2018/40)

For consideration by COT in its discussions about evidence for adoption of an Upper Level for folic acid

We ask members of COT to take into account the following comments on the Background Discussion Paper (TOX/2018/40) as they consider whether there is clear evidence of risk from folic acid/folate, and whether there is a valid quantitative basis for imposing a Tolerable Upper Level, in the knowledge that this might discourage the fortification of flour or limit the magnitude of fortification and hence its efficacy in preventing neural tube defects (NTDs). The strength of our views is evident in some of our commentary. This is not intended as a criticism of the Committee or those who prepared the Background Discussion Paper (TXO/2018). It simply reflects our concern that an opportunity to save the lives of hundreds of babies each year, and to reduce suffering from folate deficiency in the general population, might be lost because of historical misinterpretation of evidence and risk.

Historical origin of the 1mg/day UL

1. The quantitative basis for the widely quoted "Tolerable Upper Level" (TUL or simply UL) of 1 mg/day for folic acid (actually originally stated for folate*) derives solely from the original, flawed analysis by the US Institute of Medicine (IOM, 1998). Despite admitting "a lack of controlled, dose-response data" (IOM, 1998, p 280) the report concluded that folic acid administration could exacerbate B12 deficient neuropathy, with a claimed dose-response relationship with elevated risk at doses above 5mg/day. This was taken by the IOM as the

Lowest Observed Adverse-Effect Level (LOAEL) and a very cautious Uncertainty Factor of 5 was applied to derive the UL of 1mg/day (IOM, 1998, pp 279-280).

2. Numbered paragraph 5 (and also 21) of the COT Discussion Paper reports that, at the meeting of COT in July 2018, "members agreed that the end-point used by the IOM, SCF and EVM was correct and appropriate and requested that the data be reanalysed to see if a dose response relationship could be determined between folic acid intake and the masking of neuropathy in vitamin B12-deficient patients". But the end-point adopted by IOM was not hypothesized "masking" (i.e. hiding the symptoms and signs) of B12 deficiency neuropathy, but was **explicit initiation or acceleration of neuropathy by folic acid**:

   > "The weight of the limited but suggestive evidence that excessive folate intake may precipitate or exacerbate neuropathy in vitamin B12-deficient individuals justifies the selection of this endpoint as the critical endpoint for the development of a UL for folate." (IOM, 1998, p 277).

3. The IOM presented no quantitative evidence that "excessive intake of folate supplements may obscure or mask and potentially delay the diagnosis of vitamin B12 deficiency" and they rejected this as a possible end-point for the determination of a TUL. The IOM admitted that "data were not available on which to set a NOAEL." (IOM, 1998, p 278) but they did propose a LOAEL of 5 mg/day, based entirely on the following summary of the evidence:

   - *at doses of folate of 5 mg/day and above, there were more than 100 reported cases of neurological progression;*
   - *at doses of less than 5 mg/day of folate (0.33 to 2.5 mg/day), there are only eight well-documented cases*

   (IOM, 1998, p 278).

Paragraph 4 of the COT Discussion Paper reproduces this summary but does not point out that these results are meaningless without a denominator!

4. Wald et al (2018) have already re-analysed the original data considered by the IOM, with the clear conclusion (not denied in the Discussion Paper) that the IOM's analysis was fundamentally flawed and that the data showed no positive dose-response relationship (indeed a negative, but non-significant, correlation between folic acid dose and progression to neuropathy). Table 1 in the COT Discussion Paper shows all the data (not selected for the quality of documentation) considered by the IOM (1998) and by Wald et al (2018). We ask COT to note that all 6 patients who received less than 1mg/day progressed to neuropathy, while only 96 of the 144 patients (58%) who received 5 mg or more did so!

5. **The results in the IOM (1998) report provide absolutely no evidence that folic acid can "precipitate or exacerbate neuropathy in vitamin B12-deficient individuals": we urge COT to acknowledge that this cannot be taken as an end-point for the establishment of a UL.**

Other possible risks and potential end-points

6. Paragraph 24 of the Discussion Paper asks the Committee to look at other possible end-points if they "consider that the data on the "masking" or exacerbation of neuropathy in vitamin B12-deficient individuals is not adequate to set a guidance level or Safe Upper Level" for folate. The IOM report presented no quantitative evidence for "masking" and delay in the diagnosis of B12 deficiency and rejected this possibility alone as an end-point. The IOM report found no clear, adequately-documented evidence of general toxicity, reproductive and developmental health or cancer; and in its most recent report on folic acid, SACN (2017) came to the same conclusions. SACN also found no consistent evidence

for effects on cognitive decline in older individuals, nor of adverse effects from unmetabolised folic acid. As noted in paragraph 36 of the COT Discussion Paper, the IOM report concluded that "there is no clear evidence of folate-induced neurotoxicity in humans" (IOM, 1998, p 276). The Expert Group on Vitamins and Minerals (EVM) agreed that: "there is no clear evidence for a folic acid-induced neurotoxicity in humans." (EVM, 2000, p 8).

7. There are now no valid uncertainties regarding cancer at any site being caused by folate. RCTs show no hazard and other categories of results do not yield a coherent set of data that even suggest a hazard. It is reasonable to conclude "no detrimental effect of folic acid/folate on cancer risk" rather than merely suggesting the absence of risk. Paragraphs 61 to 75 of the Discussion Paper provide no evidence of harm from unmetabolized folic acid in blood (although the text still appears to entertain possible harms). The Paper also provides no evidence that fortification or folic acid supplementation raises a concern if folate antagonists are needed or in respect of hypersensitivity.

The issue of "masking"

8. The IOM report did state that "excessive intake of folate supplements **may** obscure or mask and potentially delay the diagnosis of vitamin B12 deficiency" (IOM, 1998, p 274). However, they cited no supporting evidence; they did not suggest that this would, in itself, constitute a risk to health; and they did not attempt to use this as an end-point for the determination of a TUL. SACN (2017) was also unable to find convincing evidence for a risk from "masking":

    - "No systematic reviews have evaluated the risk of folic acid masking or exacerbating vitamin B12 deficiency in adults. Evidence for this outcome is mainly from folic acid interventions over 1 mg/d. The prevalence of vitamin B12 deficiency with or without

anaemia did not increase after mandatory fortification in the USA." (paragraph S13, p vii).

- "No systematic reviews or meta-analyses, evaluating the risk of folic acid masking or exacerbating adverse effects of vitamin B12 deficiency, were identified" (paragraph 52, p 10).
- "The SACN 2006 report highlighted uncertainties regarding evidence relating to potential cognitive and vitamin B12 related adverse outcomes of folic acid (masking of vitamin B12 deficiency & acceleration/aggravation of cognitive decline). It concluded that folic acid intakes up to 1 mg/d are not associated with masking anaemia associated with vitamin B12 deficiency. It noted a lack of data on trends in clinical incidence of vitamin B12 deficiency or any related neurological damage but limited data (from national hospital discharge surveys) from countries with mandatory fortification had not suggested an increase post-fortification." (paragraph 141, p 26).

Indeed, the comprehensive earlier analysis by SACN concluded: "the evidence relating to the masking of B12 deficiency by folic acid is limited to often poorly described case reports" (SACN, 2006, p 2).

9. By 1998 (the date of the IOM report), presentation with anaemia was not necessary for the diagnosis of B12 deficiency: the word "mask" appears only once in the text of the report. Even in 1993, the FDA Subcommittee on Folic Acid received expert comment that "the issue of masking of vitamin B_{12} deficiency was overstated and predated modern clinical nutrition." (FDA, 1996, p 8768). It is now recognised that about one fifth of patients with B12 deficiency do not have a macrocytic anaemia (Lindenbaum et al, 1988). The term "masking" is historical, relating to a time when the differential diagnosis of a macrocytic

anaemia was difficult. Use of folic acid supplementation to resolve anaemia due to B12 deficiency would now constitute an error of clinical judgement. The alleviation of a macrocytic anaemia with folic acid supplementation provides no guide as to whether the anaemia is due to B12 deficiency or folate deficiency.

10. With the routine availability (since the 1950s) of a variety of B12 assays (Chanarin, 1997; Hunt et al, 2014) and synthetic B12 supplements (since the 1960s), the presence or absence of an anaemia has become of secondary importance in the diagnosis of B12 deficiency. We are puzzled by the assertion in numbered paragraph 20 of the COT Discussion Paper that "there is no routine test to reliably identify vitamin B12 deficiency" in patients with pernicious anaemia. There are inexpensive, reliable, straightforward tests to measure serum B12 (see NICE, 2105) in patients with any symptoms of possible B12 deficiency, however non-specific.
11. In assessing the safety of folic acid fortification, the historical issue of "masking" is logically irrelevant, and there is no evidence that the diagnosis of B12 deficiency is now being missed, with consequent development of irreversible neurological damage. As GP Oakley (2002) put it, 16 years ago, the "myth of masking" should be discarded.
12. The presence or absence of a macrocytic anaemia no longer plays a primary role in the diagnosis of B12 deficiency. Indeed, the diagnostic label "pernicious anaemia" is outdated in focusing on the symptom of anaemia, which is not present in a significant proportion of cases (Windenbaum et al). Symptoms of anaemia might prompt a visit to the doctor, leading to tests of both B12 and folate status, resulting in a differential diagnosis. However, the early neurological symptoms of B12 deficiency (tingling, paraesthesia, numbness) are more usually the cause of the first consultation with a doctor, and they are readily reversible with B12 therapy. Anecdotal enquiry amongst consultant haematologists and neurologists

indicates that there has not been a single case of irreversible B12 neuropathy in the UK for more than a decade. The early symptoms and signs of B12 deficiency are, with appropriate medical care, reversible. If COT has residual doubt on this point, we urge the Committee to seek the opinion of senior haematologists and neurologists.

Propagation of the flawed 1mg/day UL

13. The figure of 1mg/day has become enshrined in the literature of risk assessment as a limit of safety for total folate, non-food folate or folic acid. Major agencies, including SCF, EVM and SACN have undertaken exhaustive reviews of the evidence and have all adopted the same figure of 1mg/day. It is easy to get the impression that this is based on a range of confirmatory quantitative assessments, all pointing to the same threshold of potential risk. This is not the case.
14. The 1 mg/day figure first appeared in reports from the Food and Drug Administration (FDA) earlier than the much-cited IOM (1998) report. The 1990 amendments to the Federal Food, Drug, and Cosmetic Act and the US Dietary Supplement Act of 1992 provided for extensive changes in the way foods are labelled in the US. By 1993, the FDA's Folic Acid Subcommittee was focusing on the evidence for the effectiveness of periconceptual folic acid supplementation in the prevention of NTDs (primarily the MRC Vitamin Study – Wald et al 1991). But, in parallel with endorsement of this evidence (leading eventually to the adoption of mandatory fortification in the USA in 1998), the FDA considered whether there might be risks associated with increased intake of folic acid/folate and issued a "caution statement". "Recognizing the potential for adverse effects from high intakes of folate, PHS included a caution statement in its recommendation that 'because the effects of higher intakes are not well known but include complicating the diagnosis of vitamin B12 deficiency, care should be

taken to keep total folate consumption at <1 mg per day, except under the supervision of a physician'" (FDA, 1996, p 8766).

15. The FDA report of 1996 provides a fascinating account of the origin of the tentative 1mg/day figure. The approach was not to define an end-point and assess quantitative evidence for growing likelihood of harm with dosage. The proposal was based on assertions of evidence of safety rather than evidence of harm. The FDA Folic Acid Subcommittee simply stated that extensive experience of exposure below 1mg/day suggested that it was safe, and the fact that 1mg/day was 2.5 times the Recommended Daily Intake made 1mg appear to be a plausible limit. However, they admitted that no evidence was available concerning exposure above 1mg/day! "There are no data to ensure that adverse effects are not likely to occur at daily intakes above 1 mg" (FDA, 1996). "A major factor in both the Folic Acid Subcommittee's and the Food Advisory Committee's concern about FDA's proposals was the fundamental issue of lack of documentation of safety of long-term daily intakes at levels above 1,000 mcg" (FDA, 1996). "Because there are inadequate data and information on the safety of consuming more than 1,000 mcg folate per day, the agency is unable to conclude that there is a reasonable certainty of no harm to persons consuming more than 1,000 mcg folate per day. In the absence of data on high intakes of folate, **the agency is unable to adequately define the nature or magnitude of potential risk from increased folate intakes**." (FDA, 1996).

16. **The original, tentative 1mg daily limit was not based on evidence of harm with exposure above 1mg/day. The analysis was anecdotal and does not meet current standards for the establishment of even a Guidance Level. There was no attempt to define a specific end-point, to examine dose response, to establish an NOAEL or LOAEL, to apply an Uncertainty Factor or to derive a formal SUL.**

17. The IOM report of 1998 was the first to apply such methodology and it managed to arrive at the same 1mg/day limit. Although it is now clear that the analysis and conclusions of IOM (1998) were flawed and invalid, the 1mg/day figure has had a penetrant influence.
18. SACN (2017) summarised what has happened: “In the USA and Europe, a Tolerable Upper Intake Level (UL) of 1 mg/d of folic acid was set for adults (Food and Nutrition Board, 1998; Scientific Committee on Food, 2000) … The UL was based on the risk of progression of neurological symptoms in vitamin B12 deficient patients.” (paragraph 36, p 7); and “In the UK, safe levels of intake for vitamins and minerals in food supplements and fortified foods were set by the Expert Group on Vitamins and Minerals (2003) … An SUL was not set for folic acid intake as the available evidence on adverse effects of folic acid was not considered to be sufficiently robust but a GL of 1 mg/d was set based on concerns that intakes above this level may mask signs of vitamin B12 deficiency” (paragraph 37, p 7).

Certain public benefit has been compromised by unjustified claims of harm

19. The MRC Vitamin Study (Wald et al, 1991) established that periconceptual consumption of folic acid prevents NTDs. The benefit is dose-dependent: about 80% of cases are prevented by 4mg/day of folic acid. This evidence of benefit has been universally acknowledged. However, since the preventive role of folate applies during the first weeks of pregnancy, it is important for serum folate levels to be adequate from the time of conception. Attempts to achieve adequate prevention by advice to women to take supplements in tablet form has benefited only a minority of pregnancies (Wald et al, 2018) and it is clear that mandatory fortification of cereals provides the most certain means of protection.
20. Eighty-one countries around the world have now introduced mandatory fortification and all records have confirmed an immediate and sustained reduction in the incidence of NTDs.

Tens of thousands of terminations and stillbirths have been prevented. Tens of thousands of children have been spared a life of disability. Results from countries with different levels of fortification have confirmed the dose-dependence of the benefit. The pregnancy prevalence of NTDs has roughly halved in Chile, where fortification was set to raise daily folate intake by 0.4 mg. In the United States, where fortification was designed to raise daily intake by only 0.1-0.2mg, estimates of the reduction in prevalence range between 19% and 32%. It has been estimated that about 2,000 pregnancies associated with a neural tube defect would have been prevented if the UK had adopted the same fortification as the United States from 1998 (Morris et al, 2015)

21. It is important to point out that prevention of NTDs constitutes a benefit not only to the particular pregnant mothers and their babies, but to their families, their neighbours, and the whole of society. In purely economic terms the value of prevention is enormous. Moreover, there is evidence of other general benefits from fortification. Folate deficiency and associated anaemia are significant issues in countries without folic acid fortification, especially amongst the elderly. But in the United States folate deficiency and associated anaemia have been all but eliminated by fortification (Odewole et al, 2103). There are reasons to expect an impact of increased folate intake on cardiovascular disease, notably stroke. There has indeed been a highly significant decline in the incidence of stroke in the USA and Canada, post-fortification, compared with England and Wales (Yang et al, 2006).
22. The hundreds of millions of people around the world who have been exposed to increased folate intake through supplementation and fortification, for 20 years or more, also represent a massive exposure “experiment” providing evidence about potential risks. But no indication of adverse effects has emerged from the large number of studies that have addressed this question. No attributable rise in incidence of any form of cancer; no

increased problems of reproductive health or developmental health; no pattern of increased cognitive decline. Most important of all, there is no indication whatever of a rise in B12 deficiency with or without anaemia, nor of problems due to undiagnosed B12 deficiency including untreatable neuropathy (see SACN 2017).

It has been estimated that, since 1991, there have been over five million preventable NTD pregnancies in the world (see Wald et al, 2018). The suffering and cost associated with these could have been avoided, in a dose-dependent manner, by folic acid fortification. In the UK, which funded the original study demonstrating the benefit of folic acid, fortification has still not been implemented, despite more than 20 years of recommendations for implementation from advisory bodies. A series of concerns and objections have been considered and ruled out. The only remaining obstacle to the introduction of fortification seems to be the 1mg/day UL, which rests on inadequate evidence from outdated clinical practice and on the most elementary of statistical mistakes.

We urge the members of COT to rescue the important discussion about the safety of folic acid from the historical burden of the IOM guidance. The outcome of this discussion will determine whether the UK introduces mandatory fortification and, if so, whether the level of fortification is set at a level that will maximise the benefits.

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*** Additional notes**

1. There is a confusion between folate and folic acid in some of the discussion about levels of intake that might constitute a risk. In its early discussions about this issue, in 1993, the FDA tentatively proposed a "caution statement" for labelling of folic acid supplements, suggesting that intake of 1 mg per day of "total folate" should be avoided (FDA, 1996, p 8766). The numerical presentation in the IOM (1998) report does not make clear distinctions between folic acid and folate. The stated intention was to assess evidence of risk from folate (*Folate* is the title of the chapter of the report) and all the conclusions are expressed in terms of folate. However, the data used for the analysis were from clinical studies involving administration of folic acid, and the doses reported in the analysis (see Table 1 of the COT Discussion Paper) were of folic acid. Although the IOM report describes in detail the greater

bioavailability of folate from folic acid than from food, it did not correct for this factor in its (flawed) calculations.

2. Since the data analysed by IOM (1998) came from studies of treatment with supplements, the derived LOAEL and UL were described as applying only to folate from supplements and fortification, not including food folate. This is unusual and potentially confusing, since folate derived from food (mean about 0.2 mg/day) varies substantially among individuals, yet if there were a risk from high levels of serum folate, total intake would be the relevant variable. In their re-analysis of the data considered by the IOM, Wald et al (2018) examined the potential population effects of fortification, including correcting for bioavailability (their Fig 5b). They concluded that fortification of flour providing 0.2mg/day of folate, on average, would lead to about 16% of the population having a **total** intake of available folate greater than 1mg/day, but if the UL were truly to apply only to non-food intake, the percentage exceeding this (incorrect) UL would be substantially reduced.

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