

## Response ID ANON-3MRW-NTG2-4

Submitted to **Adding folic acid to flour**

Submitted on **2019-08-08 16:24:16**

### Proposal to add folic acid to flour

**Do you agree or disagree with the proposal for mandatory fortification of non-wholemeal wheat flour in the UK with folic acid to help prevent neural tube defects?**

I agree with the proposal

#### Please explain your answer

**Can you explain the reasons why you agree or disagree?:**

This has to be an important health improvement development with prior evidence available on benefits to NTDs as well as cardiovascular health, congenital heart defects and reduction in specific cancers from countries that have been fortifying for many years.

#### Which products should be included

**Which of the following do you think mandatory fortification with folic acid should apply to? Please choose one.**

all flour in the UK and other non-wheat products such as 'gluten free'

#### Alternative approaches

**Are there any alternative ways of helping reduce the number of neural tube defects that you may prefer, other than our proposal for mandatory fortification of flour with folic acid?**

**Are there any alternative ways of helping reduce the number of neural tube defects that you prefer, other than our proposal for mandatory fortification of flour with folic acid? :**

All attempts to educate and inform about folate requirements in pregnancy have failed to have a significant impact. The problem is one of "prevention" which seems a difficult concept for some people and cultures. Thus fortifying food seems the best option to have an impact on folate sensitive conditions.

I would like to add the following remarks on FOLINIC acid for your consideration:

In our literature and laboratory research over the past 23 years we have identified issues with cerebral folate imbalance that are found in conditions such as hydrocephalus, certain types of autism, depression and similar neuropsychiatric disorders. These conditions do not respond to folic acid but do respond to natural folates, specifically FOLINIC acid.

There are many recent publications showing positive response to folinic acid in these conditions. Moreover, in our studies of congenital hydrocephalus, we found that the condition could be prevented by giving FOLINIC acid but that, in our rodent model of fetal-onset hydrocephalus at least, the condition is precipitated in susceptible fetuses by high dose folic acid (e.g. Cains et al, 2009 J.Neuropathol.Exp.Neurol.).

We have since found that human neonates with congenital hydrocephalus, acquired hydrocephalus from birth trauma/intraventricular haemorrhage or postnatal infection, and babies suffering from birth asphyxia all have a very similar folate issue in their brain fluid indicating that treatment with FOLINIC acid would be beneficial (Miyan et al, unpublished/in preparation – manuscript available, under embargo, upon request).

Analysis of the cerebral palsy brain metabolome confirms a folate issue in this severe neurological condition also (Savasan et al 2019 Metabolites 9,27).

Moreover, a subclass of "autism"-trajectory babies present, well before diagnosis of the condition, with increased brain fluid within and around the brain (Shen 2018 J.Neurodev.Disorders 10:39) as do traumatic brain injury patients (Cole et al, 2018 BRAIN 141:822).

From our research and understanding of the cerebral folate system, I am convinced that these represent low level hydrocephalus and would respond to FOLINIC acid treatment but NOT folic acid. A further subclass of autism children present with folate receptor auto-antibodies that block transfer of folate from blood to brain. This is associated with increasing severity of neurological symptoms if not treated and the best treatment has been found to be FOLINIC acid as detailed in the next paragraph.

A recent clinical trial of very high dose FOLINIC acid was found to reduce language and social impairment in children with Autism (Frye et al, 2018 Mol.Psychiatry 23: 247-256). A specific condition of CEREBRAL folate deficiency has been described which does not reflect otherwise normal folate levels in the blood circulation. This condition is caused by autoantibodies to folate receptor-alpha which may be produced by mother or the child through reactions to this molecule in cow's milk. The consequence is that cerebral folate transport is blocked and the brain is deprived of folate. Folic acid does not address this issue but FOLINIC acid can reverse the neurological consequences by by-passing the block and supplying the brain (Ramaekers et al 2016 Biochemie 126:79). These authors have since identified a number of neuropsychiatric conditions with similar cerebral folate deficiencies that respond to folinic acid including autism, depression, anxiety etc, and even more severe conditions such as Schizophrenia.

The findings that folic acid does not work for these conditions seems to be based on the fact that this artificial, man-made molecule is missing the key methyl or other one-carbon moiety that is essential in its metabolic role, also there is evidence that this synthetic molecule gets "stuck" in folate transporters obstructing normal folate transport. This may be the effect of high dose folic acid where free, unchanged folic acid passes into the blood from the gut (for discussion of negative effects see: Rosenberg & Selhub 2018 <https://doi.org/10.1016/B978-0-12-802861-2.00024-9>). This effect is not seen with the natural folate, FOLINIC acid (5-formyl tetrahydrofolate) which proved beneficial to autistic children at doses up to 50mg/day (Frye et al, 2018 Mol.Psychiatry 23: 247-256) confirming our experimental findings in rodents for hydrocephalus.

Thus, I would strongly recommend and urge that the Government consider FOLINIC acid rather than folic acid as the folate for fortification as it would have none of the negative effects of folic acid rather it would have a positive benefit not only on NTDs but also on a wide range of other conditions based in cerebral folate imbalance or deficiency with no upper limit to worry about.

Following the completion of our preclinical work, and subject to successful funding, we will be trialling our combination natural folate as a preventative and/or treatment for human fetal hydrocephalus and hope to also complete a pilot population study to test the effects on the range of conditions, including NTDs, Autism, and others mentioned above.

I am convinced, through published evidence and our own research work, that using FOLINIC acid and not folic acid will produce a sustained benefit to the health burden on society through reduction in NTDs and other serious conditions affecting the developing cerebral cortex of the brain. I would be happy to expand on the above if necessary for the benefit of the committee's deliberations.

## **How individuals and businesses are affected**

**Are there any particular groups or individuals that might be negatively affected by mandatory fortification of flour with folic acid, or miss out on the benefits?**

**Are there any particular groups or individuals that might be negatively affected by mandatory fortification of flour with folic acid, or miss out on the benefits?:**

People planning pregnancies may take supplements (e.g. pregnacare) that contain folic acid and/or natural folates (methy folate) so that they may edge towards the upper limit.

**How could we make sure these groups or individuals are supported or not affected negatively?**

**How could we make sure these groups or individuals are supported or not affected negatively?:**

Through information on flour fortification and by engaging with supplement manufacturers to adjust concentrations to take account of fortification or replace folic acid with natural folates only.

**Are there any businesses that might be negatively affected by mandatory fortification of flour with folic acid, or miss out on the benefits?**

**Are there any businesses that might be negatively affected by mandatory fortification of flour with folic acid, or miss out on the benefits?:**

Makers of folic acid tablets

**How could we make sure these businesses are supported or not affected negatively?**

**How could we make sure these businesses are supported or not affected negatively?:**

ask them to provide folic acid for fortification program (BUT certify content) and also switch to making FOLINIC acid

## **Voluntary fortification**

**If the fortification of flour with folic acid is made mandatory, do you agree or disagree that there should be limits on voluntary fortification of other food products and/or supplements with folic acid?**

I agree

**Please give reasons for your answer**

**Please give reasons for your answer:**

I believe there is an upper limit beyond which folic acid, as a synthetic, non-methylated form of folate may have negative effects. Indeed my research over the past 20 years has demonstrated a clear negative effect of high dose folic acid in precipitating congenital hydrocephalus in a rodent model (Cains S et al, 2009).

## **Impact assessment**

**Do you agree or disagree with the provisional cost/benefit analysis outlined in the impact assessment?**

I agree

**Can you provide any additional evidence to inform the impact assessment?**

**Option to upload a file for the question Can you provide any additional evidence to inform the impact assessment?:**

folate, methylation and neurotransmitters.pdf was uploaded

**Text box for the question Can you provide any additional evidence to inform the impact assessment?:**

**Do you think there are any other benefits, costs or wider impacts of this policy proposal that have not been mentioned yet?**

**Text box for the question Do you think there are any other benefits, costs or wider impacts of this policy proposal that have not been mentioned yet?:**

Based on evidence published from a 15 year follow-up analysis of flour fortification in the USA, they found reductions not just in NTDs but also in cardiovascular

illness, congenital heart defects and in certain cancers.

The study did not investigate the wider range of conditions that may have benefited but there are published scientific works demonstrating positive benefits of low dose folic acid to neurodevelopmental conditions including Autism Spectrum Disorder, depression/anxiety, Schizophrenia, multiple loss of pregnancies and others. These positive benefits were with low level folic acid fortification and are balanced by suspected negative effects at higher doses.

Given the decrease in folate content of foods and complete loss in most processed foods, it seems imperative to provide this minimal level for general health. Folate metabolism feeds into a variety of processes including methylation (important for gene expression control and hence underlying birth defects and potential cancers), nitric oxide synthesis for cardiovascular health and neurotransmitter synthesis for mental health.

I would be happy to provide further information on my work and any of the points raised above, in writing or in person.

## **Practicalities for businesses**

### **What are the practical issues that need to be thought about for mandatory fortification with folic acid?**

#### **What are the practical issues that need to be thought about for mandatory fortification with folic acid?:**

In the USA experience flour fortification did not have an impact on people of hispanic origin. This was found to be due to their preference for corn flour rather than wheat. Since that report USA has been fortifying corn flour as well as wheat flour. This would need to be considered for the dietary habits of particular ethnic groups and for those with wheat intolerance.

### **Are there any further trade implications for industry that need to be considered?**

Text box for the question **Are there any further trade implications for industry that need to be considered?:**

### **Are there any effects on small businesses and medium businesses that need to be considered?**

Text box for the question **Are there any effects on small businesses and micro businesses that need to be considered?:**

## **About you**

### **What is your name?**

#### **First name:**

Jaleel

#### **Surname:**

Miyan

### **What is your email address?**

#### **Email:**

j.miyan@manchester.ac.uk

### **Contact you - Is it okay for the Department of Health and Social Care to send you updates about our consultations?:**

Yes

### **Contact you - Is it okay for the Department of Health and Social Care to contact you about your response?:**

Yes

### **In what capacity are you responding?**

As an individual

#### **If other, please specify:**

Expert researcher in cerebral folate metabolism

## **About you as an individual**

### **How old are you?**

Over 56

### **What is your annual household income?**

£40,000 - £59,999

### **What is your gender?**

Male

**If other, please give specify:**

**What is your ethnicity?**

Asian/Asian British

**If other, please provide details of your ethnic background:**

**Where do you live?**

England

**If other, please specify:**

**Home postcode:**

M34

**About you and your organisation**

**What is the name of your organisation**

**Name of organisation:**

The University of Manchester

**Type of business/organisation:**

Education and Research

**What is your role**

**What is your role in your organisation:**

Senior lecturer in Neuroscience. I am a principle investigator running my own research lab that has been involved in understanding cerebral folate metabolism and neonatal hydrocephalus for the past 23 years and in neuroscience research for the past 35+ years

I believe that my expertise and knowledge on cerebral folate is relevant to the committee's decision making through this consultation.

**How many employees does your business/organisation have?**

250 people or more

**Where is your organisation based**

**Please enter the first part of your work post code :**

M13

England