TOX/2023/41

Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment.

Discussion paper on the assessment of the risk of allergic reaction from fortification of non-wholemeal wheat flour with folic acid

Background

1. The UK Health Departments plan to implement a public health intervention that requires food business operators to fortify non-wholemeal wheat flour with folic acid at a level of 250 µg per 100 g of flour to help prevent an estimated 200 neural tube defects in foetuses (e.g. spina bifida and anencephaly) per year. This will affect an estimated 22 billion units of food sold in the UK annually.

2. Pursuant with labelling requirements the fortification of the non-wholemeal wheat flour should be reflected in labelling. However, concerns have been raised that there will be challenges in changing labelling and it has been suggested that there could be transitional arrangements to facilitate the change which could mean that for a 3-month period the presence of folic acid is not reflected on the label.

3. The Food Standards Agency (FSA) has been asked by the Department of Health and Social Care (DHSC) to establish the risk of allergic reactions to folic acid at the intended level of fortification if it is not labelled on final products (or in the case of food sold loose, not conveyed by other means) during the derogation period. The draft risk assessment has been attached at Annex A.

4. Overall if non-wholemeal flour is fortified with folic acid at 250 µg per 100 g without its presence being labelled on the packaging of the final food or, in the case of food sold loose, not conveyed by other means during a 3 month derogation period then we estimate the risk of allergic reactions to folic acid in UK consumers to be as follows:

- The **frequency of allergic reactions to folic acid in food** to be **very low** (i.e. very rare but cannot be excluded).
- The **severity of illness in relation to allergic reactions to folic acid in food** to be **medium** (i.e. moderate illness: incapacitating but not usually life-threatening, sequelae rare, moderate duration).
- The **level of uncertainty** to be **medium** (i.e. there are some but no complete data available; evidence is provided in small number of references).

Questions for the Committee

4. The Committee are invited to consider the following questions in relation to Annex A:

i. Do Members agree with the approach used to undertake the risk assessment?
ii. Do members agree with the estimates of the frequency of allergic reactions to folic acid in food, severity of illness in relation to allergic reactions to folic acid in food or the associated level of uncertainty?
iii. Do Members have any comments on the reference to allergy or allergic reaction in relation to folic acid? Should it be defined more generally as hypersensitivity?
iv. Do Members have any other comments?

Secretariat
September 2023

This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

Annex A to TOX/2023/41

Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment Assessment of the Codex report on food allergen thresholds

Draft assessment of the risk of allergic reaction from fortification of non-wholemeal wheat flour with folic acid

Secretariat
August 2023

This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

Draft Risk Assessment:

What is the risk of allergic reactions to folic acid in UK consumers if non-wholemeal flour is fortified with folic acid at 250 µg per 100 g without its presence being labelled on the packaging of the final food or, in the case of food sold loose, not conveyed by other means during a 3 month derogation period?

Risk Assessment Unit

Science, Evidence and Research Division, FSA

Version 1.0
25 August 2023

Contents

This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

Executive Summary

This risk assessment considers the risk in terms of allergy to UK consumers if folic acid is used to fortify non-wholewheat flour at 250 µg per 100 g without its presence being labelled on the packaging or not conveyed by other means during a 3 month period.

The UK prevalence of allergy to folic acid is not known. Leading UK allergy specialists and the UK wide charity operating for people at risk from severe allergic reactions and anaphylaxis were contacted to inform the risk assessment and were not aware of evidence of food allergy to folic acid in the UK. A small number of cases have been reported in the literature although these were mostly linked to supplements rather than the consumption of food.

An allergen reference dose for folic acid has not been established and so the usual approach for assessing allergen risk could not be followed. Instead, the 75th and 97.5th percentile amount of folic acid that would be consumed if non-wholemeal flour is fortified at the proposed level was estimated and found to be lower than the amount reported to have caused the majority of allergic reactions described in the published literature, with the exception of two cases.

This suggests that while it may be possible for the proposed amount of folic acid in fortified non-wholemeal wheat flour to potentially trigger reactions, this is only likely to occur very rarely in highly sensitive individuals and is not significant on a population basis.

Symptoms of the reported allergic reactions to folic acid range from mild to severe (including anaphylaxis) although no deaths have been reported in the literature.
Overall if non-wholemeal flour is fortified with folic acid at 250 µg per 100 g without its presence being labelled on the packaging of the final food or, in the case of food sold loose, not conveyed by other means during a 3 month derogation period then we estimate the risk of allergic reactions to folic acid in UK consumers to be as follows:

- the **frequency of allergic reactions to folic acid in food** to be **very low** (i.e. very rare but cannot be excluded).

- the **severity of illness in relation to allergic reactions to folic acid in food** to be **medium** (i.e. moderate illness: incapacitating but not usually life-threatening, sequelae rare, moderate duration).

- the **level of uncertainty** to be **medium** (i.e. there are some but no complete data available; evidence is provided in small number of references).

Statement of Purpose

This risk assessment focuses on the immediate acute hazard of concern in terms of allergic reactions in UK consumers if folic acid is used to fortify non-wholemeal wheat flour.
It should be noted that this risk assessment does not cover consumption of final products made outside the UK or dietary intake from other sources of folic acid or folate, including dark green leafy vegetables, beans, fresh fruit, aquatic foods, eggs and other foods fortified with folic acid such as cereals, spreads and supplements where this is already labelled.

Background

The neural tube is part of the developing foetus's nervous system, and its development can be impaired for a number of reasons including folate deficiency during early pregnancy. The number of neural tube affected pregnancies (e.g. spina bifida and anencephaly) in the UK remains a concern to UK Health Departments. Advice to women to take folic acid supplements prior to conception and up to the 12th week of pregnancy has been in place for many years but this public health issue remains, particularly for unplanned pregnancies where a woman may not find she is pregnant until well into the crucial 12-week period when the neural tube is closing.

UK Health Departments plan to implement a public health intervention (Consultation – 'Amending the Bread and Flour Regulations 1998 and the Bread and Flour Regulations (Northern Ireland) 1998'). The proposed intervention requires an amendment to the Bread and Flour Regulations lead by the Department of Health and Social Care (DHSC) and Department for Environment, Food and Rural Affairs (Defra), and requires food business operators to fortify flour (at the milling stage) with folic acid at a level of 250 µg per 100 g of non-wholemeal wheat flour. This level was chosen based on the impact model commissioned by Food Standards Scotland (FSS) (Stochastic modelling to estimate the potential impact of fortification of flour with folic acid in the UK).

The fortified flour will be used in a wide range of food products which in turn will increase folic acid consumption across the UK including by pregnant women thereby reducing the likelihood of neural tube defect-affected pregnancies.

Food Business Operators using the flour products will need to ensure that labelling reflects the addition of folic acid when flour mills start adding it to the flour. However, concerns have been raised that there will be challenges in changing labelling on such a vast array of products and so it has been suggested that there could be transitional arrangements to facilitate the change which could mean that for a 3-month period within an overall period of

up to 2 years (a) folic acid is not present in products labelled as containing it or (b) products contain folic acid but this is not reflected on the label. FSA has therefore been asked to consider whether this could present a food allergy risk, for example because the risk of anaphylaxis from folic acid has been highlighted by NHS advice (Side effects of folic acid – NHS (www.nhs.uk) although it is unclear whether these concerns are relevant to food hypersensitivity as opposed to reactions to supplements or medicines containing folic acid.

The Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) previously assessed the safety of folic acid (Folic Acid Statement Final (food.gov.uk)); whilst this did not focus on allergenicity the Committee did comment that "a small number of case reports have described hypersensitivity reactions to oral folic acid therapy (generally more than/equal to 1 mg/day). One short-term, uncontrolled supplementation trial reported adverse symptoms (mental changes, sleep disturbances and gastrointestinal symptoms) in healthy volunteers given very high doses of folic acid (15 mg/day) for one month, but other studies have not observed similar effects".

Hazard Identification

In the UK there are 14 types of food or food groups that are recognised as allergenic foods of public health importance and therefore regulated. These are celery, cereals containing gluten, crustaceans, eggs, fish, lupin, milk, molluscs, mustard, nuts, peanuts, sesame seeds, soya and sulphur dioxide. Folic acid is not included in the list of 14 regulated allergens. However, adverse reactions to folic acid have been reported in the literature.

Folic acid hypersensitivity

As opposed to most allergens, folic acid is not a protein but a synthetic form of folate (vitamin B9) which is fully oxidised. Folic acid is not found naturally in foods (Gaeta, et al. 2020). Dietary intakes of folic acid consist mainly of the polyglutamate form. This slowly breaks down in the small intestine into the monoglutamate form (Apraxine et al. 2022). Folic acid has higher bioavailability meaning more can be taken into the body and used in comparison to natural folate found in foods. Folate needs to be broken down in the intestine whereas folic acid does not before it passes into the blood stream. Folic acid can be detected in the blood at doses as low as 200 µg once saturation levels in the red blood cells are reached. Folic acid can then be broken down in the blood similar to having intravenous administration (Schrijvers et al. 2015).

Some studies have suggested that an immediate type of allergic response to folic acid occurs because of the potential presence of IgE antibodies to folic acid in sensitised individuals (Smith et al. 2007; Dykewicz et al. 2000; Nucera

et al. 2018). However, another study could not detect the presence of IgE specific to folic acid in a patient that presented with a positive food oral challenge (Valdivieso et al. 2009).

Gaeta et al. 2020, in discussing two cases reported that folic acid could be recognised as an allergen by the intestinal mucosa as it triggers a reaction within a few minutes after ingestion. Despite limited in vitro cross-reactivity of IgE with reduced folates, the folic acid sensitisation produces an in vivo cross-reactivity and this was illustrated by consecutive anaphylactic reactions against folic acid and methyl folate in one case and cross-reactivity between folic acid, methyl folate and folinic acid in skin tests in another case. Cross-reactivity has also been reported between folic acid and medicines such as methotrexate (when given in conjunction) and those that have a sensitivity to folic acid could have an increased risk to folic acid in supplements or fortified food.

Hazard Characterisation

Uses of folic acid

Folic acid is currently widely used as a fortificant in foods such as breads and breakfast cereals. The Expert Group on Vitamins and Minerals (EVM) reviewed the occurrence of folic acid in foods in 2002 and estimated that 80-90% of breakfast cereals consumed have been fortified with folic acid with the exception of muesli that is not normally fortified. It was stated that most products that have been fortified with folic acid contain between 125 and 200 µg/100g although some products can contain substantially higher amounts (333 µg/100g). Fortification of bread is less widespread and mainly found in soft grain varieties with approximately 120 µg/100g (Department of Health, 2000). Some low-fat spreads are also fortified up to 200 µg/20g. These measurements are based on data obtain from Great Britain (EVM, 2002). In the UK there have been more calls for the fortification of food products with folic acid and this is currently on a voluntary basis (EVM, 2002).

Folic acid is also used as a dietary supplement and women of child-bearing age trying to conceive are advised to take 400 µg/day prior to conception and for the first 12 weeks of pregnancy (Scientific Committee on Food (SCF), 2000, NHS, 2022). Folic acid can also be used for the treatment of folate deficiency anaemia or if a patient has been prescribed methotrexate (an immunosuppressant used in the treatment of certain inflammatory conditions such as psoriasis, Crohn’s disease and rheumatoid arthritis, and is also used in some types of cancers).

Other countries have already started using folic acid as a fortificant in food. In 1998, the U.S Food and Drug Administration (FDA) required 140 µg folic acid / 100g to be added to enriched breads, cereals, flours, cornmeals, pastas, rice and other grain products to reduce the risk of neural tube defects. The fortification programme increased mean folic acid intake in the US in 2002 by about 190 µg/day. In 2016, the FDA approved voluntary addition of up to 154 µg folic acid/100g to masa (corn) flour (National Institute of Health (NIH), 2022). Canada have also required folic acid to be added to many grains including white flour, cornmeal and enriched pasta at 150 µg folic acid / 100g since 1998. There are now around 80 other countries that have established folic acid fortification including Costa Rica (180 µg/100g), Chile (220 µg/100 g flour) and South Africa (150 µg/100 g) resulting in a decrease of 19-55% in NTD cases (CDC, 2010; Wald, 2022).

Prevalence and severity of folic acid allergy

The worldwide literature on folic acid allergy is limited and true prevalence is unknown in the UK. There are no adverse reactions reported in the literature associated with consumption of foods fortified with folic acid. The following studies from around the world show examples of adverse reactions to folic acid supplements.

The earliest case report was from 1949 which reported a patient who developed maculopapular dermatitis during a course of oral folic acid treatment at 15 mg/day for 2 weeks. Subsequently, the patient suffered a severe anaphylactoid reaction following an intravenous administration of 50 mg of folic acid (Mitchell et al. 1949).

Chanarin et al. (1957) reported a case of a male volunteer who after taking 20 mg folic acid orally developed symptoms of general malaise, aching pain in the lower thoracic region, itching and general pruritus and breathing difficulties. The patient had previously been given 3 mg of oral folic acid with no adverse effects.

A report published in 1966 described the case of a 9 month old infant who displayed adverse reactions (including urticaria) on two separate occasions after treatment with 5 mg folic acid tablets (Mathur, 1966). This was followed by a positive intradermal test for folic acid sensitivity. Woodliff and Davis (1966) also described an allergic reaction to two patients after intravenous administration of folic acid.

A 36 year old male experienced pruritus on beginning 1 mg/day oral folic acid supplementation with the symptoms disappearing once treatment stopped but reoccurred when treatment was restarted three months later (Sesin and Kirschenbaum, 1979).

Sparling and Abela (1985) reported a case of a 62 year old male who suffered a severe hypersensitivity reaction (bronchospasm, generalised itchy rash) after taking one 5 mg folic acid tablet and suffered a similar reaction to 5 mg folic acid given in a sugar base. This was confirmed by a positive reaction to intradermal test.

In 2000, Dykewicz et al. reported on a 32 year old woman who developed urticaria, facial angioedema, nausea and repeated vomiting 20 minutes after ingesting a multivitamin tablet. After receiving treatment at the hospital and recovering it was noted that she had had a similar reaction to a different brand of multivitamin years earlier, but not to a liquid high-potency vitamin mixture. The constituents present in the multivitamin but absent from the liquid formulation were folic acid and yellow dye No. 6. A skin prick test was positive for folic acid but negative to yellow dye No. 6.

Another case that was reported in 2007 was of a woman who had adverse reactions including anaphylaxis after taking synthetic folic acid. The first was after taking a 5 mg folic acid tablet where she suffered from an itchy throat, nausea, generalised rash, diarrhoea and light headedness which was treated by antihistamines. The second episode occurred after she consumed 800 mL of lime flavoured water that was fortified with 20 µg/100 mL folic acid. Again, she suffered from an itchy throat, nausea and generalised pruritus and was treated with adrenaline and antihistamines. The final episode occurred after she consumed 150 mL of a beverage containing feijoa (a fruit of the Myrtaceae family) and supplements including 53.5 µg/100 mL folic acid. She was administered adrenaline en route to the hospital after suffering generalised rash, vomiting and light-headedness. Intradermal testing with folic acid was positive (Smith et al. 2007).

Schrijvers et al. 2015 reported a case of a 53 year old woman who presented with anaphylactic shock 10 minutes after consuming a 5 mg folic acid tablet, along with prednisone, vitamin B1 and B6 complexes, magnesium oxide and simethicone. She received treatment of adrenaline, antihistamines, corticosteroids and volume expanders. She reported tolerating the same dose the previous day but had milder symptoms of pruritus, flush, diarrhoea after consuming beverages and food fortified with vitamins which included folic acid. The skin prick test was positive for folic acid. The patient was advised to avoid foods and beverages fortified with folic acid and given an allergy card and rescue medication.

In 2018, Nucera et al. reported 3 new case studies on hypersensitivity to folic acid . The first 2 cases (one male, one female) were both experiencing severe anaemia and were treated with 5 mg of folic acid. The female suffered with generalised urticaria and was treated with oral antihistamines and was noted that she had previous allergies (grass pollen and wall pellitory). The male lost consciousness within 15 minutes of administration of the folic acid and was treated with intravenous steroids and antihistamines; he had no previous allergies reported. Both patients had positive skin prick tests and both patients were diagnosed with an allergy to folic acid.

The third case was a female patient but there is no information on what she was being treated for with the folic acid therapy. However, after 15 days of folic acid therapy (concentration not specified) she presented some cutaneous reactions which resolved after 7 days from therapy interruption. There was no history of previous allergic reactions and it was suspected to be a fixed drug eruption based on the clinical manifestation and a positive food oral challenge (Nucera et al. 2018).

Two more cases were reported in 2020. The first of these cases was a 34 year old woman who suffered an anaphylactic reaction 5 minutes after consuming a 400 µg folic acid tablet. The second case occurred in a 30 year old woman who had an anaphylactic reaction with urticaria, dyspnoea, tachycardia, hypotension and lipothymia an hour after taking a 5 mg tablet of folic acid. She was treated at the hospital with adrenaline therapy. One month later she ingested a Kellogg's brand cereal which had been fortified with folic acid and 2 hours later had an extensive erythematous rash. The skin prick test gave a positive response with folic acid (Gaeta et al. 2020).
FSA contacted two leading UK allergy specialists including Dr Michael Perkin (Consultant in Paediatric Allergy & Reader in Clinical Epidemiology), to seek expert opinion on the prevalence and severity of allergy to folic acid. They reported that they had not seen any clinical evidence of food allergy or even sensitisation to folic acid in the UK during their careers spanning over 20 years.

The Anaphylaxis Campaign is the only UK wide charity operating solely for people at risk from severe allergic reactions and anaphylaxis. They have a database of people who have contacted them for advice which includes information on the foods they are allergic to. No one has reported adverse reactions to folic acid.
The Canada Vigilence database and the FDA website were searched for evidence of hypersensitivity reactions linked to fortification programmes used in Canada and USA, but no relevant information was found.

Exposure Assessment

For deterministic allergen risk assessments, 75th percentile (P75) acute amount of food consumed during a single eating occasion is considered the optimal point estimate to be used as it meets a safety objective and is adequately conservative for a public health context (Blom et al. 2019). In addition, for this risk assessment, 97.5th percentile (P97.5) acute consumption amounts were also used to represent a worst-case scenario.
The estimated acute consumption (P75 and P97.5) amounts for non-wholemeal wheat flour as an ingredient in different food products such as bread, cakes, pies and pizza (Table 1) was determined using data from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) and the National Diet and Nutrition Survey (NDNS) (Bates et al. 2014, 2016, 2020; Roberts et al. 2018).

The amount of folic acid consumed if non-wholemeal wheat flour is fortified with folic acid at 250 µg/100g of flour was then estimated and shown in Table 1.

Table 1. Estimated acute 75th percentile and 97.5th percentile consumption of non-wholemeal wheat flour in g/person (with recipes which includes a range of food including breads, cake, pies and pizza that contain flour) and estimated acute consumption of folic acid from non-wholemeal wheat flour fortified at 250 µg/100g flour.

Age group	Number of consumers in data set	75th percentile* consumption of non-wholemeal wheat flour (g/person)	Acute folic acid consumption using 75th percentile (µg/person)	97.5th percentile* consumption of non-wholemeal wheat flour (g/person)	Acute folic acid consumption using 97.5th percentile (µg/person)
4 - 18 months	2462	39	98	80	200
Toddlers (1-3 years)	1151	76	190	110	275
4 - 10 years	2531	110	275	180	450
11 - 18 years	2653	150	375	250	625
19 - 64 years	5028	140	350	250	625
65 + years	1531	100	250	180	450

Allergen thresholds

Allergen risk assessments usually involve comparing the amount of allergen consumed during a single eating occasion with population reference doses, for example to determine whether precautionary allergen (or “may contain”) labelling would be appropriate.

Population reference doses are established levels of allergen exposure that would protect the large majority of the allergic population from experiencing an allergic reaction to a food. They are based on data generated from controlled exposure of allergic individuals to low levels of allergen (e.g. where allergenic foods are fed to patients in a controlled hospital setting to test how much allergen they react to). The data are then used to determine a level of exposure at which the majority of the allergic population (e.g. 99% or 95%)

would not be expected to react with objective symptoms (although at these levels of exposure, significant subjective symptoms such as gastrointestinal symptoms may result). The aim of reference doses is to protect allergic consumers at the population level; they do not protect every individual on every occasion against every reaction.

A key limitation of this risk assessment is that reference doses for folic acid have not been established, and so the usual approach for assessing risk could not be followed. Instead, other information from the published literature and other risk assessment bodies was considered.

Published data on amount of folic acid eliciting allergic reactions

The hazard characterisation section of this risk assessment includes information on the amount of folic acid reported to have elicited hypersensitivity reactions in individual cases in the published literature. The majority of these cases were reported to have consumed supplements containing ≥ 1 mg folic acid. Only two cases were reported to have experienced reactions at levels lower than this, (i.e. one case on two separate occasions at 160 µg and 80 µg and the other case at 400 µg). The 75th percentile and 97.5th percentile amount of folic acid estimated to be consumed on a single occasion if non-wholemeal wheat flour is fortified at 250 µg/100g flour, ranged from 97.5 µg - 375 µg and from 200 µg - 625 µg respectively depending on the age and sex of the individual.

Tolerable Upper Limits

Tolerable Upper Limits (TULs) or equivalent for folic acid have been established by a number of risk assessment bodies, including the US Institute of Medicine Food and Nutrition Board (IOM, 1998), the EU Scientific Committee on Food (SCF, 2000) and the UK Expert group on Vitamins and Minerals (EVM, 2003). All of these bodies set a maximum recommended intake of 1 mg/day folic acid based on observations of neurological effects in numerous case series and small studies of folic acid supplementation in patients with pernicious anaemia. Hypersensitivity reactions to folic acid were considered in all of these reports but did not influence the TULs.
In 2018/2019, COT reconsidered the EVM Guidance Level. In the discussion paper on the basis for the Upper Level for Folic Acid (TOX/2018/40), COT considered available information on hypersensitivity from EVM, SCF and IOM, although this was not the main reasoning for Members' views on the Guidance Level. Instead, when COT reaffirmed the use of 1 mg/day for

supplemental folic acid this was on the basis of possible masking of pernicious anaemia in vitamin B12-deficient subjects (COT 2019).

According to the EVM report of Safe Upper Levels for Vitamins and Minerals, a small number of case reports have described hypersensitivity reactions to oral folic acid therapy (generally ≥ 1 mg/day). One short-term, uncontrolled supplementation trial reported adverse symptoms (mental changes (including depression, mild confusion, impaired judgment and difficulty concentrating), sleep disturbances and gastrointestinal symptoms) in healthy volunteers given very high doses of folic acid (15 mg/day) for 1 month to elucidate the effects of folic acid at pharmacological doses on serum vitamin B12 levels, but other studies have not observed similar effects (EVM 2003; Hunter et al. 1970).

The SCF Opinion on the Upper Tolerable Intake Level of Folate indicated that a limited number of case reports have been published on hypersensitivity reactions to oral and parenteral folic acid, but it cannot be excluded that these reactions were due to other components in the formulations. So, hypersensitivity may occur, but is most likely very rare (see Campbell, 1996) (SCF, 2000).

IOM noted that individual cases of hypersensitivity reactions to oral and parenteral folate administration were reported (Gotz and Lauper, 1980; Mathur, 1966; Mitchell et al., 1949; Sesin and Kirschenbaum, 1979; Sparling and Abela, 1985). Such hypersensitivity is rare, but reactions have occurred at supplemental folate doses as low as 1 mg/day (Sesin and Kirschenbaum, 1979) (IOM, 1998).

A report commissioned by Food Standards Scotland (FSS) estimated the potential impact of fortification of flour with folic acid in the UK using stochastic modelling. The data in Table 2 shows the modelling information for folic acid at 250 µg/100 g flour and compares this intake to the tolerable upper limits of 1mg/day for adults set by the EVM and those set for children by the SCF for 1 to 3 year olds (200 µg/day); 4 to 6 years old (300 µg/day); 7 to 10 year olds (400 µg/day); 11 to 14 year olds (600 µg/day); and 15 to 17 year olds (800 µg/day). It should be noted that the tolerable upper limit is based on medical conditions other than hypersensitivity.

Table 2. Effects of fortification of all non-wholemeal wheat flour assuming no capping produced by FSS-funded modelling of fortification with folic acid of 250 µg/100g flour.

Age/Gender Group	Mean folic acid (µg/d)	Median folic acid (µg/d)	Tolerable upper limit set by EVM and SCF (µg/d)	% above UL (folic acid)
1.5 to 3 years males and females	104	98	200	4.37
4 to 6 years males and females	142	127	300	1.38
7 to 10 years males and females	166	156	400	1.09
11 to 13 years males and females	178	171	600	0.00
14 to 49 years females	164	127	Between 600 and 1000	0.47
14 to 18 years females	150	136	Between 600 and 1000	0.00
14 to 18 years males	198	181	Between 600 and 1000	0.06
19 to 34 years females	178	129	1000	0.53
19 to 34 years males	204	184	1000	0.00
35 to 49 years females	154	122	1000	0.54
35 to 49 years males	190	163	1000	0.48
50 years and over males and females	182	129	1000	0.69
50 to 64 years males and females	173	126	1000	0.71
65 to 74 years males and females	183	133	1000	0.47
75 years and over males and females	206	128	1000	0.97
Overall population	176	139	NA	0.63

Risk Characterisation

The UK prevalence of folic acid allergy is not known. Cases have been reported in the published literature although the numbers are small. The UK allergy specialists that were contacted to inform this risk assessment had not seen any clinical evidence of food allergy or sensitisation to folic acid in the UK during their careers spanning over 20 years and the Anaphylaxis Campaign has not received any reports of adverse reactions to folic acid. Although hypersensitivity to folic acid may occur it appears to be very rare and linked to higher dose supplements rather than the fortification of food.

Allergen reference doses for folic acid have not been established (e.g. by challenge testing patients in a controlled hospital setting to test how much folic acid they react to), likely because this is not significant at a population level. Consequently, the usual approach for assessing allergen risk could not be followed. However, the 75th percentile and 97.5th percentile/maximum amount of folic acid estimated to be consumed by UK consumers if non-wholemeal wheat flour is fortified with folic acid at 250 µg per 100 g was found to be lower than the amount of folic acid reported to have caused the majority of the allergic reactions in the published literature, with the exception of two cases.

This suggests that while it may be possible for the proposed amount of folic acid in fortified non-wholemeal wheat flour to potentially trigger reactions, this is only likely to occur very rarely in highly sensitive individuals and is not significant on a population basis.

In terms of severity of illness, the symptoms of reported allergic reactions to folic acid have ranged from mild to severe (including anaphylaxis) although no deaths have been reported in the published literature. It should be noted that these reactions were linked to the consumption of supplements rather than fortified foods and the majority were triggered by larger amounts of folic acid than has been estimated to be consumed by UK consumers on a single occasion if non-wholemeal wheat flour is fortified with folic acid at 250 µg per 100 g.

In this risk assessment, we used the qualitative scales for the frequency of occurrence and severity of foodborne risks and level of associated uncertainty that is described in the multidimensional risk assessment framework outlined by the
Advisory Committee on the Microbiological Safety of Food (ACMSF, 2020), as described in Annex I. The key sources of uncertainty are listed in the next section.

Overall if non-wholemeal flour is fortified with folic acid at 250 µg per 100 g without its presence being labelled on the packaging of the final food or, in the case of food sold loose, not conveyed by other means during a 3 month derogation period then we estimate the risk of allergic reactions to folic acid in UK consumers to be as follows:

- The **frequency of allergic reactions to folic acid in food** to be **very low** (i.e. very rare but cannot be excluded).

- The **severity of illness in relation to allergic reactions to folic acid in food** to be **medium** (i.e. moderate illness: incapacitating but not usually life-threatening, sequelae rare, moderate duration).
- the **level of uncertainty** to be **medium** (i.e. there are some but no complete data available; evidence is provided in small number of references;).

Key sources of uncertainty

The key sources of uncertainty in this risk assessment are:

- The amount of folic acid that needs to be consumed in food on a single occasion to elicit an allergic reaction, given that allergen thresholds have not been established (although there are some data in the published literature on the amount that led to reactions in individual case). If the amount of folic acid that needs to be consumed in food by sensitive individuals in order to elicit an allergic reaction is lower than anticipated in this risk assessment, then the risk will be higher.

- The amount of folic acid that will be consumed on a single occasion if non-wholemeal wheat flour is fortified with folic acid at 250 µg per 100 g. This risk assessment is based on the 75th percentile and 97.5th percentile data obtained from DNSIYC and NDNS for non-wholemeal wheat flour (with recipes). It is possible that a higher amount of fortified flour could present in the final products and consumed by an individual leading to a higher exposure dose. If the amount of folic acid consumed by sensitive individuals is higher than estimated in this risk assessment, then the risk will be greater.

- Folic acid allergy in the UK population is likely to be very rare but the true prevalence is not known. There is uncertainty regarding whether the limited confirmed clinical data on allergic reactions to folic acid could be due to under-reporting. If the UK prevalence is higher than estimated in this risk assessment, then the risk will be higher.

9. References

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Annex 1

Interpretation of probability categories used in this risk assessment

(Tables from ACMSF (ACM/1065) adapted from EFSA 2016 modified from OIE 2004).

Frequency category	Interpretation
Negligible	So rare that it does not merit to be considered
Very Low	Very rare but cannot be excluded
Low	Rare but does occur
Medium	Occurs regularly
High	Occurs very often
Very High	Events occur almost certainly

Severity category	Interpretation
Negligible	No effects, or so mild they do not merit to be considered
Low	Mild illness: not usually life-threatening, usually no sequelae, normally of short duration, symptoms are self-limiting (e.g. transient diarrhoea)
Medium	Moderate illness: incapacitating but not usually life-threatening, sequelae rare, moderate duration (e.g. diarrhoea requiring hospitalisation)
High	Severe illness: causing life-threatening or substantial sequelae or illness of long duration (e.g. chronic hepatitis)

Uncertainty category	Interpretation
Low	There are solid and complete data available; strong evidence is provided in multiple references; authors report similar conclusions
Medium	There are some but no complete data available; evidence is provided in small number of references; authors report conclusions that vary from one another
High	There are scarce or no data; evidence is not provided in references but rather in unpublished reports or based on observations, or personal communication; authors report conclusions that vary considerably between them