The Director General

Maisons-Alfort, 15 October 2024

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

on Updating the State of the Evidence on the Prevention of Neural Tube Defects by vitamin B9

On 15 January 2023, ANSES received a formal request from the Directorate General for Health to undertake the following expert appraisal: updating the state of the evidence on the prevention of neural tube defects by vitamin B9.

1. BACKGROUND AND PURPOSE OF THE REQUEST

Neural tube defects (NTDs) have clinical expressions of varying severity, ranging from spina bifida to anencephaly. These defects are screened for during ultrasound examinations of pregnant women, and the severity of the picture can lead to therapeutic abortion.

Risk factors for NTDs include a family history of NTDs, medicinal treatments (anti-epileptics, valproic acid), diabetes, obesity and insufficient folate status in the mother during the periconceptional period, which is a major determinant.

In France, according to biological data from the ENNS and Esteban studies carried out by *Santé publique France*, the proportion of adult women of childbearing age (18-49 years, non-menopausal) with serum folate deficiency has almost doubled, rising from 7.2% in 2006 to

13.4% in 2015. This increase, observed in all age groups, has been more pronounced among women with the lowest levels of education. In 2015, this prevalence stood at 21.9% among women reporting a level of education below the *baccalauréat*, while it was 5.8% among those reporting at least three years of higher education (2019 Epidemiological and Surveillance team).

In addition, the results of the 2021 National Perinatal Survey showed that the use of folic acid to prevent NTDs is initiated too late, since less than a third of women who gave birth (28.3%) had started taking a folic acid supplement before their pregnancy (Cinelli *et al.* 2022). Furthermore, no information is available on the vitamin B9 status of the supplemented women.

To reduce the prevalence of NTDs, for several years now over 80 countries have implemented folic acid fortification of staple foods (mostly flour, sometimes only bread or cereal products) (Quinn *et al.* 2024).

In 2017, the French High Council for Public Health (HCSP) pointed out that the proportion of women taking folic acid during the periconceptional period remained low in France; it made recommendations to “provide massive information to women of childbearing age and healthcare professionals on the crucial importance of supplementation, which should be started before conception and continued for three months afterwards”[1], and to “reconsider the systematic fortification of widely consumed foods (...)” (HCSP, 2017, p.88). This issue was again highlighted in a more recent HCSP opinion on the revision of the PNNS dietary guidelines for pregnant or breastfeeding women (HCSP 2022).

In this context, the Directorate General for Health asked ANSES to update the current state of the evidence on the effectiveness of folates in the prevention of NTDs, carry out a situational analysis of the folate status of women wishing to become pregnant, and issue recommendations for public health actions to improve the prevention of NTDs.

ANSES was asked to undertake:

1. a literature review on the effectiveness of folic acid supplementation in reducing the risk of NTDs;
2. an assessment of the risk of an increased incidence of NTDs associated with the increased risk of folate deficiency observed in France between 2006 and 2015 (Esteban), based in particular on the data on changes in the incidence of NTDs in France collected by *Santé publique France* (especially in 2013 and 2021), with regard to the recommendations on preconceptional supplementation;
3. an international benchmarking study identifying and assessing the strategies and measures implemented in other countries to reduce NTDs;
4. an analysis of the relevance of systematically fortifying food.

Lastly, ANSES was asked to recommend public health actions to be undertaken in France to improve the prevention of NTDs.

[1] 0.4 mg/day for all women and 5 mg/day for women with a family history of NTDs.

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French standard NF X 50-110 "Quality in Expert Appraisals – General Requirements of Competence for Expert Appraisals (January 2024)".

Question 4 of the formal request on analysing the relevance of systematically fortifying food included studying the feasibility of a cost-benefit analysis of this measure. ANSES therefore appointed two expert rapporteurs, reporting to the Expert Committee (CES) on Socio-economic analysis. Furthermore, five expert rapporteurs, reporting to the CES on Human nutrition, were also appointed for the examination of this formal request.

The expert appraisal work was regularly submitted to the CES on Human nutrition (the lead CES) and the CES on Socio-economic analysis. This work was therefore conducted by a group of experts with complementary skills. The work was presented and adopted by the CES on Human nutrition at its meeting on 5 September 2024.

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals.

The experts' declarations of interests are made public via the following website: https://dpi.sante.gouv.fr/.

3. ANALYSIS AND CONCLUSIONS OF THE CES

3.1. Assessment of the prevalence of neural tube defects in France between 2012 and 2021

The prevalence data from 2012-2021 on total births of foetuses/newborns with NTDs, from five French registries (French Caribbean, Auvergne, Brittany, Reunion Island and Paris), show average prevalence rates of 13.5 per 10,000 total births (including therapeutic abortions and *in utero* deaths) and of 1.4 per 10,000 live births. This gap is explained by the resort to therapeutic abortions following prenatal screening for these defects. It should be noted that only 10.5% of these defects were associated with an identified genetic problem.

Changes in the prevalence of NTDs over the 2012-2021 period show geographical variations, for example with higher prevalence rates in the Brittany and Reunion Island registries. Several possible risk factors for Reunion Island may explain this increase in prevalence, in particular inadequate folate intakes and insufficient folic acid supplementation, partly in areas where access to healthcare and medical information is more difficult, and a higher frequency of maternal diabetes than in metropolitan France.

In conclusion, the data from these registries are not currently sufficient to explain changes in the prevalence of NTDs over time or the geographical differences observed.

3.2. Systematic review on the effectiveness of folic acid supplementation and fortification in reducing the risk of neural tube defects

3.2.1. Method used to carry out the systematic review and assess the weight of evidence

The method used to conduct the systematic review and assess the weight of evidence is detailed in the report (see Sections 3.1 and 3.2). Two systematic reviews were carried out: one to investigate the effectiveness of folic acid supplementation in reducing the risk of NTDs, and the other to study the effectiveness of systematic folic acid fortification in reducing the risk of NTDs. For each of these reviews, the questions were formalised using the Population, Exposure, Comparator and Outcome (PECO[2]) approach, and the inclusion and exclusion criteria were determined in advance by the CES on Human nutrition (**Erreur ! Source du renvoi introuvable.**, **Erreur ! Source du renvoi introuvable.**, **Erreur ! Source du renvoi introuvable.**).

3.2.2. Systematic review on the effectiveness of folic acid supplementation in reducing the risk of neural tube defects

The systematic review included 37 scientific articles published between 1989 and 2022 that investigated the relationship between folic acid supplementation and the risk of NTDs.

Three articles described randomised controlled trials (Czeizel 1993; Czeizel and Dudás 1992; MRC Vitamin Study Research Group 1991).

Eleven articles presented evidence from prospective cohort studies (Czeizel, Dobó and Vargha 2004; B. Kallen 2007; B.A. Kallen and Olausson 2002; Kurdi *et al.* 2019; Milunsky *et al.* 1989; Moore *et al.* 2003; Zhou *et al.* 2022; Gildestad *et al.* 2020; J. Liu *et al.* 2018; Nishigori *et al.* 2019; Stevenson *et al.* 2000).

Three articles involved non-controlled interventional studies (G. Chen *et al.* 2008; Martinez de Villarreal *et al.* 2002; Berry *et al.* 1999).

Nineteen articles relate to case-control studies (Bower *et al.* 2004; Bower and Stanley 1992; Carmichael, Yang and Shaw 2010; Chandler *et al.* 2012; Czeizel, Tóth and Rockenbauer 1996; De Marco *et al.* 2011; Gong *et al.* 2010; Gong *et al.* 2016; Kancherla *et al.* 2017; Kondo *et al.* 2015; Mills *et al.* 1989; Nili and Jahangiri 2006; Shaw *et al.* 1995; Sotres-Alvarez *et al.* 2013; Suarez *et al.* 2000; Thompson *et al.* 2003; M. Wang, Wang, Gao, Gong, Sun*, et al.* 2013; M. Wang, Wang, Gao, Gong, Zhang*, et al.* 2013; Al Rakaf *et al.* 2015).

One article reported an ecological study (Klusmann *et al.* 2005).

- Characteristics of the study populations

The studies were conducted in Australia (two articles), Bangladesh (one article), China (eight articles), Germany (one article), Hungary (four articles), Iran (one article), Italy (one article), Japan (two articles), Mexico (one article), the Netherlands (one article), Norway (one article), Saudi Arabia (two articles), Sweden (two articles) and the United States (10 articles). Lastly, a multi-centre study was undertaken in the United Kingdom, Hungary, Israel, Australia, Canada, the USSR and France.

[2] In a systematic search, a PECO statement is an inventory of the parameters that will be studied concerning the population, exposure, the comparator, and the health outcome.

The number of participants varied from 106 (Kancherla *et al.* 2017) to 888,294 (Gildestad *et al.* 2020). The average age of the mothers ranged from 22 (Kancherla *et al.* 2017) to 32 (Nishigori *et al.* 2019) years.

The participants' ethnic origins were only reported in the American studies and the Italian study. In these studies, the participants were mainly "non-Hispanic white" women (Chandler *et al.* 2012; Sotres-Alvarez *et al.* 2013), "white" women (Mills *et al.* 1989; Thompson *et al.* 2003), "Hispanic" women (Shaw *et al.* 1995) and women of Mexican origin (Suarez *et al.* 2000). The Italian study exclusively included "white" women (De Marco *et al.* 2011).

- Exposure and comparator

In all the studies, exposure was folic acid (alone or in combination with minerals or other vitamins) intake. It was compared with the absence of folic acid intake. Exposure details are provided in the stratified assessment below.

- NTD assessment

NTDs were defined according to the ninth or tenth edition of the International Classification of Diseases (ICD) in eight articles (Gildestad *et al.* 2020; Kurdi *et al.* 2019; Martinez de Villarreal *et al.* 2002; Stevenson *et al.* 2000; Thompson *et al.* 2003; M. Wang, Wang, Gao, Gong, Sun, *et al.* 2013; M. Wang, Wang, Gao, Gong, Zhang, *et al.* 2013; Moore *et al.* 2003). In one article, cases of NTDs were reported by a patient association (Kondo *et al.* 2015). In the other articles, the authors reported having identified NTDs through medical diagnoses (Al Rakaf *et al.* 2015; Berry *et al.* 1999; Bower *et al.* 2004; Carmichael, Yang and Shaw 2010; Chandler *et al.* 2012; G. Chen *et al.* 2008; Czeizel 1993; Czeizel, Dobó and Vargha 2004; Czeizel and Dudás 1992; Czeizel, Tóth and Rockenbauer 1996; De Marco *et al.* 2011; Gong *et al.* 2010; Gong *et al.* 2016; B. Kallen 2007; B.A. Kallen and Olausson 2002; Kancherla *et al.* 2017; Klusmann *et al.* 2005; J. Liu *et al.* 2018; Mills *et al.* 1989; Milunsky *et al.* 1989; MRC Vitamin Study Research Group 1991; Nili and Jahangiri 2006; Nishigori *et al.* 2019; Shaw *et al.* 1995; Sotres-Alvarez *et al.* 2013; Suarez *et al.* 2000; Thompson *et al.* 2003; Zhou *et al.* 2022; Bower and Stanley 1992).

In 18 articles, the definition of NTDs encompassed anencephaly, spina bifida and encephalocele (Bower *et al.* 2004; Bower and Stanley 1992; J. Liu *et al.* 2018; Martinez de Villarreal *et al.* 2002; Milunsky *et al.* 1989; MRC Vitamin Study Research Group 1991; Nishigori *et al.* 2019; Stevenson *et al.* 2000; Suarez *et al.* 2000; Thompson *et al.* 2003; M. Wang, Wang, Gao, Gong, Sun, *et al.* 2013; M. Wang, Wang, Gao, Gong, Zhang, *et al.* 2013; Berry *et al.* 1999; Czeizel and Dudás 1992; Klusmann *et al.* 2005; Mills *et al.* 1989; Shaw *et al.* 1995; Zhou *et al.* 2022). In four articles, the definition of NTDs only covered anencephaly and spina bifida (Al Rakaf *et al.* 2015; Carmichael, Yang and Shaw 2010; Chandler *et al.* 2012; Czeizel, Dobó and Vargha 2004). In three articles, only spina bifida was considered (De Marco *et al.* 2011; Kancherla *et al.* 2017; Kondo *et al.* 2015). NTDs were not defined in 12 articles (G. Chen *et al.* 2008; Czeizel 1993; Czeizel, Tóth and Rockenbauer 1996; Gildestad *et al.* 2020; Gong *et al.* 2010; Gong *et al.* 2016; B. Kallen 2007; B.A. Kallen and Olausson 2002; Kurdi *et al.* 2019; Moore *et al.* 2003; Nili and Jahangiri 2006; Sotres-Alvarez *et al.* 2013).

- Analysis of results
  - Total NTDs

In 13 articles, for which the dose of folic acid taken during the periconceptional period was known, this intake was associated with a lower risk or prevalence of NTDs than with no folic acid intake (Berry *et al.* 1999; Czeizel, Tóth and Rockenbauer 1996; Gong *et al.* 2010; Martinez de Villarreal *et al.* 2002; Klusmann *et al.* 2005; Kondo *et al.* 2015; J. Liu *et al.* 2018; Nili and Jahangiri 2006; Shaw *et al.* 1995; M. Wang, Wang, Gao, Gong, Sun*, et al.* 2013; M. Wang, Wang, Gao, Gong, Zhang*, et al.* 2013; Zhou *et al.* 2022; Gong *et al.* 2016).

In the study by Shaw *et al.*, stratified by ethnic origin, the association between folic acid intake within three months following conception and a reduced risk of NTDs was significant only for "non-Hispanic white" women (Shaw *et al.* 1995).

In nine articles, the use of food supplements containing folic acid in the periconceptional period was associated with a lower risk or prevalence of NTDs than with no folic acid intake (Milunsky *et al.* 1989; Sotres-Alvarez *et al.* 2013; Moore *et al.* 2003; Thompson *et al.* 2003; MRC Vitamin Study Research Group 1991; G. Chen *et al.* 2008; Czeizel, Dobó and Vargha 2004; Chandler *et al.* 2012; Stevenson *et al.* 2000). However, one article did not report the dose of folic acid used in the food supplements taken (Sotres-Alvarez *et al.* 2013).

In 10 articles, no association was found between intake of folic acid, or a food supplement containing folic acid, in the periconceptional period and the risk of NTDs compared with no folic acid intake (Mills *et al.* 1989; Nishigori *et al.* 2019; Bower *et al.* 2004; Bower and Stanley 1992; Carmichael, Yang and Shaw 2010; Gildestad *et al.* 2020; B. Kallen 2007; B.A. Kallen and Olausson 2002; Kurdi *et al.* 2019; Suarez *et al.* 2000). Two of these 10 articles did not report the dose of folic acid contained in the food supplements taken (Bower and Stanley 1992; Carmichael, Yang and Shaw 2010).

Three articles did not present a statistical analysis or trends in the prevalence of NTDs (Al Rakaf *et al.* 2015; Czeizel 1993; Czeizel and Dudás 1992).

- Anencephaly

The four studies investigating intake of a known dose of folic acid in the periconceptional period showed that folic acid was associated with a lower risk or prevalence of anencephaly than with no folic acid intake (Martinez de Villarreal *et al.* 2002; J. Liu *et al.* 2018; M. Wang, Wang, Gao, Gong, Zhang*, et al.* 2013; Gong *et al.* 2016).

In two articles, no association was found between intake of a known dose of folic acid, or of a food supplement containing folic acid, in the periconceptional period and the risk of anencephaly compared with no folic acid intake (Thompson *et al.* 2003; Shaw *et al.* 1995).

- Spina bifida

In six articles, intake of folic acid in the periconceptional period was associated with a lower risk or prevalence of spina bifida than with no folic acid intake (De Marco *et al.* 2011; Martinez de Villarreal *et al.* 2002; Kondo *et al.* 2015; Gong *et al.* 2016; Shaw *et al.* 1995; Kancherla *et al.* 2017). However, one article did not report the dose of folic acid used in the food supplements taken (Kancherla *et al.* 2017).

In one article, the use of food supplements containing a known dose of folic acid in the periconceptional period was associated with a lower risk of spina bifida than with no folic acid intake (Thompson *et al.* 2003).

In three articles, no association was found between intake of a known dose of folic acid, or of a food supplement containing folic acid, in the periconceptional period and the risk of spina bifida compared with no folic acid intake (J. Liu *et al.* 2018; M. Wang, Wang, Gao, Gong, Sun*, et al.* 2013; M. Wang, Wang, Gao, Gong, Zhang*, et al.* 2013).

- Encephalocele

In one article, intake of a known dose of folic acid in the periconceptional period was associated with a lower risk of encephalocele than with no folic acid intake (Gong *et al.* 2016).

In another article, no association was found between intake of a known dose of folic acid, or of a food supplement containing a known dose of folic acid, in the periconceptional period and the risk of encephalocele compared with no folic acid intake (J. Liu *et al.* 2018).

- Assessment of the weight of evidence

The assessment of the weight of evidence highlighted the following points:

- **Bias control**: In most of the articles, the authors did not adjust the analyses for all the key confounders. Out of 37 articles, 14 gave results without any adjustment (Al Rakaf *et al.* 2015; Czeizel, Tóth and Rockenbauer 1996; Klusmann *et al.* 2005; Martinez de Villarreal *et al.* 2002; Nili and Jahangiri 2006; Stevenson *et al.* 2000; M. Wang, Wang, Gao, Gong, Zhang*, et al.* 2013; Zhou *et al.* 2022; Czeizel 1993; Czeizel and Dudás 1992; Kurdi *et al.* 2019; J. Liu *et al.* 2018; Milunsky *et al.* 1989; MRC Vitamin Study Research Group 1991), nine reported adjusted results, but without any adjustment for key confounders (Berry *et al.* 1999; Bower *et al.* 2004; Czeizel, Dobó and Vargha 2004; B. Kallen 2007; B.A. Kallen and Olausson 2002; Kancherla *et al.* 2017; Kondo *et al.* 2015; Nishigori *et al.* 2019; Shaw *et al.* 1995), and only two gave results adjusted for all the key confounders (Carmichael, Yang and Shaw 2010; Gong *et al.* 2016). The remaining 12 articles only adjusted the results for some of the key confounders: two did not report any adjustment for indicators of socio-economic status (De Marco *et al.* 2011; Thompson *et al.* 2003), five did not report any adjustment for ethnic indicators (Bower and Stanley 1992; Gong *et al.* 2010; Moore *et al.* 2003; Suarez *et al.* 2000; M. Wang, Wang, Gao, Gong, Zhang*, et al.* 2013) and seven did not report any adjustment for alcohol consumption (Bower and Stanley 1992; Gong *et al.* 2010; Mills *et al.* 1989; Sotres-Alvarez *et al.* 2013; Suarez *et al.* 2000; Thompson *et al.* 2003; M. Wang, Wang, Gao, Gong, Sun*, et al.* 2013). In addition, nine articles did not specify the doses taken or the national guidelines, which was a bias in the classification of exposure (B. Kallen 2007; B.A. Kallen and Olausson 2002; Kancherla *et al.* 2017; Kurdi *et al.* 2019; Milunsky *et al.* 1989; Sotres-Alvarez *et al.* 2013; Stevenson *et al.* 2000; Suarez *et al.* 2000; Thompson *et al.* 2003). One article also did not homogeneously report data on voluntary or therapeutic abortions or the number of stillbirths for the different countries and did not describe the types of NTDs (Sotres-Alvarez *et al.* 2013).

  The grids used to assess the risk of bias when investigating the effectiveness of folic acid supplementation in reducing the risk of NTDs are presented in the report (Section 3.3).

- **Consistency of the results:** Twenty-three articles reporting results concerning a decrease in the risk of total NTDs when folic acid supplementation was introduced in the periconceptional period were concordant. However, 10 of the 36 articles investigating total NTDs did not show any association.

- **Directness:** The populations, exposure, the comparator and the health outcomes were directly related to the systematic review question in all the included articles.
- **Precision:** For the prospective observational studies, the sample sizes were often too small given the rarity of the events. Statistical power calculations were not reported in the articles. The precision of the estimates was generally moderate, as determined based on the size of the confidence interval.
- **Generalisability:** The articles included focused on populations with varied socio-economic parameters, which meant they could not always be generalised to the French population.

■ Conclusion

The CES on Human nutrition concludes that folic acid supplementation during the periconceptional period is associated with a reduced risk of total NTDs for children born from these pregnancies. The weight of evidence is moderate[3].

3.2.3. Systematic review on the effectiveness of folic acid fortification in reducing the risk of neural tube defects

The systematic review identified 37 scientific articles published between 2002 and 2023 that investigated the relationship between systematic folic acid fortification and the risk of NTDs.

One article reported an interventional study (H. Wang *et al.* 2016).

Another involved a case-control study (Mosley *et al.* 2009).

Still another described a before & after study (Abdollahi *et al.* 2011) while the 34 remaining articles presented ecological studies (Alasfoor, Elsayed and Mohammed 2010; Amarin and Obeidat 2010; Arth *et al.* 2016; Barboza-Argüello Mde *et al.* 2015; Benavides-Lara *et al.* 2023; Bidondo *et al.* 2015; Boulet *et al.* 2008; Canfield *et al.* 2005; CDC 2004; L.T. Chen and Rivera 2004; Cortés *et al.* 2012; De Wals *et al.* 2003; De Wals *et al.* 2008; De Wals *et al.* 2007; Dean, Pauly and Stevenson 2020; Forrester and Merz 2005; Godwin *et al.* 2008; Golalipour, Arabi and Vakili 2014; Hertrampf and Cortés 2004; Honein *et al.* 2001; House *et al.* 2006; S. Liu *et al.* 2004; López-Camelo, Castilla and Orioli 2010; López-Camelo *et al.* 2005; Mathews, Honein and Erickson 2002; Orioli *et al.* 2011; Pardo *et al.* 2022; Persad *et al.* 2002; Safdar *et al.* 2007; Santos *et al.* 2016; Sayed *et al.* 2008; Simmons *et al.* 2004; J. Williams *et al.* 2015; L.J. Williams *et al.* 2002).

■ Characteristics of the study populations

The studies were carried out in Argentina (one article), Brazil (two articles), Canada (seven articles), Chile (four articles), China (one article), Costa Rica (three articles), Iran (two articles), Jordan (one article), Oman (one article), Saudi Arabia (one article), South Africa (one article) and the United States (11 articles). Two other articles undertook multi-centre analyses. In the first of these articles, the countries included were Argentina, Brazil and Chile; in the second, the analyses covered 58 countries.

[3] The possible levels for the weight of evidence are “high”, “moderate”, “low” and “cannot be estimated”

The number of births varied from 565 (Mosley *et al.* 2009) to over 17 million (Santos *et al.* 2016). The age of the mothers ranged from 26 (median) (Mosley *et al.* 2009) to 32 (mean) (Abdollahi *et al.* 2011) years.

The participants' ethnic origins were only reported in some of the American studies, although the proportions were not always specified (Boulet *et al.* 2008; Canfield *et al.* 2005; Dean, Pauly and Stevenson 2020; Simmons *et al.* 2004). The only article for which the information was available reported participants who were mainly "non-Hispanic white" women (Mosley *et al.* 2009).

- Exposure and comparator

In the studies identified, exposure was systematic folic acid fortification of food. The ingredient vector was wheat flour in the majority of the studies, with doses ranging from 140 µg/100 g wheat flour (USA) to 500 µg/100 g wheat flour (Oman). Costa Rica fortifies wheat flour (150 µg/100 g from 1997, then 180 µg/100 g from 2002), milk (40 µg/250 ml), corn flour (130 µg/100 g) and rice (180 µg/100 g). Canada fortifies wheat flour (150 µg/100 g), cornmeal (150 µg/100 g) and pasta (200 to 270 µg/100 g).

For most of the studies, the comparator was the pre-fortification periods.

- NTD assessment

In 16 out of 37 articles, NTDs were defined according to the ninth or tenth edition of the International Classification of Diseases (Alasfoor, Elsayed and Mohammed 2010; Amarin and Obeidat 2010; Bidondo *et al.* 2015; Boulet *et al.* 2008; Canfield *et al.* 2005; De Wals *et al.* 2003; De Wals *et al.* 2007; Godwin *et al.* 2008; Golalipour, Arabi and Vakili 2014; S. Liu *et al.* 2004; Orioli *et al.* 2011; Santos *et al.* 2016; Simmons *et al.* 2004; H. Wang *et al.* 2016; J. Williams *et al.* 2015; L.J. Williams *et al.* 2002).

In the remaining 21 articles, the authors reported having identified the NTDs through medical diagnoses (Abdollahi *et al.* 2011; Arth *et al.* 2016; Barboza-Argüello Mde *et al.* 2015; Benavides-Lara *et al.* 2023; CDC 2004; L.T. Chen and Rivera 2004; Cortés *et al.* 2012; De Wals *et al.* 2008; Dean, Pauly and Stevenson 2020; Forrester and Merz 2005; Hertrampf and Cortés 2004; Honein *et al.* 2001; House *et al.* 2006; López-Camelo, Castilla and Orioli 2010; López-Camelo *et al.* 2005; Mathews, Honein and Erickson 2002; Mosley *et al.* 2009; Pardo *et al.* 2022; Persad *et al.* 2002; Safdar *et al.* 2007; Sayed *et al.* 2008).

In 15 articles, the definition of NTDs encompassed anencephaly, spina bifida and encephalocele (Abdollahi *et al.* 2011; Amarin and Obeidat 2010; Barboza-Argüello Mde *et al.* 2015; Benavides-Lara *et al.* 2023; Bidondo *et al.* 2015; De Wals *et al.* 2003; Golalipour, Arabi and Vakili 2014; Hertrampf and Cortés 2004; House *et al.* 2006; S. Liu *et al.* 2004; Pardo *et al.* 2022; Persad *et al.* 2002; Sayed *et al.* 2008; H. Wang *et al.* 2016; Dean, Pauly and Stevenson 2020). In three articles, the definition of NTDs encompassed anencephaly, spina bifida and cephalocele (Cortés *et al.* 2012; López-Camelo, Castilla and Orioli 2010; De Wals *et al.* 2007). In 11 articles, the definition of NTDs only covered anencephaly and spina bifida (Boulet *et al.* 2008; Canfield *et al.* 2005; CDC 2004; Forrester and Merz 2005; Godwin *et al.* 2008; Honein *et al.* 2001; López-Camelo *et al.* 2005; Mathews, Honein and Erickson 2002; Mosley *et al.* 2009; J. Williams *et al.* 2015; L.J. Williams *et al.* 2002). In three articles, only spina bifida was considered (De Wals *et al.* 2008; Orioli *et al.* 2011; Alasfoor, Elsayed and Mohammed 2010). NTDs were not defined in five articles (Arth *et al.* 2016; L.T. Chen and Rivera 2004; Safdar *et al.* 2007; Santos *et al.* 2016; Simmons *et al.* 2004).

- Analysis of results
  - Total NTDs

Countries with a very high human development index

In 10 articles reporting results from the United States, folic acid fortification of flour (140 µg/100g) was associated with a lower risk or prevalence of total NTDs than earlier periods without fortification (Boulet *et al.* 2008; Canfield *et al.* 2005; CDC 2004; Dean, Pauly and Stevenson 2020; Forrester and Merz 2005; Honein *et al.* 2001; Mathews, Honein and Erickson 2002; Mosley *et al.* 2009; J. Williams *et al.* 2015; L.J. Williams *et al.* 2002). One article did not find this association (Simmons *et al.* 2004). In the article by Boulet *et al.,* stratified by ethnic origin, the association between folic acid fortification of flour and the risk of total NTDs was significant only for “non-Hispanic white” women compared with earlier periods without fortification (Boulet *et al.* 2008).

In five articles reporting results from Canada, folic acid fortification of wheat flour (150 µg/100 g), cornmeal (150 µg/100 g) and pasta (200 to 270 µg/100 g) was associated with a lower risk or prevalence of total NTDs than earlier periods without fortification (De Wals *et al.* 2003; De Wals *et al.* 2007; House *et al.* 2006; S. Liu *et al.* 2004; Persad *et al.* 2002).

In two articles reporting results from Chile, folic acid fortification of flour (220 µg/100 g) was associated with a lower risk or prevalence of total NTDs than earlier periods without fortification (Cortés *et al.* 2012; Hertrampf and Cortés 2004). Another article from Chile, which assessed the impact of reducing the fortification of flour from 220 to 180 µg/100 g in 2009, did not observe any difference in the prevalence of total NTDs (Pardo *et al.* 2022).

In three articles reporting results from Costa Rica, folic acid fortification of wheat flour (from 150 µg/100 g from 1997 to 180 µg/100 g from 2002), corn flour (130 µg/100 g), milk (40 µg/250 ml) and rice (180 µg/100 g) was associated with a lower risk or prevalence of total NTDs than earlier periods without fortification (Barboza-Argüello Mde *et al.* 2015; Benavides-Lara *et al.* 2023; L.T. Chen and Rivera 2004).

In one article reporting results from Saudi Arabia, folic acid fortification of flour (165 µg/100 g) was associated with a lower prevalence of total NTDs than earlier periods without fortification (Safdar *et al.* 2007).

Countries with a high human development index

In an interventional study reporting results from 11 villages in China, fortification of flour with folic acid (200 µg/100 g) and other micronutrients (vitamins B1 and B2, iron and zinc) was associated with a lower risk of total NTDs than non-fortified flour (H. Wang *et al.* 2016).

In five articles reporting results from Iran, Jordan, South Africa and Brazil, folic acid fortification of flour (150 µg/100 g) was associated with a lower prevalence of total NTDs than the pre-fortification periods,(Abdollahi *et al.* 2011; Amarin and Obeidat 2010; Golalipour, Arabi and Vakili 2014; Sayed *et al.* 2008; Santos *et al.* 2016).

  - Anencephaly

Countries with a very high human development index

In seven articles reporting results from the United States, folic acid fortification of flour (140 µg/100 g) was associated with a lower risk or prevalence of anencephaly than the pre-fortification periods (Boulet *et al.* 2008; Canfield *et al.* 2005; CDC 2004; Honein *et al.* 2001; Mathews, Honein and Erickson 2002; J. Williams *et al.* 2015; L.J. Williams *et al.* 2002). In four articles, no association was found between folic acid fortification of flour (140 µg/100 g) and the risk of anencephaly, compared with a pre-fortification period (Dean, Pauly and Stevenson 2020; Forrester and Merz 2005; Mosley *et al.* 2009; Simmons *et al.* 2004).

In one article reporting results from Canada, folic acid fortification of wheat flour (150 µg/100 g), cornmeal (150 µg/100 g) and pasta (200 to 270 µg/100 g) was associated with a lower risk of anencephaly than the pre-fortification periods (De Wals *et al.* 2007). In two articles, no association was found between folic acid fortification of wheat flour, cornmeal and pasta and the risk of anencephaly compared with a pre-fortification period (Godwin *et al.* 2008; Persad *et al.* 2002).

In four articles reporting results from Chile and Argentina, folic acid fortification of flour (220 µg/100 g) was associated with a lower risk or prevalence of anencephaly than the pre-fortification periods (Cortés *et al.* 2012; López-Camelo *et al.* 2005; Pardo *et al.* 2022; López-Camelo, Castilla and Orioli 2010).

In one article reporting results from Costa Rica, folic acid fortification of wheat flour (from 150 µg/100 g from 1997 to 180 µg/100 g from 2002), corn flour (130 µg/100 g), milk (40 µg/250 ml) and rice (180 µg/100 g) was associated with a lower risk or prevalence of anencephaly than the pre-fortification periods (Benavides-Lara *et al.* 2023).

<u>Countries with a high human development index</u>

In two articles reporting results from Iran and Brazil, folic acid fortification of flour (150 µg/100 g) was associated with a lower prevalence of anencephaly than the pre-fortification periods (Golalipour, Arabi and Vakili 2014; López-Camelo, Castilla and Orioli 2010). In one article reporting results from South Africa, no association was found between folic acid fortification of flour (150 µg/100 g) and the risk of anencephaly compared with a pre-fortification period (Sayed *et al.* 2008).

- Spina bifida

<u>Countries with a very high human development index</u>

In nine articles reporting results from the United States, folic acid fortification of flour (140 µg/100 g) was associated with a lower risk or prevalence of spina bifida than the pre-fortification periods (Canfield *et al.* 2005; CDC 2004; Dean, Pauly and Stevenson 2020; Forrester and Merz 2005; Honein *et al.* 2001; Mathews, Honein and Erickson 2002; Simmons *et al.* 2004; J. Williams *et al.* 2015; L.J. Williams *et al.* 2002). In two articles, no association was found between folic acid fortification of flour (140 µg/100 g) and the risk of spina bifida, compared with a pre-fortification period (Boulet *et al.* 2008; Mosley *et al.* 2009).

In four articles reporting results from Canada, folic acid fortification of wheat flour (150 µg/100 g), cornmeal (150 µg/100 g) and pasta (200 to 270 µg/100 g) was associated with a lower risk or prevalence of spina bifida than the pre-fortification periods (De Wals *et al.* 2008; De Wals *et al.* 2007; Godwin *et al.* 2008; Persad *et al.* 2002).

In six articles reporting results from Chile, Argentina and Costa Rica, folic acid fortification of flour (220 µg/100 g) was associated with a lower risk or prevalence of spina bifida than the pre-fortification periods (Benavides-Lara *et al.* 2023; Bidondo *et al.* 2015; Cortés *et al.* 2012; López-Camelo *et al.* 2005; Pardo *et al.* 2022; López-Camelo, Castilla and Orioli 2010).

<u>Countries with a high human development index</u>

In four articles reporting results from Iran, Jordan and Brazil, folic acid fortification of flour (150 µg/100 g) was associated with a lower risk or prevalence of spina bifida than the pre-fortification periods (Amarin and Obeidat 2010; Golalipour, Arabi and Vakili 2014; Orioli *et al.* 2011; López-Camelo, Castilla and Orioli 2010).

- Encephalocele

<u>Countries with a very high human development index</u>

In one article reporting results from the United States, no association was found between folic acid fortification of flour (140 µg/100 g) and the risk of encephalocele compared with a pre-fortification period (Dean, Pauly and Stevenson 2020).

In one article reporting results from Canada, folic acid fortification of wheat flour (150 µg/100 g), cornmeal (150 µg/100 g) and pasta (200 to 270 µg/100 g) was associated with a lower risk of encephalocele than the pre-fortification periods (De Wals *et al.* 2007).

In five articles reporting results from Chile, Argentina and Costa Rica, folic acid fortification of flour (220 µg/100 g) was associated with a lower risk or prevalence of encephalocele or cephalocele than the pre-fortification periods (Benavides-Lara *et al.* 2023; Bidondo *et al.* 2015; Cortés *et al.* 2012; Pardo *et al.* 2022; López-Camelo, Castilla and Orioli 2010).

<u>Countries with a high human development index</u>

In two articles reporting results from Iran and Brazil, folic acid fortification of flour (150 µg/100 g) was associated with a lower prevalence of encephalocele than the pre-fortification periods (Golalipour, Arabi and Vakili 2014; López-Camelo, Castilla and Orioli 2010).

- Assessment of the weight of evidence

The assessment of the weight of evidence highlighted the following points:

- **Bias control:** In most of the articles, the authors did not adjust the analyses for all the key confounders. Only six articles reported adjusted results (Abdollahi *et al.* 2011; Boulet *et al.* 2008; Canfield *et al.* 2005; Dean, Pauly and Stevenson 2020; Mosley *et al.* 2009; Simmons *et al.* 2004). These articles only adjusted for some of the key confounders: Five articles did not report any adjustment for at least one indicator of socio-economic status (Boulet *et al.* 2008; Canfield *et al.* 2005; Dean, Pauly and Stevenson 2020; Mosley *et al.* 2009; Simmons *et al.* 2004) and one article did not report any adjustment for ethnic indicators (Abdollahi *et al.* 2011). In addition, two articles had poorly defined exposure because it was at the start of the fortification period (CDC 2004; Honein *et al.* 2001), and one article only assumed fortification levels (Arth *et al.* 2016). For 17 articles, the missing data were differential[4] (CDC 2004; Arth *et al.* 2016) or therapeutic and voluntary abortions and stillbirths were not taken into account. In three articles, the coding of NTDs in the databases was modified during the study (Bidondo *et al.* 2015; Alasfoor, Elsayed and Mohammed 2010; De Wals *et al.* 2003).
- **Consistency of the results:** The studies reporting results concerning the reduction in the risk of total NTDs when systematic folic acid fortification of food was implemented are concordant. Only one article did not find an association.
- **Directness:** The populations, exposure, the comparator and the health outcomes were directly related to the systematic review question in all the included articles.

[4] Differential: Non-random distribution of missing data according to exposure level or status depending on the disease being studied.

- **Precision:** Statistical power calculations were not reported in the articles. The precision of the estimates was generally high, as determined based on the size of the confidence interval.

- **Generalisability:** The articles included focused on populations with varied socio-economic parameters, which meant they could not always be generalised to the French population.

■ Conclusion

The CES on Human nutrition concludes that systematic folic acid fortification of food is associated with a decreased risk of total NTDs. The weight of evidence is moderate.

3.3. International benchmarking of prevention strategies and measures implemented in other countries

The recommendations issued by international health organisations on the use of vitamin B9 to prevent NTDs vary from country to country. That said, most of these organisations[5] recommend a folate-rich diet and supplementation with 400 µg/day of folic acid during the periconceptional period (from four to 12 weeks before conception up to eight to 12 weeks of pregnancy) (Gomes, Lopes and Pinto 2016).

Furthermore, systematic folic acid fortification of food to prevent NTDs has been a strategy used at population level since the late 1990s and is now in effect in several dozen countries worldwide. One systematic review identified folic acid fortification policies implemented around the world (Quinn *et al.* 2024). Of the 193 countries studied, 70 had introduced systematic folic acid fortification of food. The database used by the authors (Global Fortification Data Exchange (GFDx)) came from the Food Fortification Initiative[6]. The data and reports used were reviewed by the authors to extract information on folic acid fortification policies and were corroborated by government websites to confirm the various details of such policies. The data selected to produce Figures 11 and 12 and Tables 9 and 10 (of the report), taken from the study by Quinn *et al.* 2024, correspond to countries with a policy for systematically fortifying food, with the vectors used and the dates of the legislation introducing this policy. The vectors used for folic acid fortification are mainly wheat flour, corn flour and rice (see Section 4 of the report). A map of the countries that have introduced a policy for systematic folic acid fortification of food is shown in Figure 1.

[5] 69.4% according to this survey covering 36 economically developed and emerging countries.

[6] Global Fortification Data Exchange | GFDx – providing actionable food fortification data all in one place. https://fortificationdata.org/.

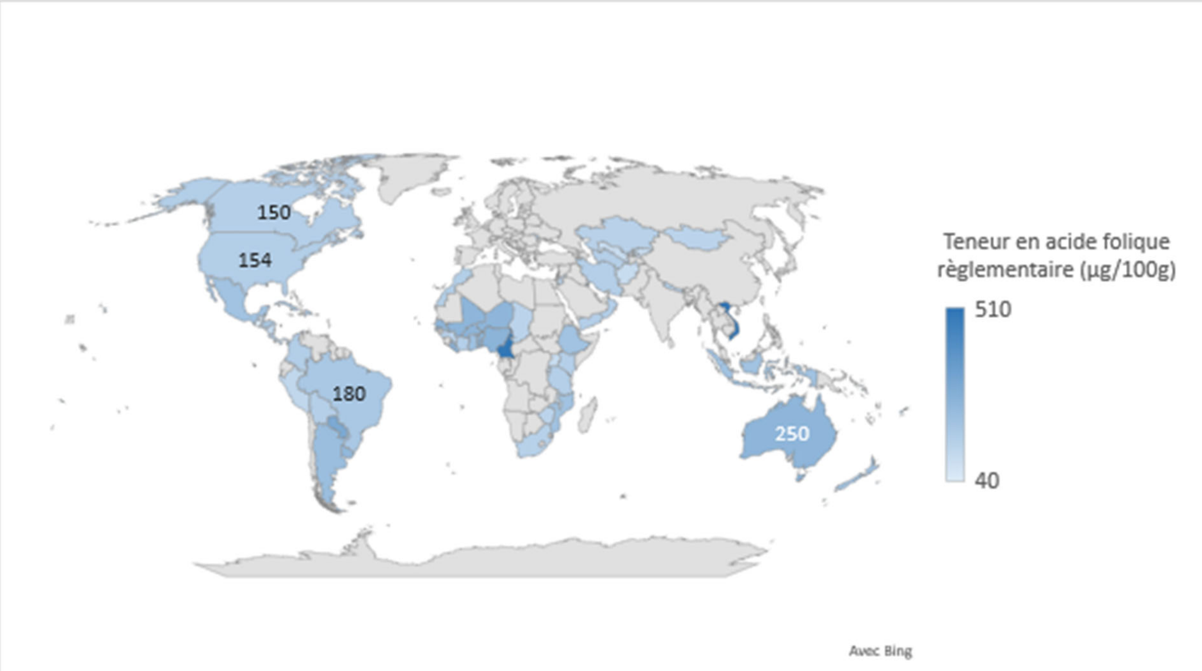

Figure 1: Systematic folic acid fortification of food by country (data from Quinn, 2024, and the Global Fortification Data Exchange of the Food Fortification Initiative)

In conclusion, systematic fortification is implemented in Western countries, with the exception of Europe, and in African, Latin American and some Asian countries. Most countries have chosen fortification levels of 100 to 200 µg/100 g of food vector.

3.4. Analysis of the relevance of systematically fortifying food

3.4.1. Criteria for assessing the relevance of a prevention scenario

The aim of the simulations was to estimate the ability of fortification to greatly reduce the prevalence of inadequate vitamin B9 intake in women of childbearing age. To do this, two fortification levels were considered. For each one, the folic acid intake distributions obtained were compared, at the low threshold with the adequate intake (AI) of 600 µg/day — which was defined in terms of preventing the risk of NTDs — and at the high threshold with the Tolerable Upper Intake Level (UL) of 1000 µg/day.

3.4.2. Simulation method

The method used to estimate intakes in France is described in the report (see Sections 5.1.1 and 5.1.2). The choice of vector was based on the results of the AFSSA study, which recommended taking account of various factors, including the eating habits of the French population and the fortification vector, which should be technologically feasible and inexpensive, so as to not penalise low-income groups (AFSSA 2003).

With a view to analysing the relevance of systematically fortifying food with folic acid, the "wheat flour" (white and wholegrain, all types) food vector was targeted.

Two flour fortification simulations were tested in light of the results of the Agency's previous work (AFSSA 2003), with doses similar to those used in other countries that systematically fortify food with folic acid:

- Simulation 1: 250 µg/100 g of flour
- Simulation 2: 200 µg/100 g of flour

Losses from cooking and storing food were not taken into account.

3.4.3. Interpretation of the simulation results

The results of Simulations 1 and 2 are described in the report (see Section 5.1.3).

The average values from the two fortification simulations show an increase in the average intake of dietary folate equivalents (DFEs) for women of childbearing age. While systematic folic acid fortification of food would enable the population reference intake (PRI) set for adults at 330 µg DFE/day to be reached for 95% (Simulation 1 at 250 µg/100 g of flour) and 90% (Simulation 2 at 200 µg/100 g of flour) of women of childbearing age, the aim is to achieve the AI to anticipate a potential pregnancy.

In both simulations, the average DFE intake of women of childbearing age is higher than the adequate intake (AI) of 600 µg defined by ANSES in 2021, whose aim is to reduce the risk of NTDs for women who are or who may become pregnant. However, the fortification simulations show that 38% of women of childbearing age in Simulation 1 and 47% in Simulation 2 do not reach this AI. These results demonstrate the need to continue recommending folic acid supplementation during the periconceptional period. Particular attention should be paid to population groups that exclude wheat flour from their diet for medical (coeliac disease, allergies) or other reasons.

For at least 95% of adults, the UL for folic acid is not exceeded in either of two fortification simulations. However, it should be noted that 1% of adults exceed the UL for Simulation 1 and 0.5% for Simulation 2. A minority of adults do not reach the AI for vitamin B12 and exceed the UL for folic acid (0.28% for Simulation 1 and 0.24% for Simulation 2), which predisposes them to the risk characterised when the UL for folic acid was established by EFSA, i.e. of an excessive amount of folic acid masking the haematological effects (megaloblastic anaemia) induced by an inadequate intake of vitamin B12 and leading to a delay in diagnosis and therefore in the management of the neurological effects associated with this inadequate intake. To prevent this, these subjects would require vitamin B12 supplementation.

In children, 4% exceed the UL in Simulation 1 and 1% in Simulation 2. However, for Simulation 1, only 2% of the children exceeding the UL for folic acid do not reach the adequate intake level for vitamin B12, exposing them to the same risk as adults. On the other hand, for Simulation 2, all children exceeding the UL for folic acid reach the adequate intake level for vitamin B12.

The CES on Human nutrition concludes that systematic folic acid fortification at a level of 200 µg/100 g of wheat flour (white and wholegrain) would help reduce the risk of neural tube defects in France, as has been observed in other countries. This value does not take into account losses from cooking or storing food.

3.5. Socio-economic analysis of systematic fortification

Question 4 of the formal request on analysing the relevance of systematic food fortification (see Section 3.4 above) included studying the relevance and feasibility of a cost-benefit analysis (CBA) of systematically fortifying food with folic acid for the primary prevention[7] of NTDs in France. The broader aim of this section is to explore the feasibility and relevance of carrying out a socio-economic analysis of this strategy compared with other possible options, including the status quo. This will help identify the various implications of the options that may be considered.

The method is detailed in Section 5.2.2 of the report.

3.5.1. Socio-economic disparities to be taken into account in the assessment

The above findings provide an opportunity to identify the pre-existing inequalities that should be taken into account in a socio-economic assessment of systematic folic acid fortification of food, in order to determine to what extent this strategy is likely to reduce or accentuate these inequalities compared with other primary prevention strategies for NTDs.

Considering that in France:

- some NTD surveillance registries collect information on the socio-economic status of parents but no NTD prevalence analysis stratified according to this status was identified (which could, in particular, explain why the prevalence of NTDs has been higher in the Reunion Island registry in some years);
- according to the Esteban study, the increase in the prevalence of the risk of serum folate deficiency[8] has affected all age groups and this prevalence is higher in women with the lowest levels of education (2019 Nutritional Epidemiology and Surveillance team);
- according to the INCA 3 survey, average dietary intakes of folates are inversely associated with level of education in adults;
- the proportion of women who are planning a pregnancy, are currently pregnant or have recently given birth, and for whom the folic acid intake reported complies with the recommendations, varies between 14.3% and 26% according to the studies identified (see Section 1 of the report), and for these women:
    - planning a pregnancy, expecting a first child, a higher level of education and older maternal age are factors associated with compliance with the recommendations, among other factors relating to health, lifestyle and socio-economic status;
    - the factors suggested in the literature to explain an inadequate intake include the absence of preconception monitoring by a healthcare professional, failure to comply with prescriptions, a lack of knowledge or understanding of the benefits of folic acid supplementation, and a reluctance on the part of women to take folic acid;
    - according to a national survey carried out in 2008, the prescribing of folic acid by healthcare professionals for women planning a pregnancy was not systematic in France (BVA-INPES 2008), and this has been corroborated by more recent local studies;

[7] Primary prevention refers to actions aimed at preventing the occurrence of a disease (WHO 1999).
[8] Data on erythrocyte folates were not available.

The socio-economic assessment of a strategy of systematic folic fortification of food for the primary prevention of NTDs in France should:

- Compare the fortification strategy with the actions already in place (status quo);
- Include, among the comparators in the fortification strategy, one or more interventions involving healthcare professionals aimed at improving their current practice of informing patients and prescribing folic acid supplements, in addition to or instead of a fortification strategy and, to this end:
    - consider using the databases of the French national health data system (SNDS) to evaluate the current use of supplements more accurately;
    - undertake specific research to clarify the conditions under which preconception consultations are held in France;
    - update data on the knowledge, perceptions and practices of healthcare professionals in relation to folic acid in order to clarify the room for improvement in current practices;
- Take account of the impact of each of the options for action compared in the assessment of the socio-economic disparities observed, with particular attention paid to people at increased risk of not complying with supplementation recommendations (e.g. young maternal age, lower level of education, low or no social or medical cover, geographical areas more affected by health issues).

3.5.2. Identification of the prevention options to be compared in the socio-economic assessment

Subject to the availability of effectiveness data applicable to the French situation, the experts recommend considering four primary prevention scenarios for NTDs:

1. **Reference scenario or status quo**: continuation of measures to raise awareness among women and healthcare professionals as currently implemented; continuation of voluntary fortification initiatives as currently practised;

2. **Alternative "systematic fortification" scenario**: systematic folic acid fortification of food in addition to the reference scenario (subject to the vectors and doses of folic acid chosen);

3. **Alternative "reinforced advice and prescription" scenario**: reinforced nutritional advice, information and prescribing of folic acid by healthcare professionals in addition to the reference scenario;

4. **Alternative "combined" scenario**: combination of the "systematic fortification" scenario and the "reinforced advice and prescription" scenario.

The socio-economic assessment should be able to study the ability of each scenario to reduce the socio-economic and geographical disparities highlighted in Section 5.2.3 of the report.

3.5.3. Challenges in the socio-economic assessment of the health burden of neural tube defects

No scientific publications were identified that involved a socio-economic assessment of the health burden of NTDs in France. The exploratory approach aimed at identifying data that may be used for such an assessment leads to the conclusion that such an assessment is feasible in France, subject to data actually being available. The associated uncertainties will need to be explored.

Each of the two approaches explored (theoretical and empirical) has advantages and disadvantages. They could be combined. Firstly, the theoretical approach would help identify, based on expert opinions and with the help of the medical and scientific literature, the different states of health in which NTD patients and their families may find themselves, as well as the various associated costs. Secondly, the empirical approach would involve exploring all the databases that could help document these different costs at population level.

According to the international literature and the analysis of the French situation, it is likely that certain costs (particularly social, psychosocial and financial costs for patients and their families) cannot be quantified and/or monetised. In this case, and given their extent, it seems necessary to analyse them in another way (descriptively or qualitatively) in order to guarantee the relevance of the assessment.

3.5.4. Challenges in the socio-economic assessment of options for the primary prevention of NTDs

The analysis of the international literature on socio-economic assessments of interventions using vitamin B9 for the primary prevention of NTDs in economically developed countries identified eight publications of interest on interventions studied in five countries (United States, Chile, Australia, Netherlands, Japan). These were *ex ante* or *ex post* analyses that were generally cost-effectiveness analyses (CEAs) or cost-utility analyses (CUAs). Most of the results converge to indicate that systematic fortification is an intervention associated with ratios below the cost-effectiveness threshold generally accepted in countries comparable to France, or even that it may be a “dominant” intervention (i.e. more effective and less costly than the status quo). However, taking into account the loss of consumer choice when assessing this strategy may alter this result. Moreover, the study by Dalziel *et al.* (2010) indicates that other strategies have achieved good results (e.g. a multi-channel information campaign and a targeted intervention using clinicians' advice to promote supplementation). It therefore seems appropriate to take them into account. Lastly, it seems important to take account of intangible costs (e.g. the psychosocial costs of NTDs), even if these cannot be quantified.

In the French context, as indicated above, a socio-economic assessment of the health burden of NTDs was considered feasible subject to the data actually being available (see Section 5.2.5.2.4 of the report). The socio-economic assessment of primary prevention strategies for NTDs is more complex, as it requires, in particular, estimating differences in the effectiveness of the strategies considered to be able to quantify and monetise the expected health impacts (benefits) of each one. In this context, the expert group considers that a CBA does not appear to be the most appropriate method, as it is not able to quantify a number of impacts. As the international literature illustrates, a CEA or CUA could be favoured, subject to the availability of the data needed to apply a rigorous method, as these analyses do not require health benefits to be monetised. The associated uncertainties will need to be explored. In this respect, the literature review drew attention to several methodological challenges: defining the states of health studied; documenting the clinical and epidemiological effects of each scenario; identifying, measuring and calculating the cost of implementing each scenario; and identifying, measuring and calculating the direct and indirect costs associated with each scenario. In addition, a qualitative analysis of (ethical, professional and technical) challenges that are difficult to quantify should be considered (see Section 5.2.6 of the report).

Lastly, it should be noted that the aim of this work was to explore the feasibility of a socio-economic assessment. A model still has to be designed before any calculations can be made. The accuracy of the resulting estimates would heavily depend on the data available and the epidemiological modelling of risk reduction associated with each possible scenario.

3.5.5. Challenges in the implementation of systematic folic acid fortification

The hearing held with the National Association of French Milling highlighted some technical and economic considerations that should be analysed in greater detail in order to assess the conditions and cost of systematically fortifying wheat flour in France. Furthermore, the example of countries where systematic fortification has been discussed (presented in Section 5.2.6.2 of the report) shows that debates and controversies are likely to arise in relation to this strategy. They may involve, for example, the persistence of fears associated with perceptions of scientific uncertainty surrounding the health effects of exposure to high doses of folic acid, and the implications of this measure for consumers' freedom of choice. These considerations have been raised in the context of draft legislation or public consultations in countries such as New Zealand and the United Kingdom, indicating that the implementation of such a measure should take account of a set of social and ethical considerations.

3.6. Conclusions of the CES

The data from the INCA 3 survey show that dietary intake of vitamin B9, excluding supplementation, is 263.2 µg/day on average for women aged 18-44, which is even lower than the nutritional reference value for the population (330 µg/day).

The prevalence data from 2012-2021 for total births of foetuses/newborns with neural tube defects, taken from French registries, show average prevalence rates of 13.5 per 10,000 births (births, stillbirths and therapeutic abortions) and 1.4 per 10,000 live births. This is due to the high percentage of therapeutic abortions following prenatal screening for these defects. It should be noted that these defects were associated with a genetic problem for 10.5% of foetuses/newborns.

The results of the systematic review show that supplementation during the periconceptional period or systematic folic acid fortification of food is associated with a reduced risk of total neural tube defects, with weight of evidence graded as moderate.

The two fortification stimulations studied show an increase in the average intake of women of childbearing age. Systematic folic acid fortification of food enables the nutritional reference value for the adult population of 330 µg DFE/day to be reached for 95% of women of childbearing age in Simulation 1 (with fortification with 250 µg/100 g of wheat flour) and for 90% in Simulation 2 (with fortification with 200 µg/100 g of wheat flour). In both simulations, the average DFE intake of women of childbearing age is also above the adequate intake of 600 µg defined to reduce the risk of neural tube defects, for women who are pregnant or who may become pregnant. Nevertheless, 38% of women of childbearing age still have intakes below this adequate intake in Simulation 1; this rate is 47% in Simulation 2. These results demonstrate the need to continue recommending the use of folic acid supplements during the periconceptional period. Particular attention should be paid to population groups that exclude wheat flour from their diet for medical (coeliac disease, allergies) or other reasons.

Ideally, to support the decision-making process, the report concludes that it would be relevant and feasible to conduct a socio-economic assessment of the strategy of systematic folic acid fortification of food for the primary prevention of NTDs, subject to the availability of data applicable to the French situation. This assessment should compare various scenarios. Four such scenarios have been proposed: a reference scenario (status quo), a scenario of systematic fortification, a scenario of reinforced supplementation, and a scenario combining the previous two scenarios. Nevertheless, such assessment comes with methodological challenges. In particular, the analysis highlights the complexity of quantifying and monetising all the costs and benefits associated with the different scenarios during the assessment. Moreover, during the assessment, the propensity of each scenario to reduce the socio-economic disparities currently observed in folic acid supplementation should be studied. The challenges associated with each of these scenarios have been presented. In particular, a structured analysis of the ethical challenges and the conditions of implementation of systematic fortification would enable its socio-economic implications to be carefully assessed.

Notwithstanding, the CES on Human nutrition concludes that systematic folic acid fortification at a level of 200 µg/100 g of wheat flour (white and wholegrain) would help reduce the risk of neural tube defects in France. This value does not take into account losses from cooking or storing food.

This fortification measure does not dispense with the need to continue recommending folic acid supplementation during the periconceptional period.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) endorses the conclusions of the CES on Human nutrition. This work has studied ways to improve the prevention of neural tube defects (NTDs) and recommends systematic folic acid fortification of food at a level of 200 µg/100 g of flour (white and wholegrain, all types), given that this fortification does not expose the rest of the population to a health risk. ANSES points out that this value does not take into account losses from cooking or storing food. Further work will therefore be required to estimate loss rates depending on the technological processes used and adjust the folic acid level upstream accordingly, before a value can be established and ultimately incorporated into a national management measure.

The fortification of flour to prevent NTDs is consistent with the resolution of the World Health Organization (WHO) which, in its draft decision of January 2023, encourages countries to fortify food with vitamin B9. In this respect, and as also suggested by the WHO in its resolution and by ANSES in its 2017 Opinion on updating dietary guidelines, similar consideration should be given to the advisability of systematically fortifying part of the diet with vitamin D in order to compensate for inadequate intakes for a large proportion of the population and thus prevent deficiencies.

On the broader issue of vitamin and mineral fortification, work is currently under way at European level. The level of fortification proposed in this Opinion should be brought to the attention of the European Working Group on Food Supplements, Addition of Vitamins and Minerals and of Certain Other Substances to Foods to help implement management measures at Community level.

From a socio-economic point of view, the feasibility study presented in the report highlights the main challenges associated with the various primary prevention options that could be considered (including the systematic fortification of staple ingredients or foods). ANSES recommends, as has been done in other countries, consulting the stakeholders concerned by the different options in order to best anticipate socio-economic challenges, taking account of issues that are likely to be controversial (role of individual consent, cost of implementing any mandatory fortification, etc.). The Agency is prepared to provide support for the implementation of a full socio-economic analysis or the organisation of a consultation of this type, based on the work carried out.

Regardless of the option chosen, ANSES recommends stepping up efforts to raise awareness among healthcare professionals and, ultimately, women of childbearing age with regard to the prevention of NTDs and the importance of an adequate vitamin B9 status, which can be achieved through a diet rich in pulses and leafy vegetables and, where appropriate, through folic acid supplementation during the periconceptional period.

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KEYWORDS

Vitamine B9, folates, acide folique, anomalies de fermeture du tube neural, compléments alimentaires, enrichissement.

Vitamin B9, folates, folic acid, neural tube defects, food supplements, fortification.

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