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## Challenges in translating scientific evidence into mandatory food fortification policy: an antipodean case study of the folate–neural tube defect relationship

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### Abstract

**Objective:** To identify challenges in translating scientific evidence of a nutrient and health relationship into mandatory food fortification policy.

**Design:** A case study approach was used in which available evidence associated with the folate–neural tube defect relationship was reviewed against the Australia New Zealand Food Regulation Ministerial Council's Policy Guideline for mandatory food fortification.

**Results:** Three particular challenges were identified. The first is knowing when and how to act in the face of scientific uncertainty. The second is knowing how to address the special needs of at-risk individuals without compromising the health and safety of the population as a whole. The third is to ensure that a policy is sufficiently monitored and evaluated.

**Conclusions:** Despite the availability of compelling evidence of a relationship between a particular nutrient and a health outcome, a definitive policy response may not be apparent. Judgement and interpretation inevitably play significant roles in influencing whether and how authorities translate scientific evidence into mandatory food fortification policy. In relation to the case study, it would be prudent to undertake a risk–benefit analysis of policy alternatives and to implement nutrition education activities to promote folic acid supplement use among the target group. Should mandatory folate fortification be implemented, comprehensive monitoring and evaluation of this policy will be essential to know that it is implemented as planned and does more good than harm. In relation to mandatory food fortification policy-making around the world, ongoing national nutrition surveys are required to complement national policy guidelines.

**Keywords**  
Food fortification  
Folate  
Evidence  
Food regulation  
Nutrition policy

Mandatory food fortification is a potentially powerful intervention for helping to achieve public health nutrition policy objectives. The intervention involves adding a nutrient(s) to a certain food(s) and thereby exposing everyone in the population who consumes the fortified food(s) to extra amounts of the nutrient(s) in their diets. Internationally, the conventional rationale for mandatory food fortification has been to counter inherent nutrient deficiencies in the food supply that subsequently contribute to the existence of a significant prevalence of clinical symptoms of nutrient deficiencies among the population<sup>1</sup>. For example, on 1 January 1991, mandatory thiamine fortification of Australian bread-making flour commenced primarily in response to evidence that the thiamine supply in the Australian diet was insufficient to maintain adequate thiamine reserves among all Australians<sup>2–4</sup>.

Because mandatory food fortification affects the vast majority of the population, often policy-makers are confronted with scientific, ethical and/or political challenges when translating scientific evidence into policies that have such population-wide impacts. These challenges need to be identified and their causes explained if food fortification policy-making and practice are to be improved.

On 24 May 2004, the Australia New Zealand Food Regulation Ministerial Council (ANZFRMC) issued a policy guideline entitled *Policy Guideline: Fortification of Food with Vitamins and Minerals* (Policy Guideline)<sup>5</sup>. The Policy Guideline provides policy principles against which a case for mandatory food fortification can be assessed. At the meeting mentioned, the ANZFRMC also agreed that Food Standards Australia New Zealand (FSANZ) should consider developing a food standard that mandates

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fortification of food with folate as a 'priority' to help reduce the incidence of neural tube defects (NTDs) in Australia and New Zealand<sup>6</sup>. Ministers were responding to epidemiological evidence that the consumption of additional folic acid during the periconceptional period can reduce the risk of NTD-affected pregnancies<sup>7-9</sup>. This is the first instance that the Policy Guideline will be used to inform decision-making and provides an opportunity to identify challenges in its application. If approved, mandatory folate fortification will create a food fortification policy precedent in Australia and New Zealand. Rather than addressing a population-wide need for extra folate in the food supply, the rationale for the policy would be to assist a small population of at-risk women to be exposed passively to a pharmacological dose of folate.

The objective of the present paper is to identify challenges in translating scientific evidence of a nutrient and health relationship into mandatory food fortification policy. The current consideration in Australia and New Zealand of mandatory folate fortification policy in response to available evidence of the folate-NTD relationship was the case study selected for this investigation.

## Method

The identification of challenges in translating scientific evidence into mandatory food fortification policy will depend on which nutrient and health relationship is selected, the scientific evidence that is available and the policy guideline(s) against which evidence is reviewed. Therefore the research design deemed most appropriate to achieve the paper's objective was a case study approach. The method used within the case study approach involved using the five policy principles for mandatory food fortification outlined in the ANZFRMC's Policy Guideline to review available evidence. According to the Policy Guideline<sup>5</sup>, 'The mandatory addition of vitamins and minerals to food should:

- Be required only in response to demonstrated significant population health need taking into account both the severity and the prevalence of the health problem to be addressed.
- Be required only if it is assessed as the most effective public health strategy to address the health problem.
- Be consistent as far as is possible with the national nutrition policies and guidelines of Australia and New Zealand.
- Ensure that the added vitamins and minerals are present in the food at levels that will not result in detrimental excesses or imbalances of vitamins and minerals in the context of total intake across the general population.
- Ensure that the mandatory fortification delivers effective amounts of added vitamins and minerals with the specific effect to the target population to meet the health objective.' (p. 2).

The following additional policy guidance for mandatory fortification is provided<sup>5</sup>:

'Assessment of alternative strategies – consideration must be comprehensive and include for example assessment of voluntary fortification and education programs. ...

Monitor/Review – any agreement to require fortification should require that it be monitored and formally reviewed to assess the effectiveness of, and continuing need for, the mandating of fortification.' (p. 2)

The evidence that was reviewed against the policy principles was that available in the *Initial Assessment Report, Proposal P295 – Consideration of Mandatory Fortification with Folic Acid* (IAR)<sup>10</sup> released by FSANZ in late 2004. This evidence represents FSANZ's systematic review of the scientific literature. Also of particular relevance from a case study perspective, it reflects the actual information environment within which stakeholders were consulted and mandatory folate fortification was considered during the formative period of policy-making in Australia and New Zealand.

## Results

In this section, the evidence of the folate-NTD relationship made available in the IAR is reviewed against each of the policy principles and additional guidance in the Policy Guideline.

### ***Is there a demonstrated significant population health need?***

The IAR (p. 7) notes that NTDs are birth defects resulting from the failure of the neural tube to close during early embryonic development. They are diseases of particular severity and contribute considerable emotional, economic and social cost to families with affected pregnancies. However, it is also noted in the IAR (p. 7) that NTD prevalence is low, with NTDs affecting approximately 11.5 and 9.1 total births and terminations per 10 000 total births each year in Australia and New Zealand, respectively.

The case that there is a demonstrated significant population health need for mandatory folate fortification would be strengthened if there was evidence either of a folate deficiency among the population or that elevated folate status may help prevent chronic disease. According to the IAR (p. 17), there is a lack of information on the prevalence of folate deficiency in Australia and New Zealand, although the available data suggest that folate status levels are sub-optimal or deficient in only 2–5% of the populations. The IAR (p. 18) notes that there may be potential benefits of elevated folate status, particularly in relation to lowering the mean blood concentrations of homocysteine in the population and a possible subsequent reduction in the incidence of cardiovascular disease. However, it is also notes that it remains uncertain whether homocysteine levels are a causative agent of

cardiovascular disease and the observational studies that have provided evidence of an association are unable to demonstrate conclusively that increasing folic acid intake will reduce cardiovascular disease risk.

***Is mandatory folate fortification the most effective public health strategy to reduce the risk of NTDs?***

According to the IAR (p. 7), women of childbearing age are the target group for a public health strategy to reduce the risk of NTDs. A summary of the key advantages and disadvantages, described in the IAR (pp. 32–36), for each of the four main public health strategies to increase the folate status of the target group and reduce the risk of NTDs, is outlined below.

***Promotion of folic acid supplementation during the periconceptional period***

The advantages of promoting folic acid supplement usage are that it targets women planning pregnancies and provides folic acid at the level recommended. The disadvantages of this strategy relate to compliance with the recommendation. Many women are unaware of the importance of supplementation and awareness does not necessarily translate into action. Moreover, approximately 50% of pregnancies are unplanned and the neural tube closes between the 22nd and the 28th day after conception, a period during which a woman may be unaware that she is pregnant.

***Promotion of diets high in naturally occurring folate***

The advantages of promoting diets high in naturally occurring folate are that it confers a low risk of adverse health effects, both in the target population and other population subgroups; and it provides wider health benefits from nutrient-dense foods. The disadvantages of this strategy are similar to those identified for compliance with folic acid supplement usage. In addition, if behaviour change did occur, it would be difficult to obtain sufficient naturally occurring folate from the diet to achieve the folate intake target.

***Voluntary fortification of the food supply with folic acid***

The advantages of voluntary fortification of the food supply with folic acid are that, assuming the fortified foods are those eaten by individuals in the target group, the strategy does not rely on an individual's behaviour change and the effect is achieved irrespective of socio-economic status. The disadvantage of this strategy is that its implementation rests with the food industry, which could result in difficulties with ensuring consistency with government objectives and with monitoring which foods are fortified and at what levels.

***Mandatory fortification of the food supply with folic acid***

The advantages of mandatory fortification of the food supply with folic acid are similar to those identified for

voluntary fortification, with the added advantage that implementation control rests with government. The disadvantages of this strategy are that it limits consumer choice of non folate-fortified foods and increases the risk of folic acid intakes of sub-population groups above safety levels.

***Will mandatory folate fortification be consistent with national nutrition policies and guidelines?***

In Australia and New Zealand, the Dietary Guidelines for Australians and the New Zealand Food and Nutrition Guidelines, respectively, broadly represent national nutrition policies and guidelines. The primary goal of these guidelines is to promote health and help prevent diseases caused by dietary imbalances. Whether or not mandatory folate fortification will be consistent with national nutrition policies and guidelines will depend largely upon the nutrient composition of foods selected for fortification and their contribution to dietary balance. For example, whether the food products selected as fortification vehicles are high sources of fat, sugar or salt.

***Will there be any safety concerns?***

Until the details of which foods might be fortified and at what level are available, it is not possible to predict with certainty the public health and safety impacts of a policy of mandatory folate fortification. However, general safety concerns have been raised. The key safety concerns described in the IAR (pp. 17–19) are outlined below.

***Safety concerns for consumers in the target group***

A trend towards increased risk of multiple gestation associated with folic acid supplementation has been described in several studies. However, this trend has not been observed in the USA, where mandatory folate fortification of cereal grains has been fully implemented since 1998.

***Safety concerns for the population as a whole***

Pharmacological doses of folate have been reported to be associated with the masking of clinical symptoms of vitamin B<sub>12</sub> deficiency. The key features of vitamin B<sub>12</sub> deficiency are macrocytic megaloblastic anaemia and neuropathy. Unless adequate vitamin B<sub>12</sub> is administered, the underlying neuropathy persists, leading to irreversible neurological damage. The prevalence of vitamin B<sub>12</sub> deficiency in the Australian and New Zealand general populations is not well defined and best estimates suggest that it is between 1 and 22%. The postulated increased risk of masking anaemia among people with vitamin B<sub>12</sub> deficiency has not been reported in the USA despite an elevated folate status in that country since mandatory fortification was introduced. In addition, large doses of folic acid may interfere with the action of certain drugs, including anticonvulsants and folate antagonists used to treat conditions such as epilepsy and cancer, respectively.

### ***Will effective amounts of folate be delivered to the target population?***

The IAR (p. 21) comments that the risk of an NTD-affected pregnancy is inversely associated with folate status during the periconceptional period in a continuous, dose-response relationship. It also notes (p. 20) that the Australian National Health and Medical Research Council (NHMRC) previously recommended, and the New Zealand Ministry of Health currently recommends, that women planning a pregnancy should take a 0.5 mg folic acid supplement daily and 800 µg of folic acid daily, respectively. Both agencies advise women with a family history of NTDs to take 5 mg folic acid per day. In addition, the IAR (p. 13) refers to the need to recognise the tolerable upper intake level of 1000 µg folate per day for adults suggested by the Institute of Medicine in response to concerns about the masking of vitamin B<sub>12</sub> deficiency.

Because mandatory folate fortification is a non-targeted intervention, it will be a challenge to design the strategy with sufficient sensitivity to deliver the recommended dose of folate to at-risk individuals while ensuring adequate specificity to avoid exposing the population to excessive levels of folic acid. For example, the IAR (p. 29) refers to experience from the USA where a higher than anticipated intake of folic acid from the diet across all sectors in the community has been observed since the advent of mandatory folate fortification. This observation is linked with the difficulty of assessing folate intake both from diet and from folate-fortified foods where the food manufacturing practice of 'overage' can lead to uncertainty in folate composition estimates. In this context overage refers to a process of adding more of a nutrient than necessary to a food product to take account of losses during processing and storage.

### ***Additional policy guidance***

#### *Assessment of alternative strategies*

The IAR (p. 48) reveals that assessing alternative strategies to mandatory folate fortification for their effectiveness to prevent NTDs is problematic because governments in Australia and New Zealand are yet to invest significantly in such strategies. Three national and five state-based campaigns to promote folate-rich foods and folic acid supplements to the target group have been implemented in Australia over the past decade. Yet, only a Western Australian (WA) campaign has been implemented for longer than 12 months. No such campaigns have been implemented in New Zealand.

When alternative strategies have been implemented, there has been a lack of systematic, coherent and sustained monitoring and evaluation, creating challenges in assessing the relative impact of the alternative strategies. According to the IAR (p. 27), the total NTD rate (comprising births and terminations where available) in Australia has been estimated to have declined by 7.3%

since the advent of voluntary folate fortification to complement education campaigns promoting folate-rich foods and folic acid supplementation. However, attributing the relative contribution of each of the strategies to the decline is complicated. For example, in WA in 1996 a 30% reduction in the prevalence of NTDs (births plus terminations) was observed and the prevalence has remained stable at this level<sup>11</sup>. It is unlikely that a significant proportion of this reduction in NTD prevalence would be attributable to voluntary folate fortification as the first folate-fortified food product did not appear on supermarket shelves in Australia until April 1996<sup>12</sup>. Any benefit, in terms of reduced birth prevalence, from the availability of folate-fortified foods could not have been detected until early 1997. The most likely explanation for the majority of the 30% reduction in NTD prevalence in WA is the state's education campaign that was implemented during the two-and-a-half years prior to 1996<sup>13</sup>.

Assessing the potential effectiveness of mandatory folate fortification to help prevent NTDs in Australia and New Zealand requires extrapolation from evaluation data from other countries. The IAR (p. 29) notes that in the USA the prevalence of NTDs has decreased by 27% since the introduction of mandatory folate fortification of cereal grains in the late 1990s. It is a challenge to determine the contribution of the mandatory folate fortification strategy in the USA to this health impact because alternative primary prevention strategies have been implemented there since the late 1990s. Moreover, the IAR (p. 15) reports that a reduction in NTD prevalence has been observed in many countries, including Australia and New Zealand, over the past two decades. The explanation for the declining NTD rates is uncertain, although increases in prenatal NTD diagnosis and terminations of cases that otherwise may have been identified at birth are believed to be significant factors.

#### *Monitor and review any agreement for mandatory folate fortification*

Given the uncertainties regarding the safety, effectiveness and ethics of mandatory folate fortification, it is essential that, if such an intervention were to proceed, timely and comprehensive monitoring and review of the policy processes and outcomes be undertaken. However, the IAR (pp. 23–28) reveals that the Australian and New Zealand governments previously have demonstrated a failure to invest adequately in such monitoring and review.

### **Discussion**

In reviewing the scientific evidence associated with the folate-NTD relationship against the policy principles and additional guidance in the Policy Guideline, three particular challenges for the development of a mandatory food fortification policy can be identified. The first challenge is knowing when and how to act in the face of

scientific uncertainty. Among the uncertainties of the folate–NTD case are the incomplete understanding of the mechanism by which folate exerts its protective effect; the optimum dose; the safety consequences of exposure to higher levels of folic acid; the current dietary folate intake and folate status of the target group and population as a whole; the folate composition of food products; the relative effectiveness of alternative policy strategies; and whether the prevalence of NTDs is diminishing irrespective of an explicit policy intervention.

The second challenge is knowing how to balance the special needs of at-risk individuals with the population as a whole. The prevention of any one NTD is cause for celebration; however, mandatory food fortification is a 'blunt' policy instrument and it is critical that it does not compromise the public's health and safety. Mandatory folate fortification would expose people in the target group and the population in total who consume the fortified foods to a lifetime of high levels of folic acid. Whereas increased exposure to naturally occurring folate in foods is not regarded as a safety concern<sup>14</sup>, concerns about the unknown metabolic consequences of an increased presence in plasma of unmetabolised folic acid derived from folate-fortified foods have been raised<sup>15,16</sup>. Paradoxically, it is because of folate's integral role in gene function and biochemical pathways critical for promoting health and preventing disease that public health and safety considerations become especially significant. As Smith<sup>17</sup> comments: 'But folate being involved in so many of life's fundamental processes not only leads to its possibilities as a panacea but also to the prospect that "messing around with folate" could do extensive harm'.

The third challenge is to ensure that policies are sufficiently monitored and evaluated. Unfortunately, Australia has a lamentable record in this regard. In 1994, when the NHMRC's Expert Panel on Folate Fortification prepared its recommendations that ultimately led to the present policy of voluntary folate fortification in Australia and New Zealand, it stated that monitoring would be undertaken to enable the reporting of progress against policy targets within 3 years<sup>18</sup>. Yet, 7 years later in its interim report on voluntary folate fortification, the Australian Food and Nutrition Monitoring Unit commented that no monitoring of the folate levels of folate-fortified foods had been undertaken and there were serious gaps in Australia's capacity to monitor changes in rates of NTDs. The Unit concluded<sup>19</sup> that: 'In Australia, it is too early to assess the impact of folate fortification on the occurrence of NTDs, and mechanisms are not in place to monitor other health outcomes' (p. xi).

The generalisability of the identified challenges to preparing policy responses to evidence of the folate–NTD relationship in other countries is dependent upon the relevance of the Policy Guideline as a reference standard and the accuracy and completeness of the evidence provided in the IAR. Policy guidelines for mandatory food

fortification vary from country to country and hence the challenges identified in this case study may not necessarily extrapolate to experiences in all countries. Also, since the release of the IAR evidence of folate and health relationships has continued to emerge and as knowledge evolves the challenges identified above may change.

A major explanation for the existence of the identified challenges is that the folate–NTD relationship is associated with unusual circumstances. It is known that the cause of NTDs is linked to common single nucleotide polymorphisms of several genes coding for folate-dependent enzymes<sup>20</sup>. However, knowledge about genotype associations is incomplete and it is not possible to screen for women at risk of having an NTD-affected pregnancy. Also, as described earlier, the significant proportion of unplanned pregnancies and closure of the neural tube early in pregnancy are likely to limit compliance with targeted primary prevention approaches that otherwise might be developed. These circumstances present a peculiar dilemma for food policy-makers in those countries that currently are considering whether to recommend mandatory folate fortification. If mandatory folate fortification were to proceed, it would help certain individuals meet their special needs for extra folate intake irrespective of the unusual circumstances. However, it would represent a 'mismatch' between the scope of the response and the nature of the health problem being addressed. Mandatory folate fortification is a non-targeted, population-wide intervention and its use to address a metabolic abnormality in at-risk individuals needs to be considered in the context of protecting the health and safety of the overall population.

Given the unusual circumstances associated with the folate–NTD relationship, it might be argued that the identified challenges have little relevance to translating scientific evidence of other nutrient and health relationships into mandatory food fortification policy. However, three additional explanations for the existence of the challenges, with a broader bearing on mandatory food fortification policy, can be derived from the data.

The first additional explanation for the existence of the challenges is the lack of implementation of non-fortification policy approaches combined with a lack of evaluation of those policy approaches that have been implemented. Consequently, it is difficult to conduct a risk–benefit analysis of the different policy approaches in Australia and New Zealand. Local policy-makers frequently have deferred to data from overseas experience to help predict public health and safety outcomes for policy approaches. This deference to overseas experience assumes that circumstances and populations are sufficiently similar to permit data extrapolation to the local setting. Also it assumes that what should be assessed is known and that other countries have undertaken the necessary studies to assess potential unintended adverse outcomes from increased folate intakes, a situation

disputed by some<sup>21</sup>. As Mills<sup>22</sup> comments: '... the absence of evidence of toxicity is not evidence of the absence of toxicity'.

The second additional explanation is the lack of broader food and nutrition monitoring and surveillance activities. It is 10 and 8 years since Australia and New Zealand, respectively, have conducted comprehensive national nutrition surveys. There is a lack of baseline data on the population's dietary nutrient intake and nutrient status to inform food fortification policy-making. Also, there has been little commitment to the development of sustainable monitoring systems that would allow both countries to track important trends and act on these in a timely manner. Since the mid-1990s, dietary behaviours and food product availability appear to have changed significantly. The lack of up-to-date information has been noted as a concern by FSANZ because it affects the applicability of food composition data to current dietary patterns, which underpin its dietary modelling and risk assessment procedures<sup>23</sup>.

The third additional explanation is that the nutrient reference values for Australia and New Zealand were being reviewed<sup>24</sup> and FSANZ's 'Fortification Implementation Framework' was being developed<sup>25</sup> when the policy development process began. Even if monitoring and surveillance data of previous policy approaches were available, an up-to-date nutrition reference standard and technical framework for applying the Policy Guideline were not available to stakeholders during the formative stage of the public consultation process to support the data interpretation.

## Conclusion

Rarely in the field of nutrition has there been such compelling epidemiological evidence linking a single nutrient with protection against a disease as exists for the role of folate in reducing the risk of NTDs. However, the case study illustrates that despite the existence of compelling evidence for this nutrient and health relationship and the severity of the disease, it is not always possible to apply national policy guidelines to construct a definitive case for a mandatory food fortification policy. Indeed, despite having available similar evidence of the folate-NTD relationship, national expert committees in North America<sup>26,27</sup> have recommended a policy of mandatory folate fortification, while several of their European counterparts<sup>28-30</sup> have recommended policies of voluntary folate fortification and/or health education. Judgement and interpretation often play significant roles in influencing whether and how authorities decide to translate scientific evidence into mandatory food fortification policy.

In relation to the Australian and New Zealand policy review of the folate-NTD relationship, there is an immediate need to implement nutrition education

activities to promote folic acid supplement use among the target group and it would be prudent to undertake a risk-benefit analysis of the alternative policy approaches. Should mandatory folate fortification be implemented, it will be essential that comprehensive monitoring and evaluation of the intervention be undertaken to know that it is implemented as planned and does more good than harm. The precedent nature of such a policy intervention would present special challenges to policy-makers in interpreting and applying the Policy Guideline when next responding to scientific evidence of a relationship between a particular nutrient and a health outcome. For mandatory food fortification policy-making in general, ongoing national nutrition surveys are required to complement the application of national policy guidelines.

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