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Mandatory fortification with folic acid

What would Hippocrates say?

In October 2006, the Australian and New Zealand Food Regulation Ministerial Council asked for a review of the proposed food standard permitting mandatory fortification of bread with folic acid. This article contributes to the policy debate associated with the standard's review by discussing the potential benefits and risks to the target population and the wider Australian population with emphasis on recent (2006) literature.

There is strong evidence that raised levels of folate during the periconceptional period reduces the risk of neural tube defects (NTDs).^{1,2} On 4 October 2006, Food Standards Australia New Zealand (FSANZ) released its Final Assessment Report³ presenting two regulatory options: mandatory fortification of 80–180 µg of folic acid per 100 g of bread; or the maintenance of the current voluntary folic acid fortification policy, with mandatory folic acid fortification being the recommended option. On 25 October 2006 the Ministerial Council considered this mandatory folic acid fortification recommendation and asked FSANZ to review the proposed standard due to technical considerations with its implementation, and compliance issues, within 6 months.

Mandatory folic acid fortification is a controversial policy and is generating considerable debate.^{4,5} Notwithstanding the tragic nature and associated social, emotional and economic burden of NTDs, mandatory folic acid fortification is associated with many scientific and ethical uncertainties.⁶ Mandatory fortification will expose all children, adolescents, adult women and men, and older people to raised levels of synthetic folic acid to address a suspected congenital abnormality in a relatively small number of at risk individuals. This proposed policy represents a disjunction between the medical nature of the problem and the public health impact of the solution. This disjunction casts doubts over whether the interest of either the target group, or the population as a whole, would be best served by this policy. The aim of this article is to contribute to the policy debate particularly by considering to what extent Hippocrates' principle of 'first do no harm' is being observed?

Why has this policy debate arisen?

Mandatory food fortification is uncommon in Australia, although it has been implemented when there has been strong evidence of population wide deficiency. For instance, thiamine is added to bread making flour in response to evidence of suboptimal thiamine status within the population.^{7,8} This is not the same rationale as mandatory folic acid fortification. Although the biological mechanism and precise dose required for folic acid to exert its protective effect is uncertain, it is thought to be a compensation for a congenital defect in at risk individuals.⁹ The protective effect is consistent with a therapeutic type response and is exerted in a dose response relationship¹⁰ rather than addressing a conventional folate deficiency. Therefore, mandatory folic acid fortification would represent a policy precedent in Australia.

The policy controversy is exacerbated by the existence of other scientific and ethical uncertainties. For example, the incidence of NTDs has been decreasing in many countries for decades, irrespective of folic acid fortification.¹¹ Also, the degree of reduction in NTD incidence appears to be related to baseline NTD incidence.¹² Moreover, there has been limited support for nonfortification policy options in Australia and hence we have a lack of evidence of the effectiveness of alternative policy approaches. It is relevant to note that when preparing its recommendations FSANZ has a legislative requirement to consider a full range of risk management measures and a regulatory approach should precede only if it is deemed the most effective risk management strategy. The FSANZ risk management process did not consider all possible strategies, for example it excluded consideration of targeted interventions such as education, and/or

incorporation of folic acid supplementation into best practice guidelines for practitioners.

The central policy dilemma concerning prophylactic folic acid use is that approximately half of all pregnancies are unplanned³ and by the time many women are aware they are pregnant the neural tube will have closed. Therefore mandatory folic acid fortification is appealing because it ensures passive exposure by the target group, requiring no behaviour change during the critical periconceptional period. Also, it is equitable; all women regardless of background or circumstances will be exposed.⁶ Paradoxically, its appeal is a double edged sword. Because the intervention is nondiscriminating, it will expose the entire bread eating population to raised levels of synthetic folic acid.

Hippocrates and potential benefits/risks for the target population

An evaluation of mandatory folic acid fortification of enriched grains in the United States reported a 27% reduction in NTDs since the introduction of the intervention.¹³ However, when preparing its policy recommendations, FSANZ was confronted with the dilemma that both the Australian National Health and Medical Research Council and the US Institute of Medicine have set an upper limit of intake of folic acid of 1 mg/day due to its potential to precipitate or exacerbate neuropathy in vitamin B12 deficient individuals.^{14,15} In recognition of this concern, FSANZ has proposed a fortification level of 80–180 µg folic acid per 100 g of bread.³ At this level of fortification, FSANZ predicts that 26 NTD conceptions (95% CI: 14–49), or approximately 8% of the 300–350 pregnancies affected by NTDs in Australia each year will be prevented. Critically, targeted folic acid supplementation would avoid this dosage constraint; this potentially would have a greater reduction of risk. Folic acid supplementation is not associated with a reduction in nonneural birth defects.¹⁶

The principal potential risk identified for the target group is multiple births. While there is some conjecture over this risk (the relationship marginally misses out on significance [1.40: 0.93–2.31]¹⁷), the authors observed the findings were consistent with other studies and worthy of concern; a conclusion that persists among others.¹⁸

Hippocrates and potential benefits/risks for the wider population

Given that 20 million Australians will be exposed to significantly raised levels of synthetic folic acid for the first time in evolutionary history, it is of importance to consider its impact on the health of the wider population. Additional folic acid intake has been hypothesised to be advantageous to the wider population – by lowering plasma homocysteine levels and thereby reducing cardiovascular disease risk, by improving cognitive function, and by helping to prevent some types of cancer. In its Final Assessment Report, FSANZ draws attention specifically to these three potential benefits.³ However, the findings of several recent (2006) studies now refute these hypotheses and suggest that elevated folic acid status may be a potential risk for these conditions.^{19–24}

In the case of cardiovascular disease, three large, multicentred, randomised controlled trials have failed to demonstrate a benefit of folic acid supplementation.^{19–21} Moreover, potential harm was observed in one study with a near significant increase in myocardial infarctions.¹⁹ A recent 2 year randomised controlled trial of folic acid supplementation found no evidence of a positive effect on cognition in the elderly and provided evidence of a statistically significant decline in information processing speed with supplementation.²² A European longitudinal study observed a significant increased risk of colorectal cancer in individuals with the highest folate intakes over a 4.2 year period.²³ In a separate USA cohort study, high folate intakes attributed to supplemental folic acid, were associated with a significant increased risk of breast cancer.²⁴ Another USA study identified unmetabolised folic acid in the circulation of 78% of postmenopausal women and that there was an inverse relationship between this and a measure of immunity (natural killer cell cytotoxicity).²⁵

It is often argued that there have been no identified risks overseas – however, a strong advocate for mandatory fortification with folic acid in the USA has conceded that adequate monitoring mechanisms were not put in place to be so confident with such an assessment.²⁶ Potential benefits and risks associated with mandatory fortification with folic acid are summarised in *Table 1*.

The policy debate

Given the many uncertainties associated with mandatory folic acid fortification, we offer the following suggestions to help inform this policy debate.

Infrastructure to support data collection and management

It is over 10 years since the last national nutrition survey was conducted and the data on folate consumption patterns and folate status are outdated. In addition, there are incomplete data on the folate composition of food products. Together this lack of information does not bode well for informed policy making, nor will authorities be well placed to evaluate the outcome of any policy decision. Also, a comprehensive risk-benefit analysis – that includes data from the most recent (2006) studies – needs to be undertaken.

Should mandatory fortification with folic acid be approved, it is essential that there be adequate monitoring and evaluation of this intervention. Unfortunately, previous experience in this area does not augur well as few resources were provided for monitoring and evaluating voluntary folate fortification.²⁷ Monitoring and evaluation will be a challenging task given the uncertainties associated with this policy topic. There is the dilemma of not knowing the long term health implications of the presence of elevated unmetabolised plasma folic acid levels.

Support the promotion of targeted supplementation

Governments should invest more resources supporting a program for targeted folic acid supplementation and greater public education on the importance of periconceptional use of folic acid. Incorporation of folic acid supplementation into best practice guidelines for practitioners is also required. This approach has the advantages of not inadvertently inflicting harm on the wider population, targeting the intervention to at risk individuals and delivering the recommended dose. Indeed, a randomised controlled trial of a targeted folic acid supplementation program administered by physicians in the USA reported higher effectiveness than mandatory fortification with folic acid.²⁸

Table 1. Potential risks and benefits associated with mandatory fortification with folic acid**Effects on the target population**

Potential benefit	Effect size of potential benefit	Potential risk	Effect size of potential risk
Reduction in incidence of NTD	26 cases/year CI: 14–49 ³	Increased risk of multiple births ¹⁷	Relative risk 1.40: CI: 0.93, 2.31

Effect on wider population

Potential benefit	Effect size of potential benefit	Potential risk	Effect size of potential risk
Reduced cardiovascular disease risk	Unproven ^{19–21}	Presence of unmetabolised folic acid in blood	Reported in 78% of postmenopausal USA women ²⁵
Improved cognition in elderly	Unproven, caution warranted ²²	Precipitate or exacerbate neuropathy associated with B12 deficiency	Reported 22.9% of Sydney subjects aged 50+ years had a low serum B12 level ²⁹
		Increased risk of breast cancer	Hazard ratio: 1.32, CI: 1.04, 1.68 ²⁴
		Increased risk of colorectal cancer	Odds ratio: 3.87, CI: 1.52, 9.87 ²³
		Increased incidence myocardial infarction	Rate ratio: 1.23 CI: 0.99, 1.52 ¹⁹

Note: CI = 95% confidence interval

Although FSANZ has identified in its Final Assessment Report the importance of these two activities, it also states that their establishment and funding extends beyond its statutory responsibilities.³ As such there are no guarantees that they will be implemented should mandatory folic acid fortification be permitted. This is due to the separation of the technical responsibilities from the policy responsibilities of FSANZ and the Ministerial Council respectively. Therefore, if education and monitoring and evaluation activities are to be adequately considered, they will need to be integral components of the policy decision made by the Ministerial Council.

Conclusion

Mandatory folic acid fortification in order to reduce the risk of NTDs is a far more complex and challenging policy debate than is often recognised. We all want simple answers to tragic circumstances, and as compelling as this policy first appears, it is important that the potential risks don't outweigh any potential benefits. In lieu of the many scientific and ethical uncertainties associated with this policy, we wonder what Hippocrates would have said about this policy debate?

The predicted prevention of 26 NTD conceptions represents 8% of all NTD conceptions each year in Australia. At the same time, 20 million Australians will be exposed to raised levels of synthetic folic acid for which the ethical and potential risk implications need to be considered carefully. This is a topic that generates strong emotions and presents peculiar dilemmas and challenges for policy makers. It brings together a public health nutrition approach to address a tragic medical issue. Our concern is that this disjunction might result in an outcome that both compromises effectiveness and presents a potentially greater risk than benefit. We believe a greater reduction in NTD conceptions could be achieved with a well resourced targeted folic acid supplementation program promotion.

This need for caution is all the more salient given the lack of nutrition baseline information available in Australia. It might be cautionary for the policy decision to be delayed until adequate information, including the findings from a comprehensive risk-benefit analysis, is available. If mandatory folic acid fortification is approved by the Ministerial Council it is essential that there be adequate monitoring and evaluation. Faced with the many scientific and ethical

dilemmas associated with this topic, we believe more information would help decision makers move closer to a precautionary approach to resolve this vexed policy debate.

Conflict of interest: none declared.

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