Scientific evidence of benefits and risks of an increase in folic acid intake in Australia and New Zealand

Part 1: Quantification of primary benefits – reduction of NTD risk

Part 2: Potential secondary benefits – risk reduction of cardiovascular, cancer diseases and of impaired cognitive function

Part 3: Estimates of Risk – increase in risk of some cancers

9th May 2005

PART 1 Quantification of primary benefits

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1 Reduction in neural tube defect (NTD) risk

1.1 The best estimate of current incidence (birth prevalence) of NTD-affected pregnancies (births and terminations) in Australia, and in New Zealand

Data sources

1. Data were sought from the South Australian, Victorian and Western Australian Birth Defects Registers and from New Zealand Ministry of Health Birth Defects Monitoring Program for denominators (on all livebirths and stillbirths) and for NTD-affected livebirths, stillbirths and terminations of pregnancy (by type of defect: anencephaly, spina bifida, encephalocoele) for 1999-2003. Some notifications may still be outstanding in some jursidictions, particularly for terminations of pregnancy so, data for 2004 have not been included and data for 2003 should be considered preliminary. Data on all terminations of pregnancy were also sought from these jurisdictions, but were available only for SA and WA.

2. National Australian data for NTD are known to be incomplete for terminations of NTD-affected pregnancies and hence the three-state data (with close to complete ascertainment of NTD terminations) were used to extrapolate to Australia as a whole. New Zealand data for terminations of NTD-affected pregnancies are not available and no data on stillbirths (total or with NTD) in New Zealand were available for 2002-2003.

3. The available data are shown in Tables 1 and 2.

Table 1. Numbers of total livebirths and stillbirths in South Australia, Victoria and Western Australia combined (and total terminations of pregnancy in South Australia and Western Australia combined) 1999-2003 and livebirths, stillbirths and terminations of pregnancy affected by NTD 1999-2003, South Australia, Victoria and Western Australia combined.

	1999	2000	2001	2002	2003	Total
Total livebirths	**106,187**	**104,936**	**104,040**	**104,908**	**105,226**	**525,297**
Total NTD livebirths	**33**	**37**	**25**	**22**	**21**	**138**
Spina bifida livebirths	25	27	20	16	16	104
Anencephaly livebirths	2	6	2	4	4	18
Encephalocoele livebirths	6	4	3	2	1	16
Total stillbirths	**753**	**716**	**701**	**688**	**746**	**3604**
Total NTD stillbirths	**13**	**12**	**15**	**17**	**18**	**75**
Spina bifida stillbirths	7	5	7	9	11	39
Anencephaly stillbirths	5	4	6	7	3	25
Encephalocoele stillbirths	1	3	2	1	4	11
Total terminations (WA/SA only)*	**13,883**	**13,909**	**13,950**	**13,496**	**13,021**	**68,259**
Total NTD terminations	**107**	**103**	**98**	**93**	**86**	**487**
Spina bifida terminations	46	45	38	35	32	196
Anencephaly terminations	51	47	53	52	49	252
Encephalocoele terminations	10	11	7	6	5	39
Total births	**106,940**	**105,652**	**10,4741**	**105,596**	**105,972**	**528,901**
Total NTD	**153**	**152**	**138**	**132**	**125**	**700**

**No data available from Victoria on total terminations of pregnancy. However, data on terminations of pregnancy for NTD-affected fetuses are included from all three states.*

Table 2. Numbers of total livebirths and livebirths affected by NTD 1999-2003, New Zealand, and numbers of total stillbirths and stillbirths affected by NTD 1999-2000, New Zealand.

	1999	2000	2001	2002	2003	Total
Total livebirths	**57,310**	**56,602**	**55,798**	**54,020**	**56,134**	**279,864**
Total NTD livebirths	**30**	**31**	**14**	**18**	**11**	**104**
Spina bifida livebirths	25	26	12	12	8	83
Anencephaly livebirths	1	4	0	3	1	9
Encephalocoele livebirths	4	1	2	3	2	12
Total stillbirths	**386**	**349**	**325**	**354**	**346**	**1760**
Total NTD stillbirths	**8**	**7**	***N/A**	***N/A**	***N/A**	
Spina bifida stillbirths	7	1	N/A	N/A	N/A	
Anencephaly stillbirths	1	6	N/A	N/A	N/A	
Encephalocoele stillbirths	0	0	N/A	N/A	N/A	
Total terminations**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	
Total NTD terminations**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	
Spina bifida terminations	N/A	N/A	N/A	N/A	N/A	
Anencephaly terminations	N/A	N/A	N/A	N/A	N/A	
Encephalocoele terminations	N/A	N/A	N/A	N/A	N/A	
Total births	**57,696**	**56,951**				
Total NTD	**38**	**38**				

**No data on NTD stillbirths available for 2001-2003.*
***No reliable data on termination of pregnancy for NTD or total terminations*

4. Birth prevalence (or incidence) of NTD is the sum of cases of all NTD (anencephaly, spina bifida, encephalocoele) occurring in livebirths, stillbirths and terminations of pregnancies divided by total births (livebirths plus stillbirths) and expressed as a rate per 1000 total births (livebirths plus stillbirths). Total terminations of pregnancy (ie not just those conducted because of a fetal malformation) are not included in the denominator because they are not routinely counted in all jurisdictions and they are not routinely examined for the presence of NTD.

Birth prevalence in SA, Victoria and WA, and extrapolation to Australia as a whole

5. The prevalence of NTD in the three states (SA, Victoria, WA) for 1999-2003 combined was 1.32 per 1000 total births. 69.6% of all NTD 1999-2003 in the three states (487/700) were terminations of pregnancy.

6. The birth prevalence of anencephaly for 1999-2003 for the three states combined was 0.56 per 1000 total births; for spina bifida it was 0.64 per 1000 and, for encephalocoele, 0.12 per 1000. The rate in livebirths and stillbirths only for the three states was 0.40/1000 births, similar to the rate of 0.5/1000 for all Australian births in 1997-2001 (AIHW 2004).

7. In Australia in 2002, there were 255,095 births, 9049 of which were Indigenous. Assuming the three-state rate of NTD applies to the whole population of Australia, then we would expect 338 cases of NTD a year (67 livebirths, 36 stillbirths and 235 terminations of pregnancy).

Birth prevalence in New Zealand

8. The birth prevalence of NTD in New Zealand for 1999-2000 (the only two years for which we have both livebirth and stillbirth data) was 0.66/1000 births. This does not include any

terminations of pregnancy. It is thought that terminations of pregnancy occur to a similar extent in New Zealand as in Australia (personal communication, Dr Barry Borman, Ministry of Health, New Zealand) and, hence, given the similarity between the birth prevalence in New Zealand (0.66/1000) and Australia (0.4-0.5/1000), we have assumed the same overall prevalence for New Zealand as for Australia in the model below.

Indigenous populations

9. NTD are more common (2.56 per 1000 births 1996-2000) in Indigenous infants in Western Australia and have not decreased with health promotion and voluntary fortification (Bower *et al.* 2004). Below, we have calculated the expected reductions in risk of NTD for Indigenous Australians separately, using the WA data, as no other Australian data were available. However, because NTD rates are similar or slightly lower in Maori compared with non-Maori populations of New Zealand (Borman *et al.* 1993), we have not performed separate calculations for Maori and non-Maori populations.

1.2 A synopsis of the range of dose-response models published in the scientific literature that associate folic acid intake or haematological folate status with changes in NTD risk. Comment on their rigour and appropriateness for application to the Australian and New Zealand context.

10. In this report, the term 'folic acid" refers to the form of the vitamin in supplements and added to food when it is fortified. The term "folate" is used to reflect any form of vitamin and includes folic acid and all the forms of the vitamin found naturally in food.

11. Many studies of the association of NTD and folate have used periconceptional folic acid supplement use as the exposure (Smithells *et al.* 1980; Laurence *et al.* 1981; Mulinare *et al.* 1988; Mills *et al.* 1989; Milunsky *et al.* 1989; Vergel *et al.* 1990; MRC Vitamin Study Research Group 1991; Bower *et al.* 1992; Czeizel *et al.* 1992; Kirke *et al.* 1992; Werler *et al.* 1993; Shaw *et al.* 1995; Berry *et al.* 1999; Bower *et al.* 2004) some have attempted to quantify the intake of folate from diet (Bower *et al.* 1989; Milunsky *et al.* 1989; Werler *et al.* 1993; Friel *et al.* 1995; Shaw *et al.* 1995; Bower *et al.* 2004) and one has used haematological measures of folate status in early pregnancy (Kirke *et al.* 1993; Daly *et al.* 1995). Not all studies have examined the data for a dose-response relationship of risk of NTD with differing levels of folate. Those that have reported a dose-response analysis are summarised below.

Daly LE, Kirke PN, Molloy A, Weir DG, Scott JM. Folate levels and neural tube defects. JAMA 1995;274:1698-1702.

12. In this study, blood was collected and stored from a cohort of women in early pregnancy in Ireland (Kirke *et al.* 1993) and the pregnancies followed to identify those resulting in a NTD. A nested case-control study was then conducted, with unmatched controls being selected. Blood samples for cases (n=84) and controls (n=266) were retrieved and red cell folate and serum folate were measured. A dose-response effect was found for both serum folate and red cell folate, with decreasing risks of NTD with increasing levels of folate. Using these data, they calculated the reduction in NTD that would be expected under two prevention strategies: targeting high risk individuals and targeting the whole population.

Wald N. Quantifying the effect of folic acid. Lancet 2001;358:2069-2073.

13. Wald and colleagues used data from the Daly *et al* study (Daly *et al.* 1995), in conjunction with data from trials on the association of folic acid supplement intake and serum folate, and they corrected for regression dilution bias. They used the data from the trials, which reported the effect on serum folate of specified doses of folate up to 1 mg/day. For every 100 μg/day rise in folate intake, serum folate increased by about 2.5 μg/L. Wald *et al* noted that a similar analysis could be done using red cell folate, but no data were available for the regression dilution correction factor for red cell folate. They generated a table estimating the preventive effect of

specified increases in intake of folic acid for given baseline serum folate levels. Wald *et al* provided evidence of the validity of their model by direct observation from three independent sources: the MRC trial, a meta-analysis of case control studies and the US fortification program (Wald 2001; Wald *et al.* 2001).

Moore LL, Bradlee ML, Singer MR, Rothman KJ, Milunsky A. Folate intake and the risk of neural tube defects: an estimation of dose-response. Epidemiology 2003;14:200-205.

14. Moore and colleagues estimated a dose-response based on self-report in early pregnancy of folic acid supplement use and dietary intake of folate (for most women this was before they knew that their fetus had a NTD), using additional data from the study originally published by Milunsky et al (Milunsky *et al.* 1989). Decreasing risk of NTD was observed for increasing folate intake (supplements, diet and both).

Other studies

15. Of the studies using folic acid supplements as the exposure measure, most have either compared use with no use of periconceptional supplements, or have quantified intake based on the timing or frequency of use. Two studies (Shaw *et al.* 1995; Werler *et al.* 1993) presented risk of NTD by dose of daily folic acid from supplements. Several studies have reported risk of NTD by levels of dietary intake of folate, often expressed as quantiles (Bower *et al.* 1989; Werler *et al.* 1993; Friel *et al.* 1995; Shaw *et al.* 1995; Bower *et al.* 2004).These are all case control studies and all relied on self-report of supplement use and dietary intake to estimate folate intake. All found a reduction in risk with increased intake of folate.

Summary

16. All studies where a dose-response effect of folic acid was estimated have shown a reduced risk of NTD with increased levels of folate. We consider that the most reliable data come from measures of blood levels of folate, rather than self-report of supplement use or diet. Blood levels are not subject to recall or reporting bias. Serum (or red cell folate) is a better measure of folate status as it is a biological marker that is closer to the developing embryo. Measures of folate intake do not take into account variation in digestion and absorption, whereas blood measures do. Thus, we consider the best available data to be those of Daly *et* al (Daly *et al.* 1995) and the best model to be the one described by Wald et al (Wald *et al.* 2001), which incorporates the Daly study (Daly *et al.* 1995), uses serum folate levels as the measure of folate status, attempts to account for regression dilution bias and has been shown to have external validity.

1.3 A description of the suitability and quality of the available Australian and/or New Zealand input data for folic acid intake (including from supplements) or folate status as relevant to insert into these models.

Sources of input data - serum folate levels in the target population (women of childbearing age)

17. The data we used were from the 1989 Perth Risk Factor Prevalence Cohort (PRFPC) that was re-surveyed in 1995/6, 1999 and 2001 (Siobhan Hickling - personal communication). In this cohort, blood was taken from a random sample of men and women living in Perth in 1989, using the Electoral Roll as the sampling frame. All data were log-normally distributed with geometric means and medians approximately similar. There were large changes in serum folate levels between 1995 and 1999 but not from 1999 to 2001. Because of this and because there was some sample attrition in 2001 and the same people were eligible for inclusion in all three time periods, just the 1999 data were used. There were 93 women aged 30-45 years not taking

folic acid supplements and 23 taking supplements, with serum folate geometric means of 7.9 and 12.6 (ng/ml) respectively. These values were used in the calculations below.

18. Published data on blood folate levels in the target population in Australia and New Zealand are limited. A study from WA (Bower *et al.* 1997) reported serum and red cell folate in groups of women attending antenatal clinics in 1992, 1993, 1994 and 1995, all prior to voluntary fortification of food with folate. For women taking folic acid supplements in these four surveys, the median serum folate level ranged between 7.9 and 18 ng/ml. For women not taking supplements, the range of median serum folate levels was 5.2-8.9 ng/ml. Data from a University of Otago (New Zealand) report for a random sample of Dunedin women (18% were taking folic acid supplements three times a week or more) show a median serum folate of 5.9ng/ml (Ferguson *et al.* 1999). A further study from Dunedin in 2000, of volunteer women aged 18-40 years and not taking folic acid supplements, found plasma folate geometric means ranging from 7.9 ng/ml to 9.3 ng/ml (Norsworthy *et al.* 2004). In two studies of male and female volunteers not taking supplements in Dunedin in 1999, the median serum folate was found to be 7.9ng/nl (18nmol/L) (Venn *et al.* 2002; Venn *et al.* 2002). Thus, the levels found in these studies are similar to those in the. PRFPCC.
19. There are obvious limitations to all these data. They are not current and hence may not reflect the current levels of voluntary fortification of food with folate or current use of folic acid supplements. Further, they are not representative of all relevant segments of the target population (only some states or regions, not necessarily random samples, include male subjects, and do not include some important subsets of the population, for example Indigenous women).

1.4 *Providing the available input data are of suitable quality and appropriateness, employ the most appropriate dose-response model to predict the reduction in the number of NTD-affected pregnancies (or if possible, more precisely as NTD births, and NTD-related terminations), according to incremental levels of additional folic acid intakes up to 1 mg/day. If a haematological variable was selected for your model, also describe the dose response relationship between folic acid intake and that variable.*

20. Although the input data on serum folate are not ideal, we believe they are satisfactory for use in the model as a guide to estimating the reduction in NTD possible with increasing intake of folate in Australia and New Zealand.

21. The overall value for the rate in Australia (1.3/1000) fitted well on the model used by Wald et al in their Figure 2 for a serum folate of 7.9 ng/ml.

22. Assumptions made in the estimation of prevented NTD were:
    - The total annual population at risk was 255095 in Australia and 54373 in New Zealand (numbers of births in 2002);
    - The annual number of NTDs in Australia was 338;
    - There were 9049 Indigenous Australian mothers at risk with a rate of NTD of 2.56 per 1000);
    - The rate of NTD in New Zealand was the same as in Australia;
    - The dose-response relationship derived by Wald *et al* was appropriate (it is the only reliable one available); and
    - 36% of the total population at risk took folate supplements in early pregnancy – this assumption was based firstly on surveys indicating between 29-45% uptake (Allen *et al.* 2000; Chan *et al.* 2001; Maats *et al.* 2002; Bower *et al.* 2004)* and an iterative process of

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* In a presentation at the recent Australian Birth Defects Society Annual Scientific Meeting in Melbourne (28 April 2005), it was reported that 36% of Victorian women (data collected in Victorian Survey of Recent Mothers 2000) and 46% of NSW women (collected in the NSW Child Health Survey 2001) took folic acid supplements

using the ratio of serum folate in supplement users to non-users from the RFPS to predict the NTD rate ratio from Wald et al's study and then to average to the overall current rate.

23. Given these assumptions, the fall-off in rates of NTDs and the corresponding prevented numbers of NTD are as follows:

Table 3. Rates and numbers of NTD - prevented in Australia according to incremental levels of additional folic acid intakes up to 1 mg/day.

Mg/day increase in folic acid intake	**Supplemented (N=91,834)**		**Unsupplemented (N=163,261)**	
	Rate/1000 Current rate=1.01	**Prevented NTD**	**Rate/1000** Current rate=1.50	**Prevented NTD**
0.1	0.95	5	1.37	21
0.2	0.90	10	1.26	39
0.3	0.86	14	1.17	53
0.4	0.82	18	1.10	66
0.5	0.78	21	1.03	77
0.6	0.75	24	0.97	86
0.7	0.72	27	0.92	95
0.8	0.69	29	0.87	102
0.9	0.67	32	0.83	109
1.0	0.64	34	0.80	115

Table 3a. Rates and numbers of NTD - prevented in Indigenous Australians according to incremental levels of additional folic acid intakes up to 1 mg/day.

Mg/day increase in folic acid intake	**Indigenous mothers (N=9,049)**	
	Rate/1000 Current rate=2.56	**Prevented NTD**
0.1	2.12	4
0.2	1.82	7
0.3	1.60	9
0.4	1.43	10
0.5	1.30	11
0.6	1.19	12
0.7	1.10	13
0.8	1.03	14
0.9	0.96	14
1.0	0.90	15

24. Table 3 indicates, for example, that an increase in folate intake of 0.2mg/day would prevent 10 NTD in the infants of supplemented mothers and 39 NTD in the infants of unsupplemented mothers, a total of 49 cases of NTD prevented each year. As 69.6% of cases of NTD in Australia occur in terminations of pregnancy, at this level of increase in daily folate, 34 terminations of pregnancy with NTD would be avoided and 15 births would be spared from having a NTD. These estimates include Indigenous infants.

25. However, we have also separately shown the effects for Indigenous infants in Table 3a. All were assumed to be unsupplemented. An increase of 0.2mg folate a day would result in the prevention of NTD in 7 Indigenous infants in Australia each year.

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in the periconceptional period. Watson L, Brown S, Davey M-A. Use of periconceptional folic acid supplementation in Victoria and NSW.

26. For New Zealand, the corresponding figures, but without considering Indigenous mothers separately, are shown in Table 4:

Table 4. Rates and numbers of NTD prevented in New Zealand according to incremental levels of additional folic acid intakes up to 1 mg/day

Mg/day increase in folic acid intake	Supplemented (N=19,574)		Unsupplemented (N=34,799)	
	Rate/1000 Current rate=1.01	Prevented NTD	Rate/1000 Current rate=1.50	Prevented NTD
0.1	0.95	1	1.37	5
0.2	0.90	2	1.26	8
0.3	0.86	3	1.17	11
0.4	0.82	4	1.10	14
0.5	0.78	4	1.03	16
0.6	0.75	5	0.97	18
0.7	0.72	6	0.92	20
0.8	0.69	6	0.87	22
0.9	0.67	7	0.83	23
1.0	0.64	7	0.80	24

27. Table 4 indicates that ten New Zealand infants would be spared a NTD (~7 terminations; 3 births) each year if the intake of folate increased by 0.2mg daily.

1.5 A description of the minimum requirements for input data that would optimise the accuracy of the model. Compare these requirements with the quality of currently available data and make any recommendations as to future input data collections including for purposes of post implementation monitoring.

Measures of folate

28. There is a need to obtain data on serum and red cell folate levels, in conjunction with use of folic acid supplements (and, ideally, estimates of folate intake from natural and voluntarily fortified sources) from sufficiently sized random samples of all segments of the target population (including groups such as indigenous women, rural women, all Australian states, New Zealand) to calculate precise estimates of serum and red cell folate. This would provide current data that could be used to refine the output from the model and, importantly, to provide a baseline assessment of folate status against which to measure the effects of any future interventions to increase folate intake.

Neural tube defects

29. We believe the current data on NTD from SA, WA and Victoria are complete and accurate and a satisfactory representation of national rates. However, improved data, particularly with respect to terminations of pregnancy for all states and New Zealand are preferable.

30. As the above information becomes available, the output from the model can be refined to give more accurate estimates of the prevention of NTD in Australia and New Zealand.

Acknowledgements

We are grateful to:

- The staff of the South Australian Birth Defects Register, the Victorian Birth Defects

Register, the Western Australian Birth Defects Registry, WA Department of Health and Dr Barry Borman from the Ministry of Health, New Zealand for supplying data on NTD and births; and

- Ms Siobhan Hickling for supplying data on serum folate levels in samples of women of childbearing age.

- Dr Peter O'Leary, Dr Liz Geelhoed and the staff of the Genomics Directorate, WA Department of Health.

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