Benefits and Risks of Fortifying Flour with Folic Acid to Reduce the Risk of Neural Tube Defects

The SBU report is based on a systematic and critical review of the scientific literature. It is one of a series of scientific reports published by SBU (The Swedish Council on Technology Assessment in Health Care).

The Summary and Conclusions of the report, presented in this booklet, have been approved by the SBU Board of Directors and the Scientific Advisory Committee.

Benefits and Risks of Fortifying Flour with Folic Acid

to Reduce the Risk of Neural Tube Defects

A Systematic Review

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Summary and Conclusions of the SBU Report:

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A Systematic Review

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SBU's Conclusions

The primary objective of the project was to systematically examine the scientific evidence for the benefits and risks of fortifying flour with folic acid. Benefits refer to the possibility that the incidence of neural tube defects (NTDs) is lower with fortification than without fortification. Risks refer to the possibility that a higher intake of folic acid increases the likelihood of twin pregnancy. Other possible effects of fortification were not included in the examination.

The main conclusion of the Swedish Council on Technology Assessment in Health Care is that mandatory fortification of flour with folic acid cannot be unequivocally recommended based on the scientific evidence in this report.

- ❑ An overall assessment indicates that fortification reduces the incidence of NTDs (Evidence Grade 2, moderately strong scientific evidence).

Due to uncertainty about the extent to which pregnancies that are terminated due to diagnosed NTDs are under-reported in both Sweden and countries from which the results of fortification are available, promising how much NTDs can decrease in Sweden is not deemed reasonable.

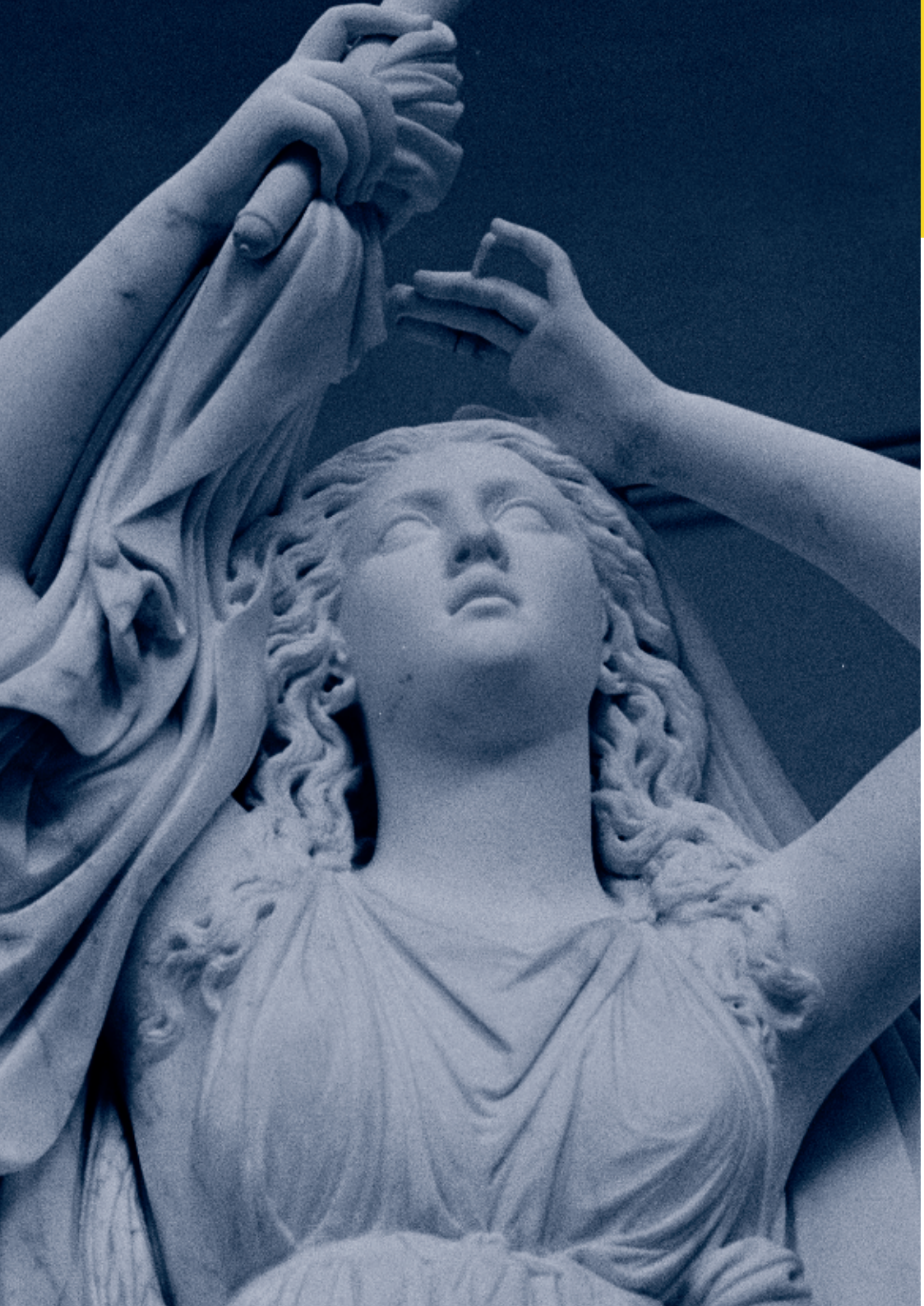
- ❑ The results concerning the association between folic acid intake and the risk of twin pregnancy are conflicting (contradictory scientific evidence).

The results that have been presented on the effects of fortifying flour do not indicate that the incidence of twin births would increase. However, data from randomised controlled trials suggest a possible increase. If so, larger doses of folic acid would be involved than have been of interest for fortification so far. The results of a large prospective cohort study, which administered the same dose as two of the controlled trials and controlled well for potential sources of error, do not support the hypothesis that dietary supplements with folic acid increase the risk of twin birth. The results of five observational studies, four of which were based on self-reported intake of tablets containing folic acid and one of which concerned dietary intake of folate, are conflicting.

Folates play an important role in cell production and may theoretically be expected to stimulate growth of existing tumours, as well as possibly accelerate the transformation of precancerous stages to active malignancy. Some animal experimental studies support that hypothesis, and a few studies suggest an association between high folate levels and colorectal cancer. Addressing such questions was not the objective of a systematic literature search for this report.

Mandatory fortification of flour with folic acid (140–160 micrograms per 100 grams) in Sweden would probably reduce the number of NTD pregnancies. However, it is not possible to determine with any degree of assurance how large the decrease would be. The main reason is uncertainty about the number of pregnancies in Sweden and elsewhere that are currently terminated with the indication of NTDs. Assuming for the sake of argument that the reduction would be 25%, foetuses with NTDs would decrease from 100 to 75, late terminations would decrease from 80 to 56, and newborns with NTDs would decrease from 20–25 to 15–20.

conclusions



SBU's Summary

Neural Tube Defects

The neural tube is formed during the first few weeks after conception, early in the development of the central nervous system. During this period, the woman is usually unaware that she is pregnant. Folate, a B vitamin, plays an important role in the normal development of the neural tube. Low levels of folate in serum and erythrocytes (red blood cells) increase the risk of NTDs.

The most common NTD is spina bifida, which usually results in significant functional disabilities, ie, loss of control of the bladder and bowel and paralysis of the legs.

Dietary studies suggest that only a small percentage of Swedish women of childbearing age have a daily folate intake that meets the recommendations for pregnant women.

The recommendation in many countries, including Sweden, is that women of childbearing age increase their folate intake – by either dietary modification or vitamin supplements – as a preventive measure. Some countries, such as the United States and Canada, accompany the recommendation with mandatory fortification of flour or breakfast cereals by 140–160 micrograms of folic acid per 100 grams. Both the United States and Canada also recommend the continuance of folic acid intake in tablet form, usually 400 micrograms per day, before and during pregnancy.

A certain, largely unknown, percentage of all foetuses with NTDs are aborted spontaneously at an early stage. Nowadays the majority of NTDs are subsequently detected during the ultrasound examination offered in the 16th–17th week of pregnancy. NTD pregnancies are estimated to have remained relatively constant since the 1970s at about 10 per 10 000. Before the introduc-

tion of ultrasound diagnosis, there were few terminations with this indication. At present, 20–25 newborns (about 2 per 10 000) have NTDs every year. Other pregnancies are terminated.

Incidence of NTDs

The incidence of NTDs in foetuses varies among countries and regions due to both genetic and environmental differences. The incidence in Sweden has been estimated at 10–15 cases of NTDs per 10 000 pregnancies. The figure has probably remained unchanged since the 1970s.

The incidence of NTDs in newborns has decreased steadily since the 1970s. About 100 000 children are born in Sweden every year. Currently, 20–25 have NTDs, ie, the incidence in newborns is about one fourth of the incidence in foetuses.

The main reason for this improvement is our greater ability to detect foetal injury with prenatal ultrasound examinations and to terminate the pregnancy if the parents so decide. About 80 terminations are carried out each year after the 16th week due to NTDs.

According to one survey, the incidence of newborns with NTDs in 2000 was 13.6 per 10 000 in the UK and Ireland, as opposed to 7–9 per 10 000 in other parts of Europe. The same source reported 3–4 cases in Finland and fewer than 2 cases per 10 000 in Norway. The data indicate that Sweden, like its Scandinavian neighbours, has a relatively low incidence of newborns with NTDs.

NTDs and Folates – Folic Acid

Basic research has shown that folate, which is found in green vegetables and certain other foods, most likely plays a central role in the formation of the neural tube during the first few weeks of pregnancy. A high intake of folate, as well as folic acid (its synthetic variant), before and at the time of conception has been shown to generally protect against the development of NTDs, including women who earlier had a child with NTDs. Studies have shown that low folate levels in serum (reflecting current intake) and erythrocytes (reflecting longer-term intake) are a risk factor for NTDs.

Intake of Folate and Folate Status in Sweden

Dietary studies in Sweden indicate that about one third of all women have a folate intake that is lower than the average daily requirement of 200 micrograms. Only a marginal percentage of women of childbearing age have a diet that provides 400 micrograms per day, ie, the intake recommended during pregnancy to prevent NTDs. Our knowledge about folate status in the blood of the Swedish population is incomplete.

Information About the Need to Increase Folate Intake during Pregnancy

Considering that the incidence of NTD pregnancies has remained unchanged since the 1970s, efforts to inform women of childbearing age that they should increase their intake of natural folates and folic acid before pregnancy have clearly been inadequate. There are a couple of probable reasons. Knowledge about the importance of taking a sufficient quantity of folate varies among women of childbearing age, and far from all pregnancies are planned.

NTDs and Fortification of Flour

In the late 1990s, the United States, Canada, Chile and other countries adopted mandatory fortification of flour or breakfast cereals with 140–160 micrograms of folic acid per 100 grams. Published follow-up studies show that the incidence of NTD pregnancies subsequently decreased.

The results of several studies concerning the association between fortification of flour with folic acid and NTDs are considered, when taken individually, to have limited value as evidence that mandatory fortification reduces the risk of NTDs. However, the results suggest without exception that the risk of NTDs after fortification (voluntary and/or mandatory) and recommendations of dietary supplements is lower than before these measures were adopted. The association between reduced incidence of NTDs and increased intake of folic acid is confirmed by the observation that the percentage of women of childbearing age with low concentrations of folate in erythrocytes has decreased substantially during the time periods under comparison. Therefore, the overall evidence is deemed to be moderately strong.

Despite fortification, certain groups of women do not have an intake that protects against NTDs. For that reason, the United States and Canada still recommend a daily supplement of 400 micrograms of folic acid before and during pregnancy in addition to mandatory fortification.

Side-effects of High Folate Intake

Mandatory fortification of food assumes that the intake of folic acid is dependent on dietary habits. People who eat a lot of bread and fortified pasta will have a high intake, while certain subgroups – such as children and adolescents who consume large quantities of bread – are likely to exceed the maximum Swedish nutritional recommendation. Following are the side-effects most commonly discussed in the literature.

Masking of Symptoms of Vitamin B_{12} Deficiency

High doses of folic acid can correct the type of anaemia that is an early sign of vitamin B_{12} deficiency. A possible risk of fortification is that B_{12} deficiency will be discovered later, thereby increasing the risk of neurological damage. Studies that have followed up on fortification have not confirmed these concerns. Available data indicate that the dose provided by the diet after fortification is insufficient to correct anaemia.

Increased Incidence of Twin Births

Results concerning the association between intake of folic acid and the risk of twin birth are conflicting. The results that have been reported on the effects of fortification of flour do not indicate that the risk of twin birth would increase. However, results based on the analysis of data from randomised controlled trials suggest a possible increase. If so, larger doses of folic acid would be involved than have been of interest for fortification so far. The results of a large prospective cohort study, which administered the same dose as two of the controlled trials and controlled well for potential sources of error, do not support the hypothesis that dietary supplements with folic acid would increase the risk of twin birth. The results of five observational studies, four of which were based on self-reported intake of tablets containing folic acid and one of which concerned dietary intake of folate, are conflicting.

Increased Incidence of Cancer

The association between vitamin B_{12} and cancer is currently the subject of intense research. It is biologically plausible that folic acid stimulates the growth of existing tumours, and possibly accelerates the transformation of precancerous stages to active malignancy as well. Some animal experimental studies support this hypothesis, and a few studies suggest an association between high folate levels and colorectal cancer. A marginal increase in colorectal, prostate and breast cancer – possibly after long latency periods – could essentially eliminate the value of a lower incidence of NTDs.

Estimated Effect of Fortification on the Incidence of NTDs in Sweden

The effect of fortification cannot be calculated exactly. However, based on data from the United States and Canada, the percentage of NTD pregnancies can reasonably be expected to decrease. Nevertheless, it is impossible to predict how large the decrease might be. The main reason is uncertainty about the number of pregnancies in Sweden and elsewhere that are currently terminated with the indication of NTDs. Assuming for the sake of argument that the reduction would be 25%, foetuses with NTDs would decrease from 100 to 75, late terminations would decrease from 80 to 56, and newborns with NTDs would decrease from 20–25 to 15–20.

Ethical Aspects

As is evident from the above conclusions, fortification of foods with folic acid confronts society with a basic ethical dilemma. The ability to prevent NTDs in a limited number of foetuses every year must be weighed against difficulties in making assessments and the unquantifiable risk of an increased incidence of some relatively common forms of cancer. At present, it is impossible to determine on strictly scientific grounds whether exposing the entire Swedish population to an increased intake of folic acid by mandatory fortification of flour would be justified.

Need for Research and Development

The primary objective of the report of the Swedish Council on Technology Assessment in Health Care was to examine the scientific evidence pointing to the benefits (smaller likelihood of NTDs) and risks (increased incidence of twin pregnancies) for women of childbearing age of fortifying flour with folic acid. In order to correctly assess the long-term effects of mandatory fortification, a complete scientific analysis of all other scientifically documented advantages and disadvantages is urgent. For example, low folate intake and/or deficiency have been reported to increase the risk of miscarriage, cardiovascular disease and some forms of cancer. Meanwhile, a few studies have associated high folate intake with colorectal cancer. The impact of folic acid on the incidence of foetal abnormalities other than NTDs should also be the subject of a systematic examination.

The analysis showed that knowledge about folate intake and folate levels in serum and erythrocytes – of both the Swedish population in general and pregnant women in particular – is incomplete. National representative studies are lacking on folate intake and levels in women of childbearing age. Knowledge is inadequate concerning the extent to which current recommendations that women consume a folate-rich diet – as well as supplements before and during pregnancy – are followed. These gaps need to be addressed.

Independent of any decision about fortification, administrative routines that ensure registration of all NTD pregnancies – including terminations with this indication – are called for. The present voluntary reporting system is inadequate.

Any decision to introduce fortification should be coupled with a research programme.

Because flour is a staple food, mandatory fortification would expose the entire population to folic acid and generally raise folate levels in the blood. People who eat a lot of bread and fortified pasta would have a high intake, while certain sub-groups – such as children and adolescents who consume large quantities of bread – would be likely to exceed the maximum Swedish nutritional recommendation. The extent and magnitude of the risk of such exposure cannot be scientifically assessed at present.

The ethical dilemma can be formulated as follows. Is it justifiable to try to prevent NTDs in a limited number of foetuses and newborns while exposing the entire population to an increased risk of serious disease that is both amorphous and difficult to quantify?

The conclusion of the Swedish Council on Technology Assessment in Health Care is that the question cannot be answered from a strictly scientific point of view on the basis of the present report.

Thus, policymakers face two primary options (not necessarily in order of feasibility or desirability).

1. Use mandatory fortification to focus on reducing the incidence of NTDs. In other words, prioritise women of childbearing age and disregard the difficulty of evaluating the possibility of an increased risk of cancer in the general population and twin pregnancy. Mandatory fortification would not eliminate the recommendation to take a vitamin supplement before and during pregnancy.

2. Adopt a wait-and-see attitude concerning fortification but take an active approach to following up the beneficial and harmful effects of mandatory fortification. Systematically analyse other possible beneficial effects, such as cardiovascular, of fortification. Systematically and critically examine the literature on the association between folates, folate levels and cancer. Apply the precautionary principle until there is greater clarity about that association. Such a strategy would presumably accept that the incidence of NTD pregnancies remains unchanged.

Refraining from mandatory fortification does not imply that society should stop trying to reduce the incidence of NTDs. Choosing that option requires an active, sustained informational effort that emphasises the importance of taking folic acid supplements before and during pregnancy. The option is based on the belief that, despite the experience of prevous attempts, a determined effort can increase folate levels in women of childbearing age.

Recommendations and information about folic acid supplements during pregnancy can be combined with voluntary for tification of flour. Such fortification can be supported by special measures that ensure that both fortified and unfortified flour are available to consumers. Women of childbearing age, the primary target group, would be encouraged to use fortified flour and products.

The main conclusion of the Swedish Council on Technology Assessment in Health Care is that mandatory fortification of flour with folic acid cannot be unequivocally recom mended based on the scientific evidence in this report.

Fact Box 1 Study Quality and Relevance, Evidence Grade.

Study quality and relevance refers to the scientific quality of a particular study and its ability to reliably address a specific question.

Evidence Grade refers to the total scientific evidence for a conclusion.

Evidence Grade 1 – Strong Scientific Evidence
A conclusion assigned Evidence Grade 1 is supported by at least two studies with high study quality and relevance among the total scientific evidence. If some studies are at variance with the conclusion, the Evidence Grade may be lower.

Evidence Grade 2 – Moderately Strong Scientific Evidence
A conclusion assigned Evidence Grade 2 is supported by at least one study with high study quality and relevance, as well as two studies with medium study quality and relevance, among the total scientific evidence. If some studies are at variance with the conclusion, the Evidence Grade may be lower.

Evidence Grade 3 – Limited Scientific Evidence
A conclusion assigned Evidence Grade is supported by at least two studies with medium study quality and relevance among the total scientific evidence. If some studies are at variance with the conclusion, the scientific evidence may be insufficient or contradictory.

Insufficient Scientific Evidence
If no studies meet the study quality and relevance criteria, the scientific evidence is rated as insufficient to draw any conclusions.

Contradictory Scientific Evidence
If different studies are characterized by equal study quality and relevance but generate conflicting results, the scientific evidence is rated as contradictory and no conclusions can be drawn.

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Below is a brief summary of the mission assigned to SBU by the Swedish Government:

- SBU shall assess healthcare methods by systematically and critically reviewing the underlying scientific evidence.
- SBU shall assess new methods as well as those that are already part of established clinical practice.
- SBU's assessments shall include medical, ethical, social and economic aspects, as well as a description of the potential impact of disseminating the assessed health technologies in clinical practice.
- SBU shall compile, present and disseminate its assessment results such that all parties concerned have the opportunity to take part of them.
- SBU shall conduct informational and educational efforts to promote the application of its assessments to the rational use of available resources in clinical practice, including dental care.
- SBU shall contribute to the development of international co-operation in the field of health technology assessment and serve as a national knowledge centre for the assessment of health technologies.