Livsmedelsverket

L – 2022 nr 11

Risk and benefit assessment of whole grain intake in the Swedish adult population

Denna titel kan laddas ner från: Livsmedelsverkets publikationer

Författare:
Daniel Edgar, Salomon Sand, Åsa Svanström, Hanna Eneroth, Bettina Julin och Helena Bjermo

Rekommenderad citering:
Livsmedelsverket. Edgar D, Sand S, Svanström Å, Eneroth H, Julin B och Bjermo H. 2022. L 2022 nr 11: Risk and benefit assessment of whole grain intake in the Swedish adult population. Livsmedelsverkets rapportserie. Uppsala.

L 2022 nr 11
ISSN 1104-7089
Omslag: Livsmedelsverket

Foreword

The Swedish Food Agency has food-based dietary guidelines that advise the population to choose whole grains instead of refined grains to decrease the incidence of several diet-related diseases. Compared with refined grains, however, whole grain products contain more cadmium and certain other undesirable substances such as mycotoxins. In order to be able to answer whether the current recommendation on increased whole grain consumption is scientifically motivated based on existing data on both risks and benefits, a risk and benefit assessment of whole grain products is needed.

This report will assist risk managers at the Swedish Food Agency to take scientifically based decisions on this issue.

Responsible for the content of the report are Daniel Edgar, Salomon Sand, Åsa Svanström, Bettina Julin, Hanna Eneroth and Helena Bjermo at the Risk and benefit assessment department of the Swedish Food Agency. Information specialist at the Swedish Food Agency, Mikaela Bachmann Weiss, assisted the literature searches. The report has been scientifically reviewed by Eva Warensjö Lemming and Mia Kristersson at the Department of Risk and Benefit Assessment of the Swedish Food Agency, Agneta Åkesson and Daniel Borch Ibsen at the unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet as well as Morten Poulsen at the National Food Institute, Technical University of Denmark.

October 2022

Per Bergman
Head of department

Department of Risk and Benefit Assessment

Swedish Food Agency

Table of contents

Abbreviations and glossary

B2M	Beta-2 microglobulin
BMD	Bench Mark Dose
BMDL	Bench Mark Dose Level
Cd	Cadmium
CI	Confidence interval
DON	Deoxynivalenol
DTU	Technical University of Denmark
EFSA	European Food Safety Authority
EnB	Enniatin B
FFQ	Food frequency questionnaire
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HbA1c	Hemoglobin A1c
IARC	International Agency for Research on Cancer
JECFA	Joint FAO/WHO Expert Committee on Food Additives
MI	Myocardial infarction
MOE	Margin of exposure
N	Number
OTA	Ochratoxin A
RCT	Randomised controlled trial
RR	Relative risk
Sd	Standard deviation
SCFA	Short-chain fatty acids
TDI	Tolerable daily intake
TWI	Tolerable weekly intake
USDA	United States Department of Agriculture
WHO	World Health Organisation

Summary

The Swedish Food Agency has food-based dietary guidelines that advises the population to choose whole grains instead of refined grains because the former contains for example more fibre, vitamins, minerals, and phytochemicals that are positive for our health. At the same time, whole grains contain varying levels of undesirable substances like cadmium or mycotoxins that can have a negative effect on health. The aim of the present assessment was to evaluate the risk-benefit of increased whole grain consumption in the Swedish adult population to conclude if the net effect is positive or negative.

The overall results from observational data suggest an inverse association between whole grain consumption and mortality (all-cause, cardiovascular-related, stroke-related, and total cancer-related) as well as incidences of coronary heart disease, type 2 diabetes, and colorectal cancer. Randomized controlled trials show significantly lower body weight when comparing higher with lower intakes of whole grains. Among considered toxicological and microbiological risks associated with whole grain consumption, an increased cadmium exposure was determined to be most relevant.

There is limited knowledge on the association between whole grain intake from different types of whole grains and health outcomes. This is because most studies do not have this level of detail in their assessment of whole grain or in their analysis. However, there is some data available where whole grain rye and oats (but not wheat) have been associated with lower risk of myocardial infarction. Furthermore, whole grain rye, wheat, and oats have been associated with a lower risk of type 2 diabetes. In data analysed at the Swedish Food Agency, rye and oats generally contained lower levels of cadmium than wheat, both in the whole grain and the refined fraction.

To quantify the risk versus the benefit, three scenarios of increased whole grain consumption were evaluated with respect to risks associated with an increased cadmium intake versus the lower risk of myocardial infarction. In the scenarios either a) 50 percent, b) 75 percent, or c) 100 percent of consumed cereal products were whole grain products. Across all three scenarios, the reduction in the estimated number of myocardial infarctions was higher than the estimated increase in the number of individuals that exceed EFSA’s critical cadmium level, during one specific year. It was therefore concluded that the benefit of increased whole grain consumption outweigh the associated risk of increased cadmium exposure. In addition, myocardial infarction is a clinical outcome and more severe compared to exceedance of the critical cadmium intake over time, which is a biomarker of early kidney damage.

The net benefit was increased with increased consumption of whole grains up to 100% whole grain product.

Sammanfattning på svenska

Livsmedelsverket har livsmedelsbaserade råd till befolkningen om att välja fullkornsprodukter eftersom dessa innehåller mer hälsofrämjande komponenter såsom fibrer, vitaminer, mineraler och phytokemikalier jämfört med raffinerade spannmålsprodukter. Dock innehåller fullkornsprodukter högre kadmiumhalter och vissa andra oönskade ämnen som till exempel mögelgifter (mykotoxiner) som kan vara skadliga för hälsan. Målet med den här rapporten är att väga risken mot nyttan med att öka fullkornsintaget i den svenska befolkningen.

Sammantaget visar data från observationsstudier att det finns ett omvänt samband mellan fullkornsintag och dödlighet oavsett orsak, dödlighet i hjärt- och kärlsjukdom, stroke respektive cancer samt insjuknande i kranskärlssjukdom, typ 2-diabetes och tjock- och ändtarmscancer. Det vill säga risken för dessa sjukdomsutfall minskar med ökat fullkornsintag. Randomiserade interventionsstudier visar på lägre vikt hos de som äter mer fullkorn. Av studerade toxikologiska och mikrobiologiska risker med fullkorn bedömdes ökad kadmiumexponering vara mest relevant.

De flesta studier är inte detaljerade nog för att kunna användas till att bedöma sambandet mellan olika typer av fullkorn och hälsotillstånd. Ett högre fullkornsintag från råg, havre, men inte vete, har kopplats till lägre risk för hjärtinfarkt medan ett högre fullkornsintag av råg, vete och havre har kopplats till en lägre risk för typ 2-diabetes. Baserat på livsmedel analyserade vid Livsmedelsverket hade råg och havre generellt lägre halter av kadmium än vete i både kli- och kärndelen.

För att beräkna risken och nyttan med ökat fullkornsintag undersöktes tre olika scenarier. Ett intag där a) 50 procent, b) 75 procent eller c) 100 procent av alla spannmålsprodukter är fullkornsprodukter analyserades med avseende på risk från ökat kadmiumintag och nyttan med minskad risk för hjärtinfarkt. I alla tre scenarier var antalet individer som skyddades mot hjärtinfarkt högre än antalet individer som översteg Efsas kritiska kadmiumnivå under ett specifikt år. Att drabbas av en hjärtinfarkt värderades även som allvarligare än att överstiga den kritiska kadmiumhalten i urin motsvarande en förändring av en biomarkör som tidig indikation på möjlig njurskada. Det bedömdes därmed att nyttan av ett ökat fullkornsintag var större än risken.

Nettohälsovinsten ökade med ökad konsumtion av fullkorn upp till scenariot med 100% fullkornsprodukter.

Background

Whole grains contain vitamins, minerals, phytochemicals and fibre that are positive for health. At the same time, it contains varying levels of undesirable substances that can have a negative effect on health. Different amounts of undesirable substances can be found in most types of food. A risk-benefit assessment evaluates the potential health effects of consuming a certain type of food, taking both the desirable and the undesirable substances into account. The aim is to evaluate if a certain food or food group has a positive or negative net effect. A risk-benefit assessment typically builds on scenarios of different amounts of certain foods consumed, and how these different consumption patterns affect the total negative or positive health effects.

Through food-based dietary guidelines, the Swedish Food Agency promotes choosing whole grains, to contribute to the decrease of the risk of several diet-related diseases in the population. Whole grain products, however, have higher content of certain contaminants, compared to refined cereal products. To be able to answer whether current guidelines on whole grains are scientifically motivated with regard to both risk and benefit, a risk-benefit assessment of whole grain products is required, as well as subsequent risk-benefit management and communication.

The report choses to focus on adults only. The Swedish Food Agency has separate advice for children regarding whole grain consumption.

Definition of whole grain

Whole grain is defined as the whole kernel of the cereal (the bran, the germ, and the endosperm), Figure 1. The kernel can be ground, crushed or similar, but the components should be included, in their original proportions, for each type of cereal (Mejborn et al., 2008). Grains included in this definition are wheat, including spelt and durum wheat, rye, oats, barley, corn, rice, millet, durra and other types of sorghum.

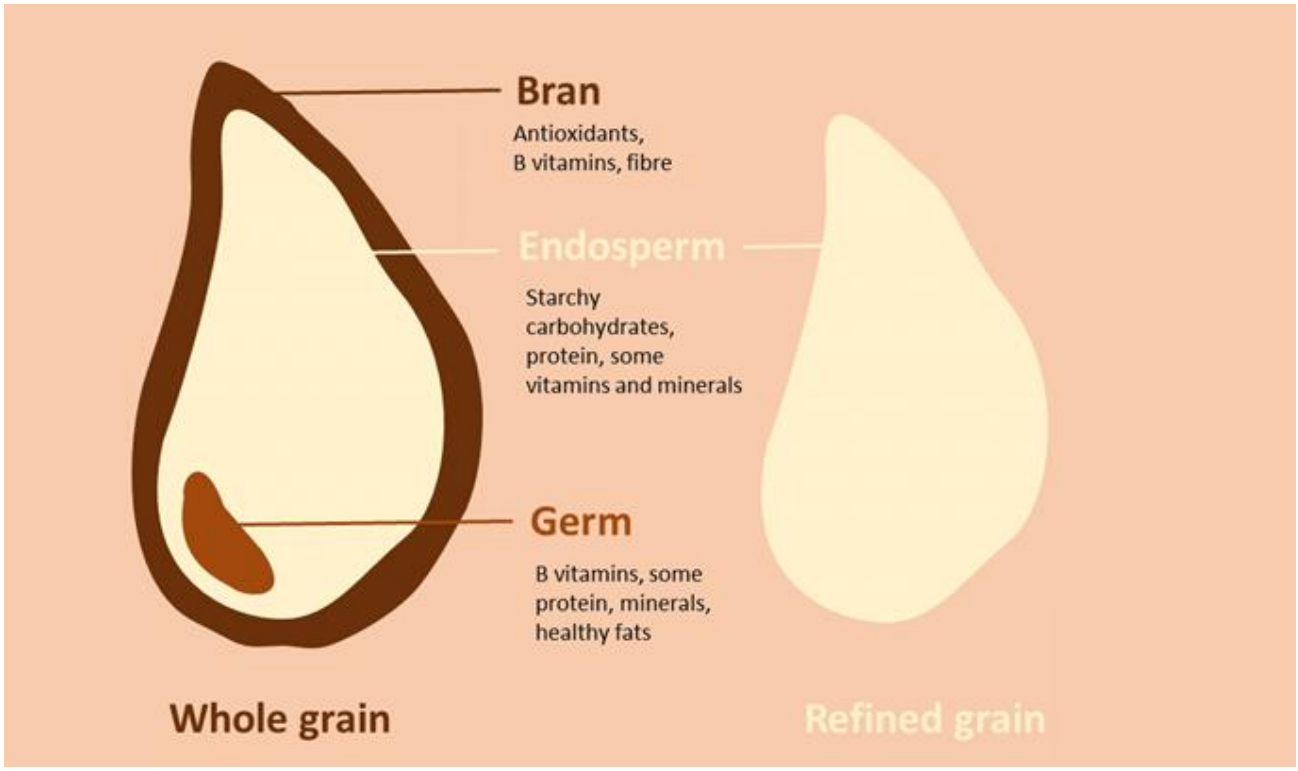

Figure 1. The grain consists of the bran, the germ and the endosperm.

Risk-benefit question/terms of reference

The main objective was to evaluate if the net effect of whole grain consumption is positive or negative. To assess the net effect of whole grain consumption, the beneficial health effects of whole grain consumption at a certain intake need to be evaluated against toxicological and microbiological risks.

As part of the assessment, the Department of Risk and Benefit Assessment at the Swedish Food Agency was asked upon request from the Department of Sustainable Diets to answer the following specific questions:

1. What are the largest health benefits as well as the largest toxicological and microbiological health risks with whole grain consumption?
2. Are there differences in positive or negative health effects from different types of cereals?
3. What health consequences (positive and negative) are expected should the adult population of Sweden increase their current mean whole grain consumption, according to the national dietary survey Riksmaten adult, so that:
    a) 50% of cereal consumption are whole grain products.
    b) 75% of cereal consumption are whole grain products.
    c) 100% of cereal consumption are whole grain products.
4. Is it possible to define an optimal intake of whole grains, i.e. the largest possible positive net health effect?

Methods

Consideration of beneficial effects

The literature on associations between whole grain intake and different outcomes including mortality and non-communicable diseases is extensive. We identified a publication on carbohydrate quality and human health (Reynolds et al., 2019). The publication consists of a series of systematic reviews and meta-analyses published in the Lancet in January 2019. The report by Reynolds et al was commissioned by the World Health Organisation (WHO) to provide a scientific background to update recommendations on carbohydrate intake. Due to the extensiveness and recent publication date of this report, we decided to use the report as the basis of the benefit assessment rather than conducting a separate literature search. Furthermore, the results from Reynolds et al were compared to the results from Helnaes et al, a publication based on a Danish prospective cohort study examining the association between whole grain intake and myocardial infarction (Helnaes et al., 2016). This publication was chosen because it distinguishes between intakes of whole grain products and whole grain. Moreover, the dietary intake patterns and type of whole grain foods consumed are similar in the Danish and Swedish populations (Johnsen et al., 2015, Livsmedelsverket, 2012, DTU Fødevareinstituttet, 2015), especially in a global perspective. Further, the myocardial infarction incidences are comparable between the two countries (Socialstyrelsen, 2018, Hjerteforeningen, 2018). The results of Helnaes et al could therefore be generalised to the Swedish population.

Consideration of adverse effects

To identify potential hazards in whole grains, a first prioritization of toxic compounds for inclusion in the risk-benefit analysis was performed based on results from the 2015 Swedish market basket survey (Livsmedelsverket, 2017b). This market basket survey aimed to assess the exposure of the Swedish population to a broad range of toxic compounds, by directly analysing them in several different food categories.

A risk ranking was conducted based on exposure estimates for 34 compounds using the Risk Thermometer tool (Livsmedelsverket, 2017b). The method behind the Risk Thermometer is mainly based on margin of exposure-related concepts that are typically applied as part of traditional chemical risk characterization. An important difference, however, is that the severity of the critical health effect, used as basis for the assessment, is also considered in a systematic manner, where e.g. cancer is judged as more serious than skin lesions. More details

on this methodology is given in (Livsmedelsverket, 2017b). The comparative assessment applies to a standard person (per capita exposure), and involves assessment of health concerns for the adult or its foetus (when the critical effect relates to the developing organism) (Livsmedelsverket, 2017b). Thus, it represents a screening at population/national level.

The Swedish market basket survey covers many possible contaminants but may not be exhaustive; therefore, a literature search to identify other possible risks was conducted. Searches were performed in PubMed focusing on whole grain in combination with adverse health effects/risks, different toxicities, and diseases (see Appendix 1). This effort did not identify additional chemicals in foods beyond those already considered.

Scenario analysis

Three different scenarios were analysed in which 50%, 75%, and 100% of cereal consumption was whole grain products, respectively. The proportion of whole grain varies across different whole grain products. In order to arrive at an amount of whole grain intake for the benefit part of the calculation, as well as an amount of cadmium in order to estimate the risk we used the following method:

Individual cereal consumption data was taken from the national dietary survey Riksmaten adults 2010–11 (Livsmedelsverket, 2012). The composition of the cereals was estimated by starting with the cereal components in the Swedish market basket survey 2015 (Livsmedelsverket, 2017b) and replacing the refined grain products by matching them with appropriate whole grain substitutes using expert judgement. This way an estimate of the new whole grain consumption and cadmium exposure in the different scenarios was calculated by combining data from products previously analysed at the Swedish Food Agency. This is described in more detail in section Exposure assessment – Cadmium (Table 5).

Assessment of Beneficial effects

Positive health effect identification

A number of studies have been published supporting the beneficial effects of dietary fibre and/or dietary fibre-rich foods such as whole grain cereals on a number of diseases. The overall results from observational data suggest an inverse association between whole grain intake and mortality (all-cause, cardiovascular-related, stroke-related, and total cancer-related) as well as incidences of coronary heart disease, type 2 diabetes, and colorectal cancer (Reynolds et al., 2019). Randomized controlled trials (RCTs) show that a higher intake of whole grains results in lower body weight when compared with a lower whole grain intake (Reynolds et al., 2019).

Whole grain products contribute to dietary fibre and nutrient intake

Whole grain foods contain many components such as dietary fibre, starch, fat, vitamins, minerals, antioxidants, lignans, and phenolic compounds (Slavin, 2003). Most of the components are present mainly in the outermost layer of the grain (Figure 1). Thus, whole grain cereals have a higher content of these compounds compared to refined flours where nutrients are lost in the processing (Mann et al., 2015). For example, refining whole grain wheat may lead to the loss of about 58% of fibre, 83% of magnesium, 79% of zinc, 92% of selenium, 61% of folates and 79% of vitamin E (Fardet, 2010).

Health protective mechanisms of whole grain cereals

The precise mechanisms behind the protective health effects of whole grains are not yet completely understood, due to the huge amount of bioactive compounds present and the potential synergistic effects between them (Fardet, 2010). Insoluble fibre, resistant starch and oligosaccharides are fermented in the gut where they produce short-chain fatty acids (SCFA). SCFA lower the pH-level in the colon and alter blood lipids, improving gut environment and may provide immune protection beyond the gut environment (Slavin, 2003). Whole grains are also rich in antioxidants, which are linked to disease prevention. Additionally, fibre containing foods increase satiety, lower glucose response, improve insulin sensitivity (Reynolds et al., 2019, Slavin, 2003), reduce cholesterolaemia as well as increase transit time and faecal bulking (Fardet, 2010). Mechanisms of whole grain´s beneficial effects can also be hormonal, like zinc, selenium or nicotinic acid, that participate in hormone activation and

synthesis. Some are also linked to gene regulation (flavonoids), cell signalling (polyphenols) and energy metabolism (the B-complex vitamins) (Fardet, 2010).

Different types of whole grain cereals could have different health benefits because they vary in their nutritional compositions. Rye contains the highest amount of dietary fibre of all cereals and also high amounts of lignans (Helnaes et al., 2016). Oats contain more lipids and a high content of beta-glucans, a soluble dietary fibre, as well as several antioxidants. Wheat has a higher content of insoluble fibre compared to rye and oats (Helnaes et al., 2016).

Health claims

The European Commission authorises, after evaluation by EFSA, different health claims provided they are based on scientific evidence. Beta-glucans from oat and barley bran contribute to the maintenance of normal blood cholesterol levels, and the reduction of the blood glucose rise after a meal (EFSA NDA Panel, 2011a, EFSA NDA Panel, 2009). The claim may be used only for food that contains at least 1 g of beta-glucans per quantified portion and should inform the consumer that the beneficial effect is obtained with a daily intake of 3 g of beta-glucans. Another registered health claim is fibre from barley, oat and wheat that contributes to an acceleration of intestinal transit and an increase in faecal bulk (EFSA NDA Panel, 2011b, EFSA NDA Panel, 2010).

Types of whole grains and health protection

Whole grains from different cereals have different nutrient profiles and contain different types and amounts of dietary fibre. Therefore, the health effects may vary depending on type of whole grains. There is however limited evidence of the association between different types of whole grains (Kyro et al., 2018). In an analysis of the Danish Diet, Cancer and Health cohort, assessing type 2 diabetes as the outcome, all individual whole grain cereal types investigated (rye, wheat, oats) were in general associated with a lower risk of type 2 diabetes (Kyro et al., 2018). A Scandinavian nested case-control study, including the above mentioned Danish cohort, assessed the association between whole grain intake and the risk of developing type 2 diabetes using alkylresorcinols which are dietary biomarkers of whole grain wheat and rye intake (Biskup et al., 2016). Total whole grain wheat and rye intake, reflected by alkylresorcinols in plasma, was not associated with a lower risk of type 2 diabetes in this population. In contrast, the proportion of whole grain rye to whole grain wheat intake was inversely associated with type 2 diabetes. This suggests that whole grain intake dominated by rye may be protective against type 2 diabetes (Biskup et al., 2016). Helnaes et al investigated the associations between whole grain species and myocardial infarction. Intake of whole grain rye and oats, respectively, but not wheat, were associated with lower risk of myocardial infarction in men but not women (Helnaes et al., 2016).

Positive health effect characterisation

There are no recommendations specifying the amount of whole grain consumption. The Nordic Nutrition Recommendations 2012 recommend that the intake of dietary fibre should be at least 25–35 g/day (Nordic Council of Ministers, 2014). Whole grain cereals, whole fruit, pulses, and nuts should be the major sources. An intake corresponding to 75 g of whole grains per 10 MJ is considered an appropriate amount. This means about 70 g of whole grains per day for women and about 90 g for men (corresponding to e.g. one portion of oatmeal porridge and one portion of whole grain pasta). The amount of 75 g/10 MJ is suggested in a Danish report, based on the highest intakes in Nordic populations (Mejborn et al., 2008).

Systematic review and meta-analysis used as basis of the present assessment (Reynolds et al., 2019)

Description of methods in Reynolds et al, 2019

The publication by Reynolds et al (Reynolds et al., 2019) was chosen to form the basis of the identification of beneficial effects. Prospective studies investigating health effects of whole grain consumption published through April 2017 were included. The following outcomes were considered: all-cause mortality, coronary heart disease (incidence and mortality), colorectal cancer (incidence), type 2 diabetes (incidence), stroke (incidence and mortality) as well as obesity, overweight and other measures of adiposity. Prospective studies including only participants with specified pre-existing conditions were excluded.

For randomized clinical trials, studies published through February 2018 were included. The following outcomes were considered: adiposity, fasting glucose, fasting insulin, insulin sensitivity, glycated haemoglobin A1c (HbA1c), triglycerides, cholesterol, and blood pressure. Parallel and crossover randomised clinical trials of at least 4 weeks duration that reported on higher intakes compared with lower intakes of the dietary components were included. Eligible trials could include those investigating diets with test foods provided, dietary advice, ad libitum diets, or controlled feeding trials on free living individuals.

The ROBIS assessment tool was used to assess quality and risk-of bias in systematic reviews and meta-analyses. The Newcastle-Ottawa Scale was used to assess risk of bias in prospective studies and sensitivity analysis were performed excluding studies scoring less than 6 (out of 9). Cochrane criteria were used to assess risk of bias in clinical trials. GRADE (Grading of Recommendations Assessment, Development and Evaluation) protocols were used to judge the overall quality of the body of evidence: high, moderate, low or very low.

Evidence based on prospective observational studies

Data from 42 prospective observational studies related to whole grain intake involving just over 39 million person-years were included in the meta-analyses (Reynolds et al., 2019). Evidence from observational studies were graded low or very low except for the association between whole grain intake and colorectal cancer incidence that was graded moderate based on seven studies. All associations between whole grain intake and mortality or disease incidence were inverse, with relative risks (RR) ranging from 0.66 to 0.87. Dose-response curves illustrated associations between whole grain intake and all-cause mortality, coronary heart disease incidence, type 2 diabetes and colorectal cancer, based on prospective cohort data. Data included whole grain intakes from 0 g/day up to 370 g/day in the curve for colorectal cancer, although the veracity of such a high intake could be questioned. Whole grain intake is difficult to assess and the very high whole grain intakes reported from the prospective studies is an indicator of that. In some studies, the distinction between intakes of whole grain and intake of products containing whole grains may not have been clear.

For all outcomes, a lower risk was observed per every 15 g whole grain consumed per day if linearity is assumed. However, the evidence for these outcomes in prospective studies were judged to be ranging from very low to moderate, therefore results of dose-response analysis need to be interpreted with caution. For dietary fibre, results were similar and quality of evidence were generally moderate to high. The driver for associations with total dietary fibre were cereal fibre and the authors discuss the possibility that health effects of whole grains are mainly due to their high fibre content.

Grading of the evidence from observational studies

The authors further discuss that the low grading of evidence in total is a consequence of using GRADE, which requires randomised controlled trials for high grades. Unexplained heterogeneity also reduces overall rating, but may be due to diversity of populations, methods or dietary habits, all which is expected from this type of data. The authors write: "Regarding the associations reported here between dietary fibre and whole grains and a wide range of clinical outcomes, the consistency of findings, the striking dose-response relationships, and the substantial body of mechanistic evidence all contribute to the total body of evidence and increases our confidence of the findings" (Reynolds et al., 2019). The findings are also consistent with previous reviews and meta-analyses for effects of whole grain/dietary fibre intake on health (Aune et al., 2016, Bechthold et al., 2019, Micha et al., 2017, Schwingshackl et al., 2017).

Evidence based on randomized controlled trials (RCT)

Data from 39 randomised trials with 1,772 adult participants were included in the meta-analyses by Reynolds (Reynolds et al., 2019). The following evidence were graded moderate: change in body weight (11 studies), change in total cholesterol (17 studies) and change in systolic blood pressure (8 studies). The evidence for an effect of whole grain intake on HbA1c (a marker of average blood sugar levels in the preceding 6–8 weeks) from three clinical trials was judged to be low. Change in body weight was the only statistically significant effect reported in Reynolds et al. The group with the higher whole grain intake had a lower body weight compared to the group with the lower whole grain intake (mean difference in body weight was -0.62 kg [95% confidence interval, CI: -1.19 to -0.05]). However, a more recent meta-analysis of RCTs did not find a significant beneficial effect of whole grain consumption on body weight (mean body weight difference was -0.09 kg [95% CI:-0.26 to 0.07]) (Sadeghi et al., 2020). Reasons for the different results between the two studies may be that the study by Sadeghi et al had broader inclusion criteria also including RCTs with calorie restriction and shorter duration than 4 weeks, and hence included more trials (N=19) (Sadeghi et al., 2020). Inconsistencies between studies may also be due to differences in definitions of whole grain foods and how whole grain intake is calculated. These aspects are discussed in Kissock et al, who systematically reviewed observational data on a potential association between body weight and whole grain intake (Kissock et al., 2020). The authors conclude that results from cohort studies are inconsistent. They specifically note that studies where whole grain foods were defined in more general terms were inconsistent, whereas studies that consistently/stringently calculated whole grain intake based on the U.S. Department of Agriculture (USDA) food databases or from lists of specific foods, consistently reported an inverse association between whole grain intake and body weight. Thus, the way intake of whole grain foods is reported may influence the conclusions of studies with body weight as an outcome (Kissock et al., 2020).

Causality

RCTs are traditionally considered the gold standard for causality assessment. However, dietary interventions have limitations due to lack of blinding, noncompliance, and often have a very short duration. Thus, testing various types of whole grain consumption in a long-term primary prevention randomized intervention on e.g. myocardial infarction is very complicated and will likely not be performed. Interestingly, it has recently been highlighted that RCTs and cohort studies generally ask very different research questions (Schwingshackl et al., 2021, Ibsen et al., 2021) which then could explain quite a substantial part of observed inconsistences. It is not surprising that results from RCTs differ considering that whole grains from different cereals and different types of products are used in different studies. The amount

of whole grain used can also differ between studies. Reasons for inconsistencies between RCTs and prospective studies may also be that whole grain intake often is associated with an overall healthy lifestyle (Kyrø et al., 2011). Even when adjusting for confounders like smoking, physical activity and alcohol consumption, residual confounding in observational studies can still be present. Another factor is that food frequency questionnaires (FFQ) often are not specific enough to distinguish between different types of whole grains to illustrate differences.

RCTs and prospective studies generate complementary results and Reynolds conclude that these complementary findings, a striking dose-response evidence, and the substantial body of mechanistic evidence all indicates that the relationships for whole grain intake to several non-communicable diseases could be causal (Reynolds et al., 2019).

Micha et al graded the evidence for etiologic effects of whole grain on coronary heart disease. In contrast to Reynolds et al, who used GRADE, Micha et al scored according to the nine Bradford-Hill criteria (Micha et al., 2017). In summary, there is consistent evidence from several well-designed studies with relatively few limitations for the criteria consistency, temporality, coherence, analogy, plausibility, biological gradient and experiment. For the criterion specificity, however, there is consistent evidence from several studies but with some important limitations. For the criterion strength (the magnitude of association), there is emerging evidence from a few studies or conflicting results for several studies. Taken together, the grading of the evidence support causal cardiometabolic effects of whole grains.

Effects of whole grain on myocardial infarction in the Scandinavian population

Justification for choice of dose-response model (Helnaes et al, 2016)

The Scandinavian population is well suited for exploring associations between whole grain intake and health effects. The personal identity number ensures high-quality registry data, easily linkable with data from prospective cohort studies. In addition, the populations of Scandinavian countries have a large variation in whole grain intake, both in terms of quantity and type, and otherwise relatively similar lifestyle habits. A Danish study (Helnaes et al., 2016), included in the meta-analysis of Reynolds et al, was used to quantify the effect of increased whole grain intake on myocardial infarction in a Swedish setting. The rationale behind this methodological choice is that a large study in the Scandinavian countries (Denmark, Sweden and Norway), the HELGA cohort, show that the type of whole grain foods consumed are similar (Johnsen et al., 2015). In Sweden (and Norway), the largest contributor to whole grain bread intake was mixed-grain bread, whereas in Denmark, two-thirds of the whole grain bread intake was rye bread. In all three countries, crisp bread consisted of mostly

products with a high (75%) whole grain content. About 80% of breakfast cereals were muesli, porridge, oatmeal or other whole grain cereals and the remaining 20% were refined grain products like cornflakes. The median intake of whole grain products was 94 g/day (5–95 percentile: 26–251) for women and 114 g/day (5–95 percentile: 30–318) for men in the Swedish cohort. In the Danish cohort, the corresponding numbers were 116 g/day (5–95 percentile: 38–236) for women and 137 g/day (5–95 percentile: 44–277) for men. Intake of whole grain from sources other than oat, rye and wheat was very low in all three countries.

The age-standardized incidence rate of first myocardial infarction (after 7 myocardial infarction free years) in Sweden (181/100,000 women and 372/100,000 men) (Socialstyrelsen, 2018) is similar compared to the incidence in Denmark (140/100,000 women and 320/100,000 men) (Hjerteforeningen, 2018). The fact that the Danish definition of incidence-free time include three more years compared to the data from Sweden and that the Swedish statistics include primary as well as secondary diagnosis may explain the somewhat higher rates in Sweden.

Dose-response in the Danish population (Helneas et al, 2016)

The Danish study is based on the Danish Diet, Cancer and Health cohort, a population-based prospective cohort with a wide range of whole grain intakes and where information was available also of sources of whole grain and type of whole grain products (Helnaes et al., 2016). The amount of whole grains consumed in Helnaes et al is reasonable and comparable to data from diets in Sweden (Livsmedelsverket, 2012).

In the Danish Diet, Cancer and Health cohort, a detailed self-administered FFQ provided information on daily intake of whole grain products. Intakes of total whole grain and whole-grain species (wheat, rye, and oats) were estimated. Information on whole grain content came from analyses at the Technical University of Denmark (DTU) and from manufacturers. Rye bread, whole grain bread and oatmeal/muesli were considered whole grain products. No minimum level of whole grain content was applied in the definition of whole grain products. Therefore, there was a large variation of the actual whole grain content within the product group. As a consequence, the average whole grain content in the products was low compared to the Swedish definition of whole grain bread. For example, one serving of whole grain bread (40 g) had on average a whole grain content of 3 g in the Danish Diet, Cancer and Health cohort (Kyro et al., 2018). These measurement errors are likely similar for cases and non-cases, and therefore rather attenuate the results towards null.

In the analysis of myocardial infarction, 54,871 men and women aged 50–64 years were included. During 13.6 years of follow-up, 2,329 individuals developed myocardial infarction (information on incident cases was obtained by linkage with The Danish National Patient

Register and The Danish Register of Causes of Death). Median whole grain intake was 42 g/day (5–95 percentile: 12–87) for men and 34 g/day (5–95 percentile: 11–76) for women while the consumption of products containing whole grain was 136 g/day (5–95 percentile: 42–277) for men and 115 g/day (5–95 percentile: 37–235) for women. The main whole grain type of food was rye bread, and thus the main whole grain source was rye.

In analyses adjusted for age, education, physical activity, smoking status and pack-years of smoking, alcohol intake as well as intakes of fruits, vegetables, fish, red meat and processed meat, men in the highest quartile of whole grain intake had 25% lower risk of myocardial infarction, compared to men in the lowest quartile (relative risk, RR: 0.75; 95% CI: 0.65–0.86). Among women, a 27% lower risk of myocardial infarction was observed in the highest quartile of whole grain intake compared to the lowest (RR 0.73; 95% CI: 0.58–0.91). The analysis for women was adjusted for the same confounding factors as for men in addition to menopausal status and use of menopausal hormones. Each daily 25 g increase of whole grain was associated with a 12% (RR 0.88; 95% CI: 0.83–0.93) decreased risk for myocardial infarction among men and a 13% (RR 0.87; 95% CI: 0.78–0.96) decreased risk for myocardial infarction among women. The magnitude of the association is similar to that observed in the meta-analysis of Reynolds et al (7% lower risk of coronary heart disease per 15 g increase in whole grain intake, assuming linearity) (Reynolds et al., 2019).

As regards to specific whole grain types, rye and oats (but not wheat) were associated with lower risk of myocardial infarction in men. Rye bread (in men and women) and oatmeal (in men) were significantly associated with lower risks of myocardial infarction. In sensitivity analysis excluding participants with diabetes at baseline, associations between whole grains and myocardial infarction were stronger. The results from this study suggest that especially rye and oats may be beneficial with regard to risk of myocardial infarction, which is also supported by experimental evidence (Helnaes et al., 2016).

Exposure assessment

The Swedish national dietary survey, Riksmaten adults 2010–11, was used as the basis for the exposure calculations related to the assessment of both risks and benefits in the present work (Livsmedelsverket, 2012). A representative sample of 5,000 individuals aged between 18–80 years and living in Sweden were invited to participate in the survey. The data collection took place between May 2010 and July 2011. The participants, in total 1,797 women and men, reported everything they ate and drank during four consecutive days in a web-based food diary (Livsmedelsverket, 2012).

According to Riksmaten adults 2010–11, the mean dietary intake of whole grains was 34 g in women and 40 g in men. Variability in the dietary intake is presented in Table 1. The grains included in the estimation of whole grain intake were wheat, including spelt and durum wheat, rye, oats, barley, rice, millet, durra and other types of sorghum. Corn is included in the original whole grain definition of the Swedish Food Agency (Livsmedelsverket, 2012). However, because corn was not included in the cereal fraction of the Swedish market basket study, corn was left out in the exposure estimation. Estimated intakes of whole grain in the three scenarios (where 50%, 75%, and 100% of cereal products were whole grain products, respectively) are shown in Table 2.

Table 1. Intake of whole grain (g/day), mean, standard deviation and percentiles in the national dietary survey Riksmaten adults 2010–11.

	N	Mean	Sd	P5	P50	P95
Women	1005	34	23	2,8	30	74
Men	792	40	29	1,2	35	98
All	1797	37	26	1,8	32	87

N = number of participants, Sd = standard deviation, P5 = 5th percentile, P50 = median, P95 = 95th percentile

Benefit characterisation

Quantification of positive health impacts of whole grains

Ideally, in a full risk-benefit comparison, all potential positive impacts of whole grain should be listed, evaluated for causality and quantified. The present report focuses on one of the most studied outcomes, coronary heart disease, to illustrate the beneficial effect of whole grain consumption in a quantitative way. Myocardial infarction was chosen because ischemic heart disease is the most common cause of death in Sweden (Institute for Health Metrics and Evaluation, 2020). Therefore, the prevention of myocardial infarction has potential to make up for a large part of the beneficial effects of whole grain. Myocardial infarction was also the outcome best characterised in a Scandinavian population, hence in a population with a similar whole grain intake. The analysis of one beneficial effect is also comparable to the evaluation of potential adverse health effects in this report, where only one adverse outcome was quantified as a consequence of increased whole grain consumption.

Assuming a similar size of the association in the Swedish and Danish populations, it was calculated what an increase from current intake to three different pre-defined scenarios (including recommended amount) would mean in terms of reduction in myocardial infarction

(%). Furthermore, the decrease in absolute numbers for a specific year was described by combining the effect sizes with statistics of incidence of myocardial infarction in Sweden for that specific year (Table 2). For example, in a scenario where 50% of cereal products consumed would be in the form of a whole grain product, the increase in whole grain would be on average 17 g/day or 13 and 22 g/day for women and men, respectively. This corresponds to a relative risk reduction of 7% for women and 11% for men. For the year 2019, this reduction corresponds to 530 prevented incident cases of myocardial infarction for women and approximately 1,400 incident cases in men.

The benefit characterisation was made based on the assumptions of a linear dose-response curve, that the effect size of whole grain on myocardial infarction is similar in the Swedish and Danish populations, that the Swedish adult population consume the amount specified in the scenarios, and that the proportions of whole grain species in the scenarios are similar enough to give the same effects as in the Danish population in Helnaes et al (Helnaes et al., 2016).

Table 2. Estimated effect of whole grain consumption on myocardial infarction (MI) according to different scenarios. The estimations are based on 13% (95% CI 0.78–0.96; women)/12% (95% CI 0.83–0.93; men) reduction in MI rates observed by 25 g-increment in whole grain consumption, assuming a linear dose-response association (Helnaes et al., 2016)

Scenario (proportion whole grain intake of total cereal intake)	Mean whole grain content (%)[a]	Mean whole grain intake[b] (g/day)	Reduction first MI incidence according to Helnaes et al (%)	Reduction in first MI incidence, no. of new incident cases[c] (range)[d]
Present situation	≈20%	Women: 34 Men: 40 All: 37	-	-
50% whole grain products	≈28%	Women: 47 (13 g increase) Men: 62 (22 g increase) All: 54 (17 g increase)	Women: (13/25g) x 13% ≈6.8% Men: (22/25) x 12% ≈11%	Women: 530 (160–890) Men: 1,400 (830–2,000) All: 2,000
75% whole grain products	≈41%	Women: 68 (34 g increase) Men: 90 (50 g increase) All: 78 (41 g increase)	Women: (34/25g) x 13% ≈18% Men: (50/25) x 12% ≈24%	Women: 1,400 (420–2,300) Men: 3,200 (1,900–4,600) All: 4,600
100% whole grain products	≈54%	Women: 90 (56 g increase) Men: 120 (78 g increase) All: 100 (66 g increase)	Women: (56/25g) x 13% ≈29% Men: (78/25) x 12% ≈38%	Women: 2,200 (690–3,800) Men: 5,100 (3,000–7,200) All: 7,400

Note: Calculations are based on raw data and abbreviated numbers are presented in the table therefore the sums do not agree.

MI = myocardial infarction, CI = confidence interval

[a]Proportion of whole grains in relation to total cereals based on lower limits of the Keyhole criteria. The amount thus corresponds to the minimum proportion of whole grains.

[b]Based on mean intake of total cereals (all: 189 g, women: 166 g, men: 218 g) from the Riksmaten adults 2010–11 dietary survey (corn not included in the definition of whole grains), except for the present situation where intake is based on whole grain intake data from the Riksmaten adults 2010–11 dietary survey (excluding corn from the definition of whole grains).

[c]Based on total number of new incident cases (cases with 7 preceding disease-free years) in Sweden year 2019 (The National Board of Health and Welfare). Women: 7,706 cases, men: 13,597 cases.

[d]Based on 95% confidence intervals of the risk estimates (Helnaes et al., 2016).

Optimal intake level of whole grains

Several systematic literature reviews and meta-analyses of prospective studies on food or food groups and non-communicable diseases (Micha et al., 2017, Bechthold et al., 2019) or all-cause mortality (Schwingshackl et al., 2017) have estimated the optimal intake of whole

grains. Even though both Bechthold et al and Schwingshackl et al reported a non-linear dose-response relationship between coronary heart disease and all-cause mortality, respectively, and whole grain intake, they indicate a clear beneficial dose-response relationship for whole grain intakes up to approximately 100 g/day (Bechthold et al., 2019, Schwingshackl et al., 2017). Micha et al characterized optimal population consumption levels of whole grain primarily by observed consumption levels associated with lowest risk of cardiometabolic diseases in meta-analyses, but also considering feasibility (world-wide observed national consumption levels) and consistency with other findings (Micha et al., 2017). They concluded that an optimal mean population intake was 2.5 servings/day (corresponding to 50 g whole grain per day). Reynolds et al also modelled the non-linear dose-response relationships of four outcomes (all-cause mortality, coronary heart disease, type 2 diabetes and colorectal cancer). Results were similar for all outcomes with an association close to linearity in the lower intake ranges and plateau of the beneficial effect at intakes around 60-100 g/day, except for colorectal cancer where the association follow a linear curve even in the higher intake-range (Reynolds et al., 2019). However, the uncertainty increases with increased whole grain consumption due to wider confidence intervals in the upper intake-range. The linear dose-response relationship means that even a small increase in whole grain intake is associated with positive health outcomes.

Uncertainties

Estimation of whole grain consumption

The meta-analysis of Reynolds et al (Reynolds et al., 2019) reports very high whole grain intakes. We suspect that in some studies, reported whole grain intake may actually be intake of whole grain products. One serving of a whole grain product may be 30 % whole grain in a breakfast cereal serving, or 100 % whole grain in an oat porridge serving. As whole grain bread includes 30–100% whole grains, one serving of a whole grain bread of one type can differ significantly in whole grain content compared to another type/brand.

Inconsistencies in methodology of reporting whole grain intakes causes heterogeneity in pooled data from cohort studies. Besides causing heterogeneity, the reporting of whole grain product instead of actual whole grain content of that product likely leads to an overestimation of actual whole grain intake from some studies. This would lead to an underestimation of the magnitude, a dilution of the association in pooled data (Chen et al., 2016). Thus, this major difference in reporting leads to a substantial uncertainty regarding the effect size/magnitude of association, but the estimates would tend to be conservative. In a systematic review, Kissock et al concluded that the way intake of whole grain foods is reported may influence the

conclusions of studies with body weight as an outcome (Kissock et al., 2020). Another uncertainty is that the term whole grain covers a number of different products with different health effects. Depending on type of whole grain products consumed in the study population (both in RCTs and observational studies), heterogeneous results can be expected between studies.

Most whole grain cereals are a rich source of fibre and the intake of whole grain is correlated to the intake of dietary fibre. The evidence for the association between fibre intake and health is stronger compared to the association between whole grain intake and health and show consistency between prospective study results and RCTs (Reynolds et al., 2019). The observed beneficial effects of whole grains may be weaker because some part of the effect are through the fibre content which intake is easier to estimate. Some individuals will consume enough dietary fibre from other sources than whole grains, which dilutes the potential effect between whole grains and health.

Data from the Swedish national dietary survey Riksmaten adults 2010–11 were used to assess intake of cereals (and partly whole grain). Like in all dietary surveys, a low response rate (36% in Riksmaten adults 2010–11) and that well-educated subjects are more likely to participate may have an impact on the generalisability of the results. The fact that education is often positively related to whole grain intake may lead to an overestimation of the intake. This may result in an underestimation of the associated benefit on the population level. Another problem with dietary surveys are underreporting, although cereals are not a food category especially prone to this.

The median intakes of whole grain in Helnaes et al (Helnaes et al., 2016) and Riksmaten adults 2010–11 (Livsmedelsverket, 2012) were similar despite differences in methods (34 and 42 g/day in Denmark, and 30 and 35 g/day in Sweden for women and men, respectively).

Methods used in Helnaes et al

The study by Helnaes et al has several strengths. The sample size was large with over 2,000 cases of myocardial infarction, the follow-up was long (median 13.6 years) and had minimal loss to follow-up due to linkage to Danish registries with high-cover (>90%). The FFQ used in Helnaes et al was detailed enough to differentiate between types of products and sources of whole grains. Details on whole grain content of whole grain products were collected with 24-h dietary recalls in a random subsample of the cohort. Thus, the study could distinguish between whole grain intake and whole grain product intake, which was the main reason to use this study to quantify effects of whole grains on myocardial infarction. The average whole grain intake was high with a variation in both quantity consumed and type of whole grain consumed. This enabled evaluation of independent associations of different whole grain types

and products. In addition, the study included detailed information on several potential confounding factors.

However, whole grain intake was assessed only once, therefore not capturing potential changes in intake over the follow-up period. In addition, some products may have been misclassified as containing whole grains when they did not.

The participation rate was around 35% with a higher proportion women participating. Participants also generally had a higher socioeconomic position than did non-responders (Helnaes et al., 2016), which limits the generalisability of findings. However, as this would result in a more homogeneous study population with lower variation in whole grain intake compared to the source population, risk estimates would be affected towards the null.

Confounding factors

It is difficult to rule out confounding of overall healthy diet and lifestyle that comes hand in hand with whole grain consumption, thus it is not clear whether these differences are solely due to the intake of whole grain or the combined effect of consuming a healthier diet overall. In the study by Helnaes et al, the intake of whole grains was associated with higher education and a healthier lifestyle in general (Helnaes et al., 2016). When estimating the effect size of whole grain intake on myocardial infarction in Helneas et al., several known risk factors for myocardial infarction were adjusted for (i.e. age, education, physical activity, smoking status and pack-years of smoking, alcohol intake, menopause (women), menopausal hormone replacement therapy (women) as well as intakes of fruits, vegetables, fish, red meat and processed meat). They also performed analyses in which they included additional factors which can be considered confounders or mediators (BMI, waist circumference, hypertension, hypercholesterolemia) as well as a sensitivity analysis excluding participants with diabetes. For women, these additional adjustments had little effect on the effect size indicating a robustness on the results. For men, the inverse association between whole grain intake and risk of myocardial infarction remained statistically significant but the effect size was reduced (RR 0.88 and 0.94 in model 2 and 3, respectively). To conclude, despite the careful adjustment for confounders, the possibility of residual confounding cannot be ruled out. Residual confounding should however not be a main issue of concern given the robust findings in this study. In the section below, uncertainties in the estimated effect sizes are quantified.

Quantification of uncertainties of the estimated beneficial effects of whole grains

To quantify the uncertainties of the estimated reduction in myocardial infarction incidence, the 95% confidence intervals of the exposure-disease associations of the Helnaes study (Helnaes et al., 2016) were used. By applying the uncertainty estimates on the different scenarios, ranges around the absolute estimates were generated (Table 2). For the greatest increase in intake (100% of cereal consumption is whole grain products), the relative risk reduction is 9–49% for women, corresponding to 690–3,800 prevented first incident cases of myocardial infarction in one year. The corresponding relative risk reduction among men is 22–53%, resulting in 3,000–7,200 prevented cases. For the scenario that is consistent with the recommended intake of whole grains (around 75% of cereal products are whole grain products), the corresponding numbers are 5–30% relative risk reduction, resulting in 420–2,300 fewer cases among women and 14–34% risk reduction and 1,900–4,600 fewer cases among men. With the smallest increase in whole grain consumption (50% of cereal products are whole grain products), the relative risk reduction among women is estimated to 2–12% and 160–890 fewer incident cases. The corresponding numbers among men is 6–15% relative risk reduction, resulting in 830–2,000 fewer incident cases of myocardial infarction.

Assessment of adverse effects

Hazard identification

The risk ranking in the total diet according to the Risk Thermometer (described in the methods section) showed that the exposure associated with dioxin-like compounds, aluminium, mercury, lead, nickel, and cadmium ranked the highest (risk class 3). These were used as a starting point for further prioritization. For the remaining compounds (18 compounds categorized in risk class 1, and 10 compounds categorized in risk class 2), estimated exposures appeared to be of no or low concern.

Since the exposure from whole grains is relevant for the present assessment, the relative contribution of cereals to the exposure of the different compounds was also compared based on results from the market basket study (Livsmedelsverket, 2017b). Dioxin-like compounds are not found in cereals and were therefore not further assessed. Only 7% of mercury exposure can be attributed to cereals, while a meaningful fraction of the exposure from food can be attributed to cereals for the remaining compounds. The cereal fraction contributed with 40% of the exposure for cadmium, 33% of the exposure for nickel, 22% of the exposure for aluminium, and 17% of the exposure for lead. Further prioritization was based on consideration of the percentage of the health-based guidance value associated with the exposure from cereals (Livsmedelsverket, 2017b). This percentage was 20% for cadmium, 20% for nickel, 2.9% for aluminium, and 2.6% for lead. Since the risk ranking described above, a new tolerable daily intake (TDI) of 13 µg/kg body weight for nickel has been established by EFSA (EFSA CONTAM Panel, 2020b), which is more than 4 times higher than the previous value of 2.8 µg/kg body weight. If using this new TDI, the percentage of cereals contributing to the exposure of nickel would reduce from 20% to 4.3% of the TDI. It was considered unlikely that whole grain consumption could increase the exposure of aluminium, lead, and nickel sufficiently for it to be of concern since the fraction of the health-based guidance value attributed to cereals was less than 5%. Thus, only the cadmium exposure appeared to be of relevance among considered compounds. Certain wholegrain products such as wholegrain rice have high levels of arsenic. Arsenic was, however, not prioritized in the in the initial risk ranking described previously. The Swedish Food Agency has a specific report dealing with the issue of arsenic in rice (Livsmedelsverket, 2015).

Several mycotoxins were identified as potential contaminants in whole grains in the complementary literature search (Appendix 1). These were not initially identified as a priority in the 2015 Swedish market basket study (Livsmedelsverket, 2017b), but due to the frequent

occurrence of mycotoxins in cereals and cereal-based foods, special consideration was given to this group of contaminants. Acrylamide was also identified in the literature search (Appendix 1), but was not prioritized since data on the concentration in whole grain products, e.g. cereals, was very limited. As a result, only cadmium and mycotoxins were further assessed.

Cadmium

Cadmium is a heavy metal naturally occurring in the soil at low levels. It is also continually added to the agricultural soil through sewage sludge, air pollution and cadmium contaminated fertilizer (Järup and Åkesson, 2009). Food is the main source of cadmium exposure in the general population, but smoking can be a strongly contributing factor. Smokers have, on average, twice as high cadmium levels as non-smokers due to high concentrations of cadmium in tobacco leaves and a higher absorption of cadmium through the lungs compared to the gut (Satarug and Moore, 2004).

Ingested cadmium is absorbed through the gut through a common mechanism with iron. This makes cadmium absorption higher when iron levels are low due to upregulation of this mechanism. Several studies have shown that cadmium concentration in blood and urine is increased with lower iron levels (Åkesson et al., 2002, Julin et al., 2011, Bjermo et al., 2013).

Cereal products are the largest source of cadmium in food, but potatoes and other root-vegetables also contribute significantly to the exposure. There are also certain foods that may contribute disproportionally (contain very high levels) but are seldom consumed, such as the prince/horse mushroom and brown crab meat (Livsmedelsverket, 2017a).

Mycotoxins

Mycotoxins are secondary metabolites, produced by certain filamentous fungi (moulds), and poisonous to vertebrates (Thielecke and Nugent, 2018).

Cereals and thereby whole grain products can be contaminated with a wide range of mycotoxins and cereal products are the main contributors to mycotoxin dietary exposure worldwide (Carballo et al., 2019, Duarte et al., 2010). Those mycotoxins generally considered to pose the greatest risk to human health are aflatoxins, ochratoxins, fumonisins, deoxynivalenol and zearalenon (FAO, 2020, Lee and Ryu, 2017, Thielecke and Nugent, 2018). Besides the well-known and often regulated (i.e. with maximum limits in foodstuff) mycotoxins, several less well-described and known mycotoxins can occur in cereals, for instance enniatins and beauvericin. A summary of the mycotoxins most often occurring in Swedish cereals as well as the producing mould species and affected crops is presented in Table 3.

Table 3. Mycotoxins occurring in grain, producing mould species and cereal crops most often affected from a Swedish perspective (stronger association in **bold**) (Livsmedelsverket, 2009, Livsmedelsverket, 2014).

Mycotoxin	Producing species	Affected crops
Deoxynivalenol (DON)	Fusarium graminearum, F. culmorum	Wheat, oats, barley
Nivalenol	F. poae	Oats, wheat, barley, rye
T-2 and HT-2 toxin	F. langsethiae, F. sporotrichioides	Oats, wheat, barley
Zearalenone	F. graminearum, F. culmorum	Wheat, oats, barley
Enniatins (En)	F. avenaceum	Oats, wheat, barley
Moniliformin	F. avenaceum	Oats, wheat, barley
Beauvericin	F. avenaceum	Oats, wheat, barley
Ergot alkaloids	Claviceps purpurea	Rye, wheat
Ochratoxin A (OTA)	Penicillium verrucosum	Wheat, oats, rye, barley
Alternaria toxins	Alternaria alternata	Barley, wheat, oat, rye

To establish which mycotoxins are most relevant when considering whole grain consumption in Sweden and thus the present assessment, two recent biomonitoring studies were used.

- In the national dietary survey Riksmaten Adolescents (2016 – 2017) urine and blood samples were collected from ca 1000 Swedish school students in combination with 3-day dietary recall records (Warensjö Lemming et al., 2020). Thirty-five compounds (mycotoxins and mycotoxin metabolites) were analysed. Warensjö Lemming and co-workers found that deoxynivalenol (DON), Enniatin B (EnB) and Ochratoxin A (OTA) were the most frequent mycotoxins in biofluids and intake data showed that levels of all three mycotoxins were associated with consumption of cereal grain. Furthermore, DON levels were significantly associated with intakes of whole grain as well as oats and dietary fibre.

- In the national dietary survey Riksmaten adults (2010–2011), urinary samples from approximately 250 Swedish adults were analysed for six different mycotoxins and four additional mycotoxin metabolites. All participants performed a 4-day dietary recall registration. Results showed that DON and OTA were the most frequently detected mycotoxins (EnB was not included in the analysis) (Wallin et al., 2015). In this study, no pronounced associations to dietary intake of different foods could be detected. However, in an earlier study using the same set of urine samples but a single-method for DON only, a significant positive correlation between DON levels and total cereal intake as well as whole grain consumption was shown (Wallin et al., 2013).

In line with these results, surveys of Swedish grain shows that DON and enniatins are very commonly occurring. Results from wheat and oat samples collected during 2010 and 2011 show that the proportion of positive samples was in the range of 91–95 and 96–100%, respectively (Fredlund et al., 2013, Lindblad et al., 2013). OTA is less frequently detected, but not uncommon in Swedish grain, it also occurs in a wider range of foods (Livsmedelsverket, 2009).

Based on these results, DON, EnB and OTA were prioritized for further evaluation in the present assessment. It should be noted that additional toxins (listed in Table 3) might be relevant in this context, but due to lack of data, these have not been evaluated.

DON and EnB are both produced by Fusarium moulds (see Table 3). Fusarium are so called field fungi, that is, they infect and form mycotoxins in cereal crops pre-harvest. Many factors affect the degree of infection and toxin formation, e.g. crop rotation, cereal variety selection, use of fungicides and in particular climatic conditions, especially precipitation and temperature (Blandino et al., 2012, Parikka et al., 2012). This means that the levels of fusarium toxins in cereal vary greatly between different years as well as between different geographical regions (van der Fels-Klerx et al., 2012). Like many other mycotoxins, DON can occur both as the original toxin and in modified forms (also known as masked mycotoxins) (Freire and Sant'Ana, 2018). Modified forms are altered, for example through the metabolism of infected plants or the fungus itself, to derivatives of the original toxin or conjugated to other substances, such as glucose or sulphate. Modified mycotoxins have previously been overlooked in food analyses, but today it is known that these can be converted to their free form in the gut and thereby contribute to human exposure to mycotoxins.

OTA is produced by several species belonging to Aspergillus and Penicillium. In European grain however, P. verrucosum is the main, if not only, producer (Lund and Frisvad, 2003). P. verrucosum grows in cereals post-harvest, during drying and storage if temperature and moisture conditions are favourable (Cairns-Fuller et al., 2005, Duarte et al., 2010). To prevent growth of P. verrucosum and minimize OTA-production it is essential to dry the grains to a safe moisture content (ca 15-18%) as quickly as possible after harvest. During harvest years with damp conditions and high yields, this is more problematic (Cairns-Fuller et al., 2005, Duarte et al., 2010). Thus, also OTA contamination can vary between years.

Mycotoxins are stable chemical compounds and if they are formed in grain, they often persist to a high degree during food processing (Schaarschmidt and Fauhl-Hassek, 2018). Due to the fact that mould colonization as a rule is higher in outer parts of the grain however, milling operations are known to redistribute mycotoxins unequally in different types of end products. Levels are increased in milling fractions containing higher proportion of bran and lowered in

white flour and semolina fractions. As a consequence, whole grain products often contain increased levels of mycotoxins when compared with refined grain products (Schaarschmidt and Fauhl-Hassek, 2018, Duarte et al., 2010). This effect is seen for DON, EnB and OTA as well as for many other mycotoxins. However, the relative difference in mycotoxin content between refined and whole grain products varies greatly and is affected by a number of different factors. These include for instance, cereal type and cultivar, growing and storage conditions, type and initial level of mycotoxin and the technology that is applied in the mill.

Hazard characterization – Cadmium

Historically, cadmium has been recognized as an occupational health hazard. The outbreak of the Itai-itai disease in Japan in the 1950´s showed that severe renal and skeletal damage in women was associated with consumption of heavily cadmium-contaminated rice. This highlighted the issue of environmentally exposed populations (Järup and Åkesson, 2009). Recent epidemiological studies have provided numerous evidence that even low-level environmental exposure to cadmium poses a health risk for the general population.

Kidney damage

The kidney has been recognized as the critical organ for cadmium at chronic exposure. EFSA has established a tolerable weekly intake (TWI) for cadmium from food of 2.5 µg/kg body weight/week (EFSA, 2009). Development of the TWI is based on the dose-response relationship between cadmium levels and low molecular weight proteins in urine. Using benchmark dose (BMD) analysis, combining data across populations, a critical urinary concentration of 1 µg/g creatinine was established. The lower confidence limit of the (BMDL) (adjusted to the critical concentration) describes the dose where 5% of the population were estimated to exceed a specific cut-off value (300 µg/g creatinine) for beta-2 microglobulin (B2M) in urine representing an early sign of kidney damage. Based on modelling the relation between urinary cadmium and dietary exposure, the TWI was then calculated as the intake level for which 95% of the population will not reach the critical concentration of 1 µg/g creatinine over time.

Bone effects

Cadmium can affect bone mineralization, which can lead to osteoporosis and subsequent fractures. EFSA states that effects on bone mineralization have been shown to occur at similar levels of cadmium exposure as shown to be toxic to the kidney, 1 µg/g creatinine (EFSA, 2009). Newer studies suggest that there could be effect at even lower levels (0.5 and 0.26 µg cadmium/g creatinine) (Wallin et al., 2016, Gallagher et al., 2008). Some studies fail to show

a link between cadmium exposure and bone health (Moberg et al., 2017), but a meta-analysis from 2016 concluded that most studies confirmed the link (Cheng et al., 2016).

Other effects

The International Agency for Research on Cancer (IARC) has classified cadmium as carcinogenic in humans (group 1) based on studies on lung cancer in occupationally exposed workers (IARC, 1993). As of 2009, EFSA concluded that the link between cadmium exposure and cancer are not clear enough to use for the establishment of the TWI from food (EFSA, 2009). Later studies have found an association between cadmium exposure in the general population and cancer in lungs, bladder, the endometrium, breasts, and the prostate (Julin et al., 2012a, Filippini et al., 2020, Åkesson et al., 2008, Mezynska and Brzóska, 2018, Julin et al., 2012b).

Cadmium can also adversely affect the testicles causing a decrease in sperm motility (de Angelis et al., 2017). Damage to hearing and eyesight has also been reported at concentrations similar to those that affect the kidney, reviewed in (Mezynska and Brzóska, 2018). High blood levels of cadmium are correlated with an increased level of heart disease (Barregard et al., 2016). Meta-analyses by Tinkov et al have shown that there is an association between both urinary and blood levels of cadmium and several types of cardiovascular disease (Tinkov et al., 2018).

Exposure assessment – Cadmium

The Swedish national dietary survey Riksmaten adults 2010–11, was used as the basis for the exposure calculations related to the assessment of both risks and benefits in this work (Livsmedelsverket, 2012). A representative sample of 5,000 individuals between 18–80 years and living in Sweden were invited to participate in the survey. The data collection took place between May 2010 and July 2011. The participants, all together 1,797 women and men, reported everything they ate and drank during four consecutive days in a web-based food diary (Livsmedelsverket, 2012).

In order to estimate the health effects of increased cadmium exposure from whole grains several strategies can be used. Here, cadmium exposure in the Swedish population is estimated using data from the national dietary survey Riksmaten adults 2010–11 (Livsmedelsverket, 2012). Intake data from this study was combined with cadmium levels in food groups (Table 4) measured in the Swedish market basket study 2015 (Livsmedelsverket, 2017b) in order to estimate individual cadmium exposures. The cadmium level in whole grains were estimated using the cereal fraction of the Swedish market basket study. The cereal

fraction in the market basket study conducted in 2015 consisted of whole grain rice, oatmeal, gruel, pasta, breakfast cereals, muesli, rye crisp bread, breakfast crisp bread, baguette, rye bread, and whole grain rye bread. This mixture had a cadmium level of 26 µg/kg. By replacing refined products with whole grain products in the model, the mean cadmium level of cereal fractions with modified whole grain content were estimated, while keeping the cadmium level in the other food groups constant.

Table 4. Cadmium concentrations in the different food groups in the Swedish Market Basket Survey 2015.

Food group	Cadmium concentration, µg/kg
Pastries	16
Meat	2.4
Fish	4.7
Dairy	0.1
Eggs	0.1
Fats and oils	0.3
Vegetables	10.3
Fruit	1.5
Potatoes	25
Sugar and sweets	11.8
Beverages	0.05
Cereal products	26

In order to exchange a product in the cereal fraction, an in silico cereal fraction slurry was first calculated by adding cadmium concentrations from whole grain versions of products within the cereal fraction in the Swedish market basket survey (Table 5). These cadmium concentrations were taken from products analysed at the Swedish Food Agency as part of a project aimed at tracking the cadmium and other metals in different foodstuffs (Kollander et al., 2023). In most cases, the concentrations are a mean value from several similar products. Wheat flour, rice, and pasta were substituted by whole grain flour, whole grain rice, and whole grain pasta, respectively. Wheat crisp bread was substituted by whole grain wheat biscuit, and baguette and rye bread were both substituted by whole grain bread. The other categories (oatmeal, gruel, breakfast cereal, muesli, rye crisp bread, and whole grain rye bread) were not substituted since they were already considered whole grain.

Three scenarios were defined to assess the impact of whole grain consumption on cadmium exposure where the percent whole grain product as part of cereal products (i.e., the cereal

fraction) were specified to 50, 75, and 100%, respectively. To calculate the cadmium exposure in these scenarios, the different products that make up the cereal fraction of the Swedish market basket study were substituted for their whole grain equivalent in order to satisfy the criteria of the respective scenario, as described above. These substitutions modulate the cadmium concentration of the cereal category due to differences in cadmium concentrations in the substituted products. As noted, this was achieved by replacing all products within the cereal fraction to a similar degree resulting in weighted cadmium concentration that differs across the scenarios (Table 5).

Table 5. Cadmium concentration in the different cereal products used to calculate the cadmium exposure in the different scenarios of whole grain intake and subsequent estimated cadmium intake in the scenarios. Each product contributes to the overall cadmium content in the cereal fraction with a unique weight (proportion) in each scenario (columns 4–7).

Product within cereal group	Cd content (µg/kg dry weight)[a]	Present exposure	50% of total cereal intake as whole grain products	75% of total cereal intake as whole grain products	100% of total cereal intake as whole grain products
Wheat flour	28.1	9.3	6.22	3.11	0
Sifted rye flour	28.5	0.24	0.24	0.24	0.24
Rice	16.1	5.9	3.93	1.97	0
Whole grain rice	24.3	0.44	1.97	3.93	6.40
Oats	24.1	3.47	3.47	3.47	3.47
Gruel	14.9	0.72	0.72	0.72	0.72
Pasta boiled	26.7	10.4	6.94	3.47	0
Breakfast cereal	2.40	3.59	3.59	3.59	3.59
Rye crisp bread	16.1	3.35	3.35	3.35	3.35
Crisp bread wheat flour	16	0.84	0.56	0.28	0
Baguette	13.8	24.7	16.5	8.23	0
Soft rye bread	12.8	24.7	16.5	8.23	0
Soft whole grain bread	46.7	12.3	28.8	45.3	61.7
Wheat grain	54.4	0	3.11	6.22	9.3
Whole grain crusts	52.9	0	0.28	0.56	0.84
Whole grain pasta boiled	37.1	0	3.47	6.94	10.4
Calculated cadmium concentration in cereal fraction (µg/kg)		21.8	27.4	34.3	42.6
Median Cd intake from cereals (and 95th percentile) (µg/kg bw/week)[b]		0.19 (0.53)	0.24 (0.66)	0.29 (0.83)	0.37 (1.03)
Median Cd intake from other food groups (and 95th percentile) (µg/kg bw/week)[c]		0.67 (1.28)	0.67 (1.28)	0.67 (1.28)	0.67 (1.28)
Overall median Cd intake for all food groups (and 95th percentile) (µg/kg bw/week)		0.95 (1.65)	1.03 (1.74)	1.11 (1.88)	1.22 (2.06)

[a]Cadmium concentrations from Kollander et al., (2023), and cadmium levels in samples analysed for the Swedish Food Composition Database ("Pasta bolied" and "Whole grain pasta boiled"). The latter has been recalculated to dry weight to harmonize with the Swedish market basket survey.

[b]Based on calculated cadmium concentration in the cereal fraction, and food consumption and body weight data from the Riksmaten adults 2010-11 dietary survey.

[c]Based on cadmium concentration data from Swedish market basket study 2015, and food consumption and body weight data from the Riksmaten adults 2010-11 dietary survey.

The exposure assessment was stratified according to the 12 food categories used in the market basket study, which each are associated with a measured cadmium concentration. Data from the dietary survey Riksmaten adults 2010–11 was aggregated to be compatible with these food categories (Germundson, 2013). Exposures could then be estimated for each participant in Riksmaten as the sum of exposures across the 12 food categories, allowing assessment of the fraction of the population that exceed critical intake values. This type of assessment was performed across all three scenarios, which differ in the cadmium concentration applied for the cereal group while food consumption and cadmium concentrations for all of the other 11 food categories were held constant (Table 5). It should also be noted that only cadmium from food was taken into account in this assessment since cadmium levels in drinking water were considered negligible.

Risk characterization – Cadmium

As with the benefit characterization we have chosen to focus on one effect, that of kidney damage. Although there are other toxic effects of cadmium such as osteoporosis, and potentially cardiovascular disease, the effects on the kidney are best characterized and also the basis for the current TWI.

The fraction of the population that exceeds critical dietary exposures is given in Table 6. It ranges from 0.2 to 2.5% across the four whole grain scenarios (including the present situation), and depends on the approach used for estimating these proportions besides the exposure. A simulation approach was applied to enable estimation of the actual number of people at risk since this is not achieved by direct comparison to the TWI. Amzal et al. (2009) presents the relationship between the dietary cadmium exposure and the percent of the population that over time will reach a critical urinary cadmium concentration of 1 µg/g creatinine (Amzal et al., 2009). Using this relation, the TWI has been defined in a conservative manner, i.e., as the long-term exposure that "protects" 95% of the population, as noted earlier. However, this also implies that even if the TWI is reached, the critical urinary concentration may not necessarily be exceeded for many people. This can, however, in principle be addressed by simulations that account for both the population variability in estimated exposures as well as the population variability in critical exposures/doses described in Amzal et al (Amzal et al., 2009).

Specifically, a normal distribution was fitted to log-transformed exposure estimates derived as part of this assessment for a given scenario. Then, n = 100,000 values were randomly generated from this distribution to reflect population variability in exposure, and compared with n = 100,000 values generated from another normal distribution, used to approximate the

distribution in Amzal et al. (Amzal et al., 2009), reflecting the population variability in critical exposure/doses on the logarithmic scale. The proportion of values exceeding "their" simulated critical level was then derived across the different scenarios. This approach assumes that proportion of cadmium uptake is independent of dietary exposure. A normal distribution with parameters, μ = log (0.7906) and σ = 0.4830, was used to approximate the modelled critical intakes (Amzal et al., 2009) associated with a critical urinary concentration of 1 µg/g creatinine. Setting μ = log (0.7906 × 0.5) or μ = log (0.7906 × 2) provides similar approximations for critical concentrations of 0.5 or 2 µg/g creatinine, respectively, presented in (Amzal et al., 2009).

There are uncertainties in the assessment of the population at risk for cadmium. The narrow margin of exposure implies that even a small change in the exposure could modulate the fraction of the population at risk. Based on the fact that dietary exposure assessments for cadmium differ across studies of similar populations, the simulation approach described above was supplemented with an alternative scenario that adjusts the estimated cadmium exposure by a factor 1.4. Details behind the derivation of this factor is described in the section on uncertainty analysis below. Thus, for each whole grain scenario, the fraction of the population that exceeds the critical exposure is given in Table 6 for both unadjusted and adjusted exposure distributions. Moreover, to generally address potential uncertainties associated with the critical cadmium concentration in urine (e.g. 1 µg/g creatinine), critical intakes associated with 0.5 and 2 µg/g creatinine were also considered in the simulations described above. These results are presented in the form of an uncertainty interval in Table 6.

Table 6. Whole grain intake, estimated cadmium exposure, and the fraction of the population that exceed critical exposures according to different scenarios.

Scenario (proportion whole grain intake of total cereal intake)	Mean whole grain contenta (%)	Mean whole grain intakeb (g)	Median Cd intake from cereals (µg/kg bw/week)	Overall median Cd intake (and 95th percentile) (µg/kg bw/week)	Fraction of the population that exceeds critical exposure[c]
Present situation (no change)	11	21	0.19	0.95 (1.65)	0.002 (<0.0001 - 0.04) 0.01 (< 0.001 - 0.11)
50% whole grain products	28	54	0.24	1.03 (1.74)	0.003 (< 0.0001 - 0.05) 0.012 (< 0.001 - 0.13)
75% whole grain products	41	77	0.29	1.11 (1.88)	0.004 (< 0.0001 - 0.06) 0.017 (< 0.001 - 0.16)
100% whole grain products	54	103	0.37	1.22 (2.06)	0.006 (< 0.001 - 0.08) 0.025 (< 0.001 - 0.20)

[a]Proportion of whole grains in relation to total cereals based on lower limits of the Keyhole criteria. The amount thus corresponds to the minimum proportion of whole grains.

[b]Based on mean intake of total cereals (189 g) from the Riksmaten adults 2010-11 dietary survey (corn not included in the definition of whole grains).The intake in present situation in Table 6 differs from that in Table 1 and Table 2. That is because the latter is based on whole grain intake data in Riksmaten adults 2010-11, whereas the data in the present table is based on cereal intake data in Riksmaten adults 2010-11 in combination with the products making up the cereal fraction of the Swedish market basket survey assuming lower limits of the Keyhole criteria.

[c]Percent of the population that, according to simulations, exceeds critical dietary cadmium exposures/doses corresponding to a urinary cadmium concentration of 1 µg/g creatinine. Fractions within parenthesis relate to urinary cadmium concentration of 2 and 0.5 µg/g creatinine, respectively. Results are given for unadjusted exposure distributions (lower fraction) and exposures distributions that have been adjusted by a factor 1.4 (higher fraction) according to the uncertainty analysis section.

Uncertainty analysis – Cadmium

Historically, there are discrepancies between dietary cadmium exposure assessments for the Swedish population. Results in Sand and Becker (Sand and Becker, 2012), and Glynn (Glynn, 2017) resembles the current assessment with a median exposure in the range of 1 µg/kg body weight/week for the baseline scenario (present situation). However, in EFSA (EFSA, 2009) a mean exposure for Sweden of 2.32 µg/kg body weight/week is presented, and in Sand et al (Sand et al., 2013) the corresponding mean for Sweden is 1.76 µg/kg body weight/week. Results for women in the Swedish Mammography Cohort, which are used as part of the derivation of the TWI in EFSA (EFSA, 2009), are in between the results discussed above, with a median and mean exposure of 1.4 µg/kg body weight/week (Amzal et al., 2009).

Apparently, compared to the present assessment, other assessments for the Swedish population are about a factor 1.4-2.3 higher. As noted, the exposure assessment in Amzal et al. was part of the development of the cadmium TWI (Amzal et al., 2009). While the establishment of this TWI is unique because it is fully data driven it is based on a specific exposure assessment, and as discussed, differences in cadmium exposure across studies may affect conclusions due to the relatively small margin of exposure.

As part of the TWI establishment, the conversion of urinary cadmium to daily dietary cadmium intake is based on subgroup data from a population-based prospective cohort study – the so called Swedish Mammography Cohort comprising 680 never smoking women aged 56-70 years (Amzal et al., 2009). As noted, the central estimate of the cadmium exposure in Amzal et al, was about a factor 1.4 larger than the corresponding estimates based on the national dietary survey Riksmaten adults 2010–2011 (Livsmedelsverket, 2012). However, the variability in exposure is similar across the two studies: i.e., the difference between the 5th and 95th percentile of exposure is about a factor of three, and the difference between the 1st and 99th percentile is about a factor of five, which is pointed out in the publication by Sand and Becker (Sand and Becker, 2012). This indicates a systemic difference; i.e., the current exposure distribution is shifted towards a lower value compared to Amzal et al. It can be noted that only cadmium from food was taken into account in the present assessment as well as in Amzal et al (2009).

One difference between the study population in Amzal et al., (Amzal et al., 2009) is that it is slightly older than the population included in Riksmaten adults 2010–2011. However, the exposure for the same age group (56–70 years) in Riksmaten adults 2010–2011 is similar to the other age groups in Riksmaten (about 1 µg/kg body weight/week). The mean/median urinary cadmium concentration for never smoking women in Amzal et al (2009) is 0.31/0.34 µg/g creatinine. Corresponding median levels for never smoking women aged 56–70 in the

Riksmaten adults 2010–11 (Livsmedelsverket, 2012) appear to be lower (0.23 µg /g creatinine), which would be in line with a lower intake compared to Amzal et al (2009). However, this group in Riksmaten consists of only 20 individuals that have a median/mean intake of about 0.9 µg/kg body weight/week. Also, the mean urinary values for this subgroup (0.35 µg/g creatinine) are closer to the corresponding values (0.31 µg/g creatinine) in Amzal et al (2009). While it cannot be excluded that the shift towards lower intakes in the present study compared to Amzal et al (2009) is due to differences in actual cadmium exposure it may also be due to differences in exposure assessment methodology, similar to what is discussed in Sand and Becker (2012). For example, a 4-day dietary record was used in Riksmaten adults 2010–11 while a FFQ was used in Amzal et al., (2009). Both studies use concentration data from the Swedish Food Agency, but the amount and time periods differ. Also, the approach applied for matching consumption and concentration data are likely to have an impact.

To cover this issue quantitatively, adjustment of the current exposure estimates by a factor 1.4 was applied as a scenario to reflect an exposure distribution that is calibrated to the TWI. As noted in the previous section, the percent of the population that exceeds critical exposures, and the TWI is therefore presented for both unadjusted and adjusted exposure distributions (Table 6). Observe that this exercise does not suggest which assessments best describes the actual exposure, but rather addresses an uncertainty in the case of cadmium, which arises due to the complexity of assessing dietary exposure.

As mentioned earlier, assessments based on data collected by EFSA indicate central dietary exposure estimates for Sweden that are higher than 1.4 µg/kg body weight/week. However, these results appear to be less in line with observations at the level of urinary cadmium (compared to the current assessment and Amzal et al 2009) suggesting that a few percent may exceed the critical concentration of 1 µg/g creatinine, e.g., discussed in Sand and Becker (2012). Therefore, no additional scenarios related to the issue of diverging exposure assessments were developed.

Other uncertainties relevant for the risk assessment of cadmium include the specific value for the critical urinary concentration as well as the critical effect it is based on. Based on data from a population-based study on Swedish women the concentration associated with a 5% additional increase in the probability of low bone mineral density and osteoporosis was 1-2 µg cadmium/g creatinine (lower bound estimates) (Suwansono et al., 2010). Another Swedish study observed effects on bone at a urinary cadmium level of 0.5-3 µg cadmium/g creatinine (Alfven et al., 2000). Similarly, an American study observed an odds ratio of 1.43 for osteoporosis at a urinary cadmium level of 0.5-1 µg cadmium/g creatinine (Gallagher et al., 2008). Atherosclerotic cardiovascular disease also seems to be correlated with urinary cadmium levels over 0.5 µg cadmium/g creatinine or 0.5 µg cadmium/L in blood (Fagerberg

and Barregard, 2021). If it is assumed that excess cadmium comes from whole grain it may, however, be noted that the present analysis describes an association between increased whole grain and a decreased risk for cardiovascular disease, suggesting a net benefit of whole grain consumption at population level for this effect Even lower urinary cadmium levels (0.26 µg cadmium/g creatinine) have been associated with fragile bones in men (Wallin et al., 2016). To also cover these aspects, the consequence of using critical urinary concentrations of 0.5 and 2 µg/g creatinine were assessed (see Table 6).

Hazard characterization – Mycotoxins

Deoxynivalenol (DON)

DON is also known as vomitoxin, alluding to the acute effects occurring after exposure to high doses (EFSA, 2017). These include nausea, vomiting, diarrhoea, abdominal pain, headaches, dizziness, fever and bloody stools. Several outbreaks of human mycotoxicoses are known, most of them occurring in China. Adverse effects like vomiting have been documented within 30 min after ingestion of grain products contaminated with DON. Based on these data, EFSA has established an acute reference dose of 8 µg/kg body weight per eating occasion for the sum of DON and the modified forms 3-acetyl-DON (3-Ac-DON), 15-acetyl-DON (15-Ac-DON) and DON-3-glucoside.

Human data on chronic effects after sub-acute DON exposure are lacking (EFSA, 2017). Studies on farm and experimental animals (mice) have shown that DON impacts the immune response; exposure induced increase in the levels of immunoglobulin A and lead to an increased susceptibility to infectious diseases. Further, oral exposure to DON has shown developmental and reproductive effects in rats with for instance reduced fertility, embryotoxicity, skeletal abnormalities, reduced body weight and postnatal mortality. DON is genotoxic in cells in vitro but the data on genotoxicity in vivo are inconclusive. Mutagenicity has not been shown and long-term exposure of mice has not indicated carcinogenic properties. DON is classified as a group 3 substance; not classifiable as to its carcinogenicity to humans by IARC (WHO and IARC, 1993).

Data regarding toxicity for modified forms of DON are scarce. However, since 3-Ac-DON, 15-Ac-DON are deacetylated and DON-3-glucoside is cleaved in the intestines, EFSA assumes the same toxicity as for DON. Based on reduced body weight gain in mice a group-tolerable daily intake (TDI) for the sum of DON and the modified forms has therefore been established; 1 µg/kg body weight per day (EFSA, 2017).

Enniatin B (EnB)

Few studies on the in vivo toxicity of EnB have been performed but in vitro results has shown potent cytotoxic activity in mammalian cell-lines (Prosperini et al., 2017). Several other effects are also indicated at cellular level, for instance induction of apoptosis and estrogenic activity, these results are however more preliminary and more research is needed (Prosperini et al., 2017).

EFSA has co-evaluated the risk to human and animal health related to the presence of enniatins and beauvericin in food and feed since these mycotoxins are structurally related (EFSA, 2014). Results indicated that acute exposure to enniatins does not imply concern for human health. As to the chronic exposure, EFSA states that there might be a concern, but due to lack of toxicity data no clear conclusion could be drawn. No acute reference dose or TDI has been established for EnB.

Ochratoxin A (OTA)

During 2020, EFSA published a new risk assessment of OTA in food in which the conclusions differed somewhat from previous risk assessments performed by EFSA and Joint FAO/WHO Expert Committee on Food Additives (JECFA) (EFSA, 2020a, EFSA, 2006, FAO and WHO, 2002). OTA is not acutely toxic, but various adverse effects coupled to chronic exposure are recognised in studies on experimental animals (EFSA, 2020a). Renal toxicity is the most pronounced effect and kidney damages are seen in all tested animal species as well as kidney tumours in rodents. A few epidemiological studies exists but it has not been possible to clearly establish causality between OTA-exposure and adverse effects in humans. However, an Egyptian study has shown raised protein concentrations in urine of infants exposed to high levels of OTA during pregnancy or breast-feeding, indicating kidney effects (Hassan et al., 2006).

Genotoxic properties of OTA have been demonstrated both in vivo and in vitro, however, the underlying mechanisms are unclear and it has not been possible to determine whether OTA is directly genotoxic. EFSA (2020) states that both direct genotoxicity (eg. direct physical DNA damage) and indirect genotoxicity (e.g. oxidative stress) as well as non-genotoxic modes of action might contribute to the OTA-induced tumours seen in rodents. OTA is classified as a group 2B substance; possibly carcinogenic to humans (WHO and IARC, 1993).

Since the mode of action behind renal tumours is unclear, EFSA states that a health-based guideline value is not applicable to OTA. Therefore, the previously applied tolerable weekly intake (TWI) of 120 ng/kg body weight is discarded in the latest risk assessment and the margin of exposure (MOE) is instead considered (EFSA, 2020a). Increased incidences of

kidney lesions in pigs were identified as the critical non-neoplastic effect of OTA (i.e. non-cancerous outcome) and EFSA states that a MOE ≥ 200 is considered as low health concern for these. For neoplasticity, increased incidences of kidney tumours in rats were identified as the critical effects and a MOE ≥ 10.000 is considered to indicate a safe exposure with regard to these.

Exposure assessment – Mycotoxins

Content data

Content data for mycotoxin levels in Swedish cereal consumer products are unfortunately too scarce for a relevant comparison between levels in refined and whole grain products. A similar approach as for cadmium with an in silico cereal fraction where specific products were replaced to account for varying levels of whole grain was therefore not possible. Instead, a literature search was conducted to examine how levels of mycotoxins can differ between whole grain and refined products; results are presented in Table 7. These studies show that the levels of mycotoxins are lower in refined products than in whole grain products; however, how large this difference is varies greatly between the different studies. This might be due to initial differences such as mycotoxin content, cereal type, milling practices etc., or due to differences in product types selected and experimental design.

Table 7. Literature examples on how mycotoxin levels varies in refined and whole grain products.

Mycotoxin	Type of sample	Mean level (µg/kg) Refined	Mean level (µg/kg) Whole grain	% Increase in whole grain	Reference
DON	Wheat flour, UK and Germany	48	63	31	(Wang et al., 2020)
DON	Wheat flour, China	148	309	109	(Zhang et al., 2019)
DON	Cereal based baby foods, Spain	28	49	75	(Herrera et al., 2019)
DON	Wheat flour, Germany	237	404	71	(Schollenberger et al., 2002)
EnB	Durum pasta (medium temp. drying), Spain	4020	4360	8	(Serrano et al., 2015)
EnB	Durum pasta (high temp. drying), Spain	2810	3460	23	(Serrano et al., 2015)
OTA	Wheat flour, UK and Germany	2,9	3,1	7	(Wang et al., 2020)
OTA	Bread (wheat and whole grain or	0,213	0,219	3	(Duarte et al., 2010)

Mycotoxin	Type of sample	Mean level (µg/kg) Refined	Mean level (µg/kg) Whole grain	% Increase in whole grain	Reference
	fibre enriched), Portugal				
OTA	Wheat flour, Turkey	6,9	9,3	35	(Cengiz et al., 2007)
OTA	Bread, Turkey	6,4	7,8	23	(Cengiz et al., 2007)

Several experimental studies have described how mycotoxin levels in cereals are redistributed and affected by milling, these are reviewed in (Schaarschmidt and Fauhl-Hassek, 2018) and (Cheli et al., 2013). Also in these type of studies, the results vary greatly. For instance, levels of EnB and OTA in whole grain flour has been shown to be 40–70% and 43–75% higher, respectively, than levels in white wheat flour (Schaarschmidt and Fauhl-Hassek, 2018). Other studies show no difference of OTA levels between the outer and inner parts of grain kernels, probably due to a deep penetration of the producing mould (Duarte et al., 2010). The mycotoxin that has been studied most extensively in this context is DON in wheat (Cheli et al., 2013, Schaarschmidt and Fauhl-Hassek, 2018). Most studies show a reduction of DON levels of around 20–50% in white flour compared to whole grain but reduction in the range of 11–89% has been reported.

The large variations in results between different studies makes it difficult to draw conclusions on how mycotoxin levels can vary in different product types in a Swedish context. Due to the lack of data, it was not possible to make a detailed assessment of how the exposure to mycotoxins will be affected by an increased whole grain intake. However, since DON is the mycotoxin that has the strongest association with whole grain consumption (Warensjö Lemming et al., 2020), a crude estimate of DON exposure in the three different whole grain scenarios was made.

DON exposure

The estimation of possible increase in DON exposure in the three scenarios (Table 8) followed the same approach as for cadmium, using intake data from the national dietary survey Riksmaten adults 2010–11 and content data from the cereal fraction of the Swedish market basket study 2015. The exceptions being that initial DON exposure was calculated from only the cereal fraction of the market basket and, instead of using an “in silico” fraction to account for a higher whole grain content, a theoretical and general increase of DON was made based on literature data. The content of DON in the cereal fraction in the market basket analysis was 40.4 µg/kg. An increase of 89% in DON content was added to the whole grains part of the fraction in the different scenarios, while the rest of the cereal fraction retained the initial content of DON from the market basket study. The level of 89% increase in whole

grain compared to refined products was chosen based on the highest value identified in experimental studies, representing a worst-case scenario.

Table 8. Theoretical DON content in the cereal fraction and different whole grain scenarios and resulting DON intake levels.

Scenario (proportion whole grain intake of total cereal intake)	DON content in the cereal fraction, estimation based on a worst case assumption (µg/kg)	Median DON intake from cereals (µg/kg bw/day)	99th* percentile DON intake from cereals (µg/kg bw/day)
Present situation	40.4	0.07	0.18
50% whole grain products	52.7	0.09	0.24
75% whole grain products	60.9	0.11	0.28
100% whole grain products	69.0	0.12	0.32

*99th percentile was selected to facilitate comparisons with the biomonitoring studies.

Risk characterization – Mycotoxins

In the current assessment, it has not been possible to characterize what risk the exposure to OTA and EnB would mean if the consumption of whole grain products increased in the Swedish population. For OTA, this is mainly due to lack of data on content levels in whole grain foods as compared to refined cereal foods. For EnB, both lack of content data and lack of toxicological data (no health-based guidance values have been established, see section Hazard characterisation) contributed to the difficulty of making an assessment.

For DON, unlike cadmium, a specific health effect was not chosen as focus of the assessment since lack of human epidemiological data of long-term effects makes it difficult to determine which effect would be most relevant. Instead, the risk characterization focused on if intake may lead to the tolerably daily intake of 1 µg/kg body weight per day being exceeded in any of the scenarios. The analysis was based on theoretical DON content in the cereal fraction and resulting intake levels in Table 8. Results (Table 9) show that the TDI value is not exceeded in any of the scenarios. At most, about one third of the TDI was reached, for high consumers in the 100% whole grain scenario.

Table 9. The percentage of TDI for DON reached by intake of cereals in the different scenarios.

Scenario (proportion whole grain intake of total cereal intake)	DON intake % of TDI* 1st percentile	DON intake % of TDI* Median	DON intake % of TDI* 99th percentile
Present situation	1	7	18
50% whole grain products	1	9	24
75% whole grain products	1	11	28
100% whole grain products	2	12	32

*Based on the theoretical DON content in the cereal fraction and resulting intake levels presented in Table 8.

The estimation of median exposure for the present whole grain intake (0.07 µg/kg bw/day, see Table 8) is in line with biomonitoring results from the national dietary survey Riksmaten Adolescents (Warensjö Lemming et al., 2020) where the median probable daily intake of DON was calculated from urine samples to 0.078 µg/kg bw/day (creatinine adjusted). This indicates that the median estimate for the whole grain scenarios in Table 9 is reasonably correct, and this in turn would mean that, for the majority of the population, an increase in whole grain consumption does not entail a risk of exceeding TDI for DON.

However, biomonitoring results from national dietary survey Riksmaten adults 2010–11 showed that 1% of the tested individuals had an estimated DON-intake above the TDI (Wallin et al., 2013) and the corresponding number in Riksmaten Adolescents was 1.6% (Warensjö Lemming et al., 2020). It is therefore evident that the estimated percentage of TDI in the 99th percentile in Table 9 is an underestimation for some individuals where the true value should be more than 100% of TDI. It is probable that, if whole grain intake in the population increases, a larger proportion of the population will also exceed the TDI for DON, to what extent, however, it is not possible to say at present due to lack of reliable data. Due to this, DON is not further evaluated in the combined risk and benefit characterisation.

Uncertainty analysis – Mycotoxins

The analysis of DON has several and large uncertainties. The content of DON used for the exposure assessment is uncertain, both for refined and whole grain cereal products. In the market basket survey, no levels of DON above the limit of quantification (LOQ) was found in the analysis of the cereal slurry (Livsmedelsverket, 2017b). Therefore, the instrumental level was used as the initial level in the exposure assessment, although these are less reliable than values above LOQ. Furthermore, in the market basket survey, only the free form of DON was

analysed, any modified forms contributing to the exposure would therefore be missed. Mycotoxin levels in cereal has large annual variation depending on climatic factors. Since the analysis in the market basket survey only represents one time point, this means another uncertainty factor linked to the content of DON.

To account for the presumed higher content of DON in whole grain products a general increase of 89% was assumed, based on worst case literature data. Since there is a large variability in the results from different experiments, this figure is very uncertain. The experiments on which the level of 89% was based were performed only in wheat. It is likely that an increase in whole grain intake will also lead to a change in the kinds of cereal consumed (e.g. more oats and rye), but any differences due to different types of cereal have been disregarded. Differences in content levels that might occur during for instance boiling and baking of foods has also been disregarded.

In the exposure assessment, only foods included in the cereal fraction of the market basket survey affected the outcome. However, some foods from other fractions (for instance beer), can be a source of DON and significantly contribute to the exposure for some individuals. The variation in exposure is likely underestimated in this assessment. Although the mean exposure corresponds well to what we observe in biomonitoring studies, our high end estimates are likely too low since we see that a percentage of people do indeed exceed the TDI according to biomonitoring. The contribution from other food groups than cereals may be one reason for this. Regional differences in DON levels in food and the fact that individual products may have higher variability than the mean value for cereal products as a whole, which is used to calculate exposure levels, may also contribute.

Concerning mycotoxins in general it should be noted that, several other mycotoxins than those identified in this assessment may be relevant in the context of whole grain consumption. For instance, ergot alkaloids are most often found in whole grain products, especially in rye, but due to lack of both content and biomonitoring data for these substances, no evaluation was possible. In addition, co-occurrence of two or more mycotoxins in the same raw materials is very common. However, there are still knowledge gaps concerning both occurrence patterns and methodology for risk assessment of co-occurring mycotoxins.

Risk and benefit characterisation

In this report, both positive and negative health effects relating to an increased consumption of whole grains in the Swedish adult population were considered. The potential health effects associated with three different scenarios of whole grain consumption, besides the current situation, were quantified. The present assessment was not based on the use of a common quantitative metric according to which investigated risks and benefits can be integrated (and compared quantitatively). Instead, the overall assessment of risk versus benefit was performed by qualitatively weighting the results in this report. Even though there are challenges associated with this exercise it was considered that the specific questions from risk managers could be adequately addressed using the approach taken. Further analysis may, besides the use of a common metric, consider several outcomes, particularly on the risk side, which would further advance this type of assessment.

Conclusion of the beneficial effects of whole grains

In meta-analyses, prospective studies show a reduction in all-cause mortality, coronary heart disease mortality and incidence, stroke mortality, incidence of type 2 diabetes, colorectal cancer incidence and cancer deaths following a higher intake of whole grains. The observed reductions in risk are considerable, with a 13–34% reduced risk in the outcomes assessed, comparing quantiles of the exposure distribution. Dose-response curves show clear associations with all-cause mortality, coronary heart disease incidence, type 2 diabetes and colorectal cancer with the largest health gains up to around 60 g of whole grains/day (Reynolds et al., 2019). The meta-analyses of RCTs showed a small, but statistically significant reduction in body weight, comparing higher with lower intakes of whole grains. The similar protective effects of higher intake of whole grains and dietary fibre suggest that the beneficial effects of whole grains could be because of their high fibre content.

The low grading of prospective studies (graded as very low to moderate) is a direct consequence of using the GRADE criteria, since only data from RCTs with disease endpoints are able to be categorized as high according to this grading system. The grading of the evidence for etiologic effects of whole grains on coronary heart disease show consistent evidence from several well-designed studies with relatively few limitations.

Our estimates show that even the smallest increase scenario of whole grain intake confers a 7-11% reduction of first incidence of myocardial infarction in the Swedish adult population. In this scenario, 50% of cereal intake consisted of whole grain products and a mean increase of

13 g/day from the current 37 g/day. Applying this reduction on the myocardial infarction incidence for a specific year, this translates into around 500 less incident cases among women and 1,400 less cases among men according to the incidence rate statistics of the Swedish National Board of Health and Welfare 2019 (Swedish National Board of Health and Welfare, 2020).

All together, the consistency of findings, the clear dose-response relationships, the large body of mechanistic evidence all contribute to the totality of evidence and increase the confidence in the findings for the beneficial effects of whole grains on the risk of the major non-communicable diseases (such as coronary heart disease, colorectal cancer, type 2 diabetes as well as all-cause mortality). Even small reductions in the above-mentioned clinical outcomes can result in large public health impact given the high prevalence of these diseases in the population.

Conclusion of the adverse effects of whole grains

An increased cadmium exposure was regarded to be the most relevant toxicological/microbiological risk factor associated with whole grain consumption. In order to derive a risk metric more comparable to that used for the benefit assessment (myocardial infarction cases) the fraction of individuals exceeding the long-term dietary cadmium intake that corresponds to 1 g/g creatinine was computed by simulations, accounting for population variability, instead of simply comparing results to the actual TWI. Based on the current exposure assessment (unadjusted) the associated percentage of the population at risk was then below 1% in all four whole grain scenarios, including the current situation (Table 6). However, if considering adjusted exposures that would more reflect a distribution calibrated to the TWI development the corresponding results are 1 to 2.5% (Table 6). These results are in line with those at the level of urinary cadmium, e.g., within the Swedish environmental monitoring program, indicating that a few percent of Swedish women (aged 50–59) may exceed the critical concentration of 1 µg/g creatinine (Kippler et al., 2020). At the level of the whole Swedish population, which is a conservative scenario, this translates to about 102,000 to 256,000 individuals (adjusted results in Table 6). If assuming 50 years of exposure this would describe an impact of about 2,000 to 5,000 individuals on a yearly basis, and using the present situation as a reference it corresponds to an increase of 400 to 3,000 individuals across the three whole grain scenarios that would exceed the critical concentration of 1 µg cadmium/g creatinine (Table 10).

As noted in the risk characterization, critical urinary cadmium concentrations other than 1 µg/g creatinine have been discussed, and the consequence of changing the critical

concentration in the range of 0.5 to 2 µg/g creatinine was therefore assessed. Overall, the outcome of this exercise likely contributes to covering a significant amount of the uncertainty associated with the present risk assessment. Importantly, however, it should be noted that the most recent EFSA risk assessment is based on 1 µg cadmium/g creatinine in urine. Using the present situation as a reference, the number of individuals exceeding alternative levels of 0.5 and 2 µg/g creatinine increase in the range of 0 to 18,000 across the three whole grain scenarios (Table 10).

Overall conclusion

Across all three scenarios, the reduction in the estimated number of myocardial infarctions was higher than the estimated increase in the number of individuals that exceed EFSA's critical cadmium level (1 µg cadmium/g creatinine in urine), during one specific year (Table 10). In addition, myocardial infarction is a clinical outcome and more severe compared to exceedance of the critical cadmium level. At the critical cadmium exposure it is estimated that 5% exceed a critical level of low-molecular weight proteins in the urine, which has been regarded as an early biomarker of kidney tubular damage. Even when using a lower critical cadmium concentration (i.e., allowing 0.5 µg cadmium/g to represent the same level of long term risk as that associated with 1 µg cadmium/g) the number of individuals at risk of developing kidney damage (assuming a relation to the biomarker) is likely still lower than the number of individuals protected from myocardial infarction.

Thus, it is concluded that the benefit of increased whole grain consumption outweigh the associated risk of increased cadmium exposure at the population level. The net benefits increased with increased consumption of whole grains up to 100% whole grain product (a mean of 103 g/day), which supports choosing whole grains when possible. However, higher whole grain intakes were not assessed. Studies indicate that there may be a plateau of the beneficial effect at intakes of about 100 g/day, why higher intakes are not necessarily associated with the risk-benefit profile assessed in the present report. The mean intake in the Swedish population is far below such intake (37 g/day). Practically achievable increases of the population mean intake are therefore regarded to be within the scenarios used in this risk and benefit assessment.

Table 10. Summary of quantified risks and benefits according to three different scenarios illustrating an increase in whole grain consumption in the adult Swedish population.

Scenario (proportion of whole grain products of total cereal intake)	Estimated reduction in no. of first MI incidence[a] and range[b]	Estimated increase in no. of individuals exceeding the critical cadmium urinary level (1) the corresponding no. of individuals per year (2) and adjusted proportion of the population exceeding critical cadmium urinary level (3)[c]
Present situation	-	1: N/A 2: 2,000 per year (200 – 23,000) 3: 0.01 (<0.001 - 0.11)
50% whole grain products	**All: 2,000** - Women: 530 (160-890) - Men: 1,400 (830-2,000)	**1: 400 per year (0 – 4,000)** 2: 2,400 per year (200 – 27,000) 3: 0.012 (<0.001 - 0.13)
75% whole grain products	**All: 4,600** - Women: 1,400 (420-2,300) - Men: 3,200 (1,900-4,600)	**1: 1,400 per year (0 – 10,000)** 2: 3,500 per year (200 – 33,000) 3: 0.017 (<0.001 - 0.16)
100% whole grain products	**All: 7,400** - Women: 2,200 (690-3,800) - Men: 5,100 (3,000-7,200)	**1: 3,000 per year (0 – 18,400)** 2: 5,100 per year (200 – 41,000) 3: 0.025 (<0.001 - 0.2)

Note: Calculations are based on raw data and abbreviated numbers are presented in the table.
MI=myocardial infarction

[a]based on total number of new incident cases (cases with 7 preceding disease free years) in Sweden year 2019 (Swedish National Board of Health and Welfare, 2020).

[b] based on 95% confidence intervals of the risk estimates (Helnaes et al., 2016).

[c] Fraction of the population exceeding critical dietary cadmium intake corresponding to the critical urinary cadmium concentration of 1 µg/g creatinine where 5% of the population are estimated to exceed a clinical cutoff point of about 300 µg/g creatinine for beta-2 microglobulin (B2M) in urine representing kidney damage. The associated number of individuals is based on a total population of 10,230,000 (Statistics Sweden 2019). For comparison, results associated with urinary cadmium levels of 2 and 0.5 µg/g creatinine, respectively, are given in parenthesis. Results are based on exposures distributions that have been adjusted by a factor 1.4 according to the uncertainty analysis section, see table 6.

Answers to the risk-benefit question

1. **What are the largest health benefits as well as the largest toxicological and microbiological health risks with whole grain consumption?**
   A number of studies have published supporting evidence of the beneficial effects of dietary fibre and/or dietary fibre-rich foods such as whole grain cereals on a number of diseases. The overall results from observational data suggest an inverse association between whole grain intake and mortality (all-cause, cardiovascular-related, stroke-related and total cancer-related) as well as incidences of coronary heart disease, type 2 diabetes, and colorectal cancer (Reynolds et al., 2019). Clinical trials show significantly lower body weight when comparing higher with lower intakes of whole grains. An increased cadmium exposure was regarded to be the most relevant toxicological/microbiological risk factor associated with whole grain consumption.

2. **Are there differences in positive or negative health effects from different types of cereals?**
   Most studies do not have the level of detail to assess the association between whole grain intake from different types of whole grains and health outcomes so the knowledge is limited. In the assessment by Helnaes et al (2016), only whole grain rye and oats (and not wheat) were associated with lower risk of myocardial infarction. In another analysis of the same cohort, all individual whole grain cereal types investigated (rye, wheat, oats) were in general associated with a lower risk of type 2 diabetes (Kyro et al., 2018). In addition, whole grain intake dominated by rye was observed to lower the risk of type 2 diabetes in a study using biomarkers of whole grain wheat and rye to estimate exposure (Biskup et al., 2016). In data analysed at the Swedish Food Agency, rye and oats generally contained lower levels of cadmium than wheat, both in the whole grain and refined fraction.

3. **What health consequences (positive and negative) are expected should the adult population of Sweden increase their current mean whole grain consumption, according to the national dietary survey Riksmaten adult, so that:**

a) 50% of consumed cereal products were whole grain products

b) 75% of consumed cereal products were whole grain products (i.e. ~ 75 g/10 MJ)

c) 100% of consumed cereal products were whole grain products

Across all three scenarios, the reduction in the estimated number of myocardial infarctions was higher than the estimated increase in the number of individuals that exceed EFSA's critical cadmium level (1 µg cadmium/g creatinine in urine), during one specific year. In addition, myocardial infarction is a clinical outcome and more severe compared to exceedance of the critical cadmium level, which has been used as a biomarker of kidney damage. At the critical cadmium exposure it is estimated that 5% exceed a critical level of low-molecular weight proteins in the urine (an early biomarker of tubular kidney damage). Thus, it is concluded that the benefit of increased whole grain consumption outweigh the associated risk of increased cadmium exposure at the population level.

Available data indicate that for the majority of the population, an increase in whole grain consumption does not entail a risk of exceeding TDI for DON. However, there are indications that a proportion of the population does exceed TDI for DON and that more individuals will do so if whole grain intake increases. Due to lack of reliable data it is not possible to assess how large this proportion is and therefore, DON was not further evaluated in the combined risk and benefit characterisation. Also, due to lack of toxicological data as well as content data, it was not possible to characterize the risk of OTA and EnB in relation to whole grain intake.

4. Is it possible to define an optimal intake of whole grains, i.e. the largest possible positive net health effect?

The net benefits increased with increased consumption of whole grains up to 100% whole grain product (i.e. mean intake of approximately 100 g/day), which supports choosing whole grains when possible. However, higher whole grain intakes were not assessed.

References

ALFVEN, T., ELINDER, C. G., CARLSSON, M. D., GRUBB, A., HELLSTROM, L., PERSSON, B., PETTERSSON, C., SPANG, G., SCHUTZ, A. & JARUP, L. 2000. Low-level cadmium exposure and osteoporosis. J Bone Miner Res, 15**,** 1579-86.

AMZAL, B., JULIN, B., VAHTER, M., WOLK, A., JOHANSON, G. & AKESSON, A. 2009. Population toxicokinetic modeling of cadmium for health risk assessment. Environ Health Perspect, 117**,** 1293-301.

AUNE, D., KEUM, N., GIOVANNUCCI, E., FADNES, L. T., BOFFETTA, P., GREENWOOD, D. C., TONSTAD, S., VATTEN, L. J., RIBOLI, E. & NORAT, T. 2016. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies.

BARREGARD, L., SALLSTEN, G., FAGERBERG, B., BORNE, Y., PERSSON, M., HEDBLAD, B. & ENGSTROM, G. 2016. Blood Cadmium Levels and Incident Cardiovascular Events during Follow-up in a Population-Based Cohort of Swedish Adults: The Malmo Diet and Cancer Study. Environ Health Perspect, 124**,** 594-600.

BECHTHOLD, A., BOEING, H., SCHWEDHELM, C., HOFFMANN, G., KNÜPPEL, S., IQBAL, K., DE HENAUW, S., MICHELS, N., DEVLEESSCHAUWER, B., SCHLESINGER, S. & SCHWINGSHACKL, L. 2019. Food groups and risk of coronary heart disease, stroke and heart failure: A systematic review and dose-response meta-analysis of prospective studies. Critical Reviews in Food Science and Nutrition, 59**,** 1071-1090.

BISKUP, I., KYRØ, C., MARKLUND, M., OLSEN, A., VAN DAM, R. M., TJØNNELAND, A., OVERVAD, K., LINDAHL, B., JOHANSSON, I. & LANDBERG, R. 2016. Plasma alkylresorcinols, biomarkers of whole-grain wheat and rye intake, and risk of type 2 diabetes in Scandinavian men and women.

BJERMO, H., SAND, S., NALSEN, C., LUNDH, T., ENGHARDT BARBIERI, H., PEARSON, M., LINDROOS, A. K., JONSSON, B. A., BARREGARD, L. & DARNERUD, P. O. 2013. Lead, mercury, and cadmium in blood and their relation to diet among Swedish adults. Food Chem Toxicol, 57**,** 161-9.

BLANDINO, M., HAIDUKOWSKI, M., PASCALE, M., PLIZZARI, L., SCUDELLARI, D. & REYNERI, A. 2012. Integrated strategies for the control of Fusarium head blight and deoxynivalenol contamination in winter wheat. Field Crops Research, 133**,** 139-149.

CAIRNS-FULLER, V., ALDRED, D. & MAGAN, N. 2005. Water, temperature and gas composition interactions affect growth and ochratoxin A production by isolates of Penicillium verrucosum on wheat grain. Journal of applied microbiology, 99**,** 1215-1221.

CARBALLO, D., TOLOSA, J., FERRER, E. & BERRADA, H. 2019. Dietary exposure assessment to mycotoxins through total diet studies. A review. Food and Chemical Toxicology, 128**,** 8-20.

CENGIZ, M., UZUNOGLU, İ. & SONAL, S. 2007. Ochratoxin A levels in different types of bread and flour. Uludağ Üniversitesi Veteriner Fakültesi Dergisi, 26**,** 7-10.

CHELI, F., PINOTTI, L., ROSSI, L. & DELL'ORTO, V. 2013. Effect of milling procedures on mycotoxin distribution in wheat fractions: A review. LWT - Food Science and Technology, 54**,** 307-314.

CHEN, G.-C., TONG, X., XU, J.-Y., HAN, S.-F., WAN, Z.-X., QIN, J.-B. & QIN, L.-Q. 2016. Whole-grain intake and total, cardiovascular, and cancer mortality: a systematic review and meta-analysis of prospective studies. The American Journal of Clinical Nutrition, 104**,** 164-172.

CHENG, X., NIU, Y., DING, Q., YIN, X., HUANG, G., PENG, J. & SONG, J. 2016. Cadmium Exposure and Risk of Any Fracture: A PRISMA-Compliant Systematic Review and Meta-Analysis. Medicine (Baltimore), 95**,** e2932.

DE ANGELIS, C., GALDIERO, M., PIVONELLO, C., SALZANO, C., GIANFRILLI, D., PISCITELLI, P., LENZI, A., COLAO, A. & PIVONELLO, R. 2017. The environment and male reproduction: The effect of cadmium exposure on reproductive function and its implication in fertility. Reprod Toxicol, 73**,** 105-127.

DTU FØDEVAREINSTITUTTET 2015. Danskernes kostvaner 2011-2013 (Dietary habits in Denmark 2011-2013). Søborg, Denmark.

DUARTE, S. C., BENTO, J., PENA, A., LINO, C. M., DELERUE-MATOS, C., OLIVEIRA, M. B. P. P., ALVES, M. R. & PEREIRA, J. A. 2010. Influencing factors on bread-derived exposure to ochratoxin A: Type, origin and composition. Food and Chemical Toxicology, 48**,** 2139-2147.

EFSA 2006. Opinion of the Scientific Panel on contaminants in the food chain [CONTAM] related to ochratoxin A in food. EFSA journal, 4**,** 365.

EFSA 2009. SCIENTIFIC OPINION Cadmium in food. The EFSA Journal.

EFSA 2014. Panel on Contaminants in the Food Chain Scientific Opinion on the risks to human and animal health related to the presence of beauvericin and enniatins in food and feed. Efsa Journal, 12**,** 3802.

EFSA 2017. Panel on Contaminants in the Food Chain Risks to human and animal health related to the presence of deoxynivalenol and its acetylated and modified forms in food and feed. EFSA journal, 15**,** e04718.

EFSA 2020a. Panel on Contaminants in the Food Chain Risk assessment of ochratoxin A in food. EFSA Journal, 18**,** e06113.

EFSA 2020b. Panel on Contaminants in the Food Chain Scientific Opinion on the update of the riskassessment of nickel in food and drinking water. EFSA Journal, 18**,** 6268.

EFSA PANEL ON DIETETIC PRODUCTS, N. & ALLERGIES 2009. Scientific Opinion on the substantiation of health claims related to beta glucans and maintenance of normal blood cholesterol concentrations (ID 754, 755, 757, 801, 1465, 2934) and maintenance or achievement of a normal body weight (ID 820, 823) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal, 7**,** 1254.

EFSA PANEL ON DIETETIC PRODUCTS, N. & ALLERGIES 2010. Scientific Opinion on the substantiation of health claims related to wheat bran fibre and increase in faecal bulk (ID 3066), reduction in intestinal transit time (ID 828, 839, 3067, 4699) and contribution to the maintenance or achievement of a normal body weight (ID 829) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal, 8**,** 1817.

EFSA PANEL ON DIETETIC PRODUCTS, N. & ALLERGIES 2011a. Scientific Opinion on the substantiation of health claims related to beta-glucans from oats and barley and maintenance of normal blood LDL-cholesterol concentrations (ID 1236, 1299), increase in satiety leading to a reduction in energy intake (ID 851, 852), reduction of post-prandial glycaemic responses (ID 821, 824), and “digestive function” (ID 850) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal, 9**,** 2207.

EFSA PANEL ON DIETETIC PRODUCTS, N. & ALLERGIES 2011b. Scientific Opinion on the substantiation of health claims related to oat and barley grain fibre and increase in faecal bulk (ID 819, 822) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal, 9**,** 2249.

FAGERBERG, B. & BARREGARD, L. 2021. Review of cadmium exposure and smoking-independent effects on atherosclerotic cardiovascular disease in the general population. J Intern Med, 290**,** 1153-1179.

FAO 2020. Climate change: Unpacking the burden on food safety. Food Safety and Quality Series. Rome, Italy: Food and Agricultural Organisation of the United Nations.

FAO & WHO 2002. Joint Expert Committee on Food Additives Safety evaluation of certain food additives and contaminants, World Health Organization.

FARDET, A. 2010. New hypotheses for the health-protective mechanisms of whole-grain cereals: what is beyond fibre? Nutrition Research Reviews, 23**,** 65-134.

FILIPPINI, T., TORRES, D., LOPES, C., CARVALHO, C., MOREIRA, P., NASKA, A., KASDAGLI, M.-I., MALAVOLTI, M., ORSINI, N. & VINCETI, M. 2020. Cadmium exposure and risk of breast cancer: A dose-response meta-analysis of cohort studies. Environment International, 142**,** 105879.

FREDLUND, E., GIDLUND, A., SULYOK, M., BÖRJESSON, T., KRSKA, R., OLSEN, M. & LINDBLAD, M. 2013. Deoxynivalenol and other selected Fusarium toxins in Swedish oats—Occurrence and correlation to specific Fusarium species. International journal of food microbiology, 167**,** 276-283.

FREIRE, L. & SANT'ANA, A. S. 2018. Modified mycotoxins: An updated review on their formation, detection, occurrence, and toxic effects. Food and Chemical Toxicology, 111**,** 189-205.

GALLAGHER, C. M., KOVACH, J. S. & MELIKER, J. R. 2008. Urinary cadmium and osteoporosis in U.S. Women >or= 50 years of age: NHANES 1988-1994 and 1999-2004. Environ Health Perspect, 116**,** 1338-43.

GERMUNDSON, L. 2013. Comparison of consumption and intake data in the Market Basket 2010 and Riksmaten 2010-11. Uppsala, Sweden: Sveriges lantbruksuniversitet, Institutionen för livsmedelsvetenskap.

GLYNN, A. 2017. Kadmium i livsmedel. Riskvärderingsrapport. Rapport 15 del 2. Livsmedelsverket.

HASSAN, A. M., SHEASHAA, H. A., FATTAH, M. F., IBRAHIM, A. Z., GABER, O. A. & SOBH, M. A. 2006. Study of ochratoxin A as an environmental risk that causes renal injury in breast-fed Egyptian infants. Pediatr Nephrol, 21**,** 102-5.

HELNAES, A., KYRO, C., ANDERSEN, I., LACOPPIDAN, S., OVERVAD, K., CHRISTENSEN, J., TJONNELAND, A. & OLSEN, A. 2016. Intake of whole grains is associated with lower risk of myocardial infarction: the Danish Diet, Cancer and Health Cohort. Am J Clin Nutr, 103**,** 999-1007.

HERRERA, M., BERVIS, N., CARRAMIÑANA, J. J., JUAN, T., HERRERA, A., ARIÑO, A. & LORÁN, S. 2019. Occurrence and Exposure Assessment of Aflatoxins and Deoxynivalenol in Cereal-Based Baby Foods for Infants. Toxins, 11**,** 150.

HJERTEFORENINGEN. 2018. Aldersstandardiseret rate per 100.000 personer viser antallet af nye tilfælde af blodprop i hjertet (AMI) per 100.000 personer for hvert år. [Online]. Available at: Hjertföreningens website https://hjerteforeningen.shinyapps.io [Accessed 24 September 2021].

IBSEN, D. B., M., L., CHIU, Y.-H., STERN, D. & TOBIAS, D. 2021. Re: Evaluating agreement between bodies of evidence from randomised controlled trials and cohort studies in nutrition research: meta-epidemiological study. BMJ, 374**,** n1864.

INSTITUTE FOR HEALTH METRICS AND EVALUATION. 2020. Global Burden of Disease (GBD) 2019 [Online]. Seattle, WA: IHME, University of Washington: GBD Compare VizHub. Available at: Vizhubs website https://vizhub.healthdata.org [Accessed 09 September 2021].

JOHNSEN, N. F., FREDERIKSEN, K., CHRISTENSEN, J., SKEIE, G., LUND, E., LANDBERG, R., JOHANSSON, I., NILSSON, L. M., HALKJAER, J., OLSEN, A., OVERVAD, K. & TJONNELAND, A. 2015. Whole-grain products and whole-grain types are associated with lower all-cause and cause-specific mortality in the Scandinavian HELGA cohort. Br J Nutr, 114**,** 608-23.

JULIN, B., VAHTER, M., AMZAL, B., WOLK, A., BERGLUND, M. & AKESSON, A. 2011. Relation between dietary cadmium intake and biomarkers of cadmium exposure in premenopausal women accounting for body iron stores. Environ Health, 10**,** 105.

JULIN, B., WOLK, A., BERGKVIST, L., BOTTAI, M. & AKESSON, A. 2012a. Dietary cadmium exposure and risk of postmenopausal breast cancer: a population-based prospective cohort study. Cancer Res, 72**,** 1459-66.

JULIN, B., WOLK, A., JOHANSSON, J. E., ANDERSSON, S. O., ANDREN, O. & AKESSON, A. 2012b. Dietary cadmium exposure and prostate cancer incidence: a population-based prospective cohort study. Br J Cancer, 107**,** 895-900.

JÄRUP, L. & ÅKESSON, A. 2009. Current status of cadmium as an environmental health problem. Toxicology and applied pharmacology, 238 3**,** 201-8.

KOLLANDER, B. & SUNDSTRÖM, B. 2023. Cadmium and other elements in “novel food” and in food currently contributing the most to exposure of cadmium from food in Sweden”. International Journal of Environmental Research and Public Health (IJERPH), (under pressing).

KIPPLER, M., BROBERG, K., WENNBERG, M., HOVGARD, A., SÄLLSTEN, G., LUNDH, T. & ASSARSSON, E. 2020. Hälsorelaterad miljöövervakning – biomonitorering av kadmium i urin hos svenska och utländska kvinnor. In: SYD, A.-O. M. (ed.) Rapport 5:2020. Arbets- och miljömedicin Syd.

KISSOCK, K. R., NEALE, E. P. & BECK, E. J. 2020. Whole Grain Food Definition Effects on Determining Associations of Whole Grain Intake and Body Weight Changes: A Systematic Review. Adv Nutr.

KYRO, C., TJONNELAND, A., OVERVAD, K., OLSEN, A. & LANDBERG, R. 2018. Higher Whole-Grain Intake Is Associated with Lower Risk of Type 2 Diabetes among Middle-Aged Men and Women: The Danish Diet, Cancer, and Health Cohort. J Nutr, 148**,** 1434-1444.

KYRØ, C., SKEIE, G., DRAGSTED, L. O., CHRISTENSEN, J., OVERVAD, K., HALLMANS, G., JOHANSSON, I., LUND, E., SLIMANI, N., JOHNSEN, N. F., HALKJÆR, J., TJØNNELAND, A. & OLSEN, A. 2011. Intake of whole grains in Scandinavia is associated with healthy lifestyle, socio-economic and dietary factors. Public Health Nutrition, 14**,** 1787-1795.

LEE, H. J. & RYU, D. 2017. Worldwide occurrence of mycotoxins in cereals and cereal-derived food products: Public health perspectives of their co-occurrence. Journal of Agricultural and Food Chemistry, 65**,** 7034-7051.

LINDBLAD, M., GIDLUND, A., SULYOK, M., BÖRJESSON, T., KRSKA, R., OLSEN, M. & FREDLUND, E. 2013. Deoxynivalenol and other selected Fusarium toxins in Swedish wheat—Occurrence and correlation to specific Fusarium species. International Journal of Food Microbiology, 167**,** 284-291.

LIVSMEDELSVERKET 2009. Mögel och mykotoxiner i livsmedel. Livsmedelsverkets rapportserie nr 4/2009. Uppsala, Sweden: Livsmedelsverket.

LIVSMEDELSVERKET 2012. Riksmaten vuxna 2010-11. Livsmedels- och näringsintag bland vuxna i Sverige. Uppsala, Sweden: Livsmedelsverket.

LIVSMEDELSVERKET 2014. Fusariumsvampar och dess toxiner i svenskodlad vete och havre. Livsmedelsverkets rapportserie nr 2/2014. Uppsala, Sweden: Livsmedelsverket.

LIVSMEDELSVERKET 2015. Oorganisk arsenik i ris och risprodukter på den svenska marknaden. Rapport 16.

LIVSMEDELSVERKET 2017a. Kadmium i livsmedel -riskvärderingsrapport. Livsmedelsverkets rapportserie nr 15 del 2/2017. Livsmedelsverket.

LIVSMEDELSVERKET 2017b. Swedish Market Basket Survey 2015. Livsmedelsverkets rapportserie nr 26/2017. Uppsala, Sweden: Livsmedelsverket.

LUND, F. & FRISVAD, J. C. 2003. Penicillium verrucosum in wheat and barley indicates presence of ochratoxin A. Journal of Applied Microbiology, 95**,** 1117-1123.

MANN, K. D., PEARCE, M. S., MCKEVITH, B., THIELECKE, F. & SEAL, C. J. 2015. Whole grain intake and its association with intakes of other foods, nutrients and markers of health in the National Diet and Nutrition Survey rolling programme 2008-11. The British journal of nutrition, 113**,** 1595-1602.

MEJBORN, H., BILTOFT-JENSEN, A., TROLLE, E. & TETENS, I. 2008. Definition and scientific background for recommendations of wholegrain intake in Denmark. Soeborg: Fødevareinstituttet, Danmarks Tekniske Universitet.

MEZYNSKA, M. & BRZÓSKA, M. M. 2018. Environmental exposure to cadmium—a risk for health of the general population in industrialized countries and preventive strategies. Environmental Science and Pollution Research, 25**,** 3211-3232.

MICHA, R., SHULKIN, M. L., PENALVO, J. L., KHATIBZADEH, S., SINGH, G. M., RAO, M., FAHIMI, S., POWLES, J. & MOZAFFARIAN, D. 2017. Etiologic effects and optimal intakes of foods and nutrients for risk of cardiovascular diseases and diabetes: Systematic reviews and meta-analyses from the Nutrition and Chronic Diseases Expert Group (NutriCoDE). PLoS One, 12**,** e0175149.

MOBERG, L., NILSSON, P. M., SAMSIOE, G., SALLSTEN, G., BARREGARD, L., ENGSTROM, G. & BORGFELDT, C. 2017. Increased blood cadmium levels were not associated with increased fracture risk but with increased total mortality in women: the Malmo Diet and Cancer Study. Osteoporos Int, 28**,** 2401-2408.

NORDIC COUNCIL OF MINISTERS 2014. Nordic Nutrition Recommendations 2012. Integrating nutrition and physical activity. 5th edition. Nord 2014:002.

PARIKKA, P., HAKALA, K. & TIILIKKALA, K. 2012. Expected shifts in Fusarium species' composition on cereal grain in Northern Europe due to climatic change. Food Additives & Contaminants: Part A, 29**,** 1543-1555.

PROSPERINI, A., BERRADA, H., RUIZ, M. J., CALONI, F., COCCINI, T., SPICER, L. J., PEREGO, M. C. & LAFRANCONI, A. 2017. A review of the mycotoxin enniatin B. Frontiers in public health, 5**,** 304.

REYNOLDS, A., MANN, J., CUMMINGS, J., WINTER, N., METE, E. & TE MORENGA, L. 2019. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. Lancet, 393**,** 434-445.

SADEGHI, O., SADEGHIAN, M., RAHMANI, S., MALEKI, V., LARIJANI, B. & ESMAILLZADEH, A. 2020. Whole-Grain Consumption Does Not Affect Obesity Measures: An Updated Systematic Review and Meta-analysis of Randomized Clinical Trials. Adv Nutr, 11**,** 280-292.

SAND, S. & BECKER, W. 2012. Assessment of dietary cadmium exposure in Sweden and population health concern including scenario analysis. Food Chem Toxicol, 50**,** 536-44.

SAND, S., HÉRAUD, F. F. & ARCELLA, D. 2013. The use of chemical occurrence data at European vs. national level in dietary exposure assessments: a methodological study. 62.

SATARUG, S. & MOORE, M. R. 2004. Adverse health effects of chronic exposure to low-level cadmium in foodstuffs and cigarette smoke. Environ Health Perspect, 112**,** 1099-103.

SCHAARSCHMIDT, S. & FAUHL-HASSEK, C. 2018. The fate of mycotoxins during the processing of wheat for human consumption. Comprehensive Reviews in Food Science and Food Safety, 17**,** 556-593.

SCHOLLENBERGER, M., JARA, H. T., SUCHY, S., DROCHNER, W. & MÜLLER, H. M. 2002. Fusarium toxins in wheat flour collected in an area in southwest Germany. International Journal of Food Microbiology, 72**,** 85-89.

SCHWINGSHACKL, L., BALDUZZI, S., BEYERBACH, J., BROCKELMANN, N., WERNER, S. S., ZAHRINGER, J., NAGAVCI, B. & MEERPOHL, J. J. 2021. Evaluating agreement between bodies of evidence from randomised controlled trials and cohort studies in nutrition research: meta-epidemiological study. BMJ, 374**,** n1864.

SCHWINGSHACKL, L. A.-O., SCHWEDHELM, C., HOFFMANN, G., LAMPOUSI, A. M., KNÜPPEL, S., IQBAL, K., BECHTHOLD, A., SCHLESINGER, S. & BOEING, H. 2017. Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies.

SERRANO, A. B., FONT, G., MAÑES, J. & FERRER, E. 2015. Effects of technological processes on enniatin levels in pasta. Journal of the Science of Food and Agriculture, 96**,** 1756-1763.

SLAVIN, J. 2003. Why whole grains are protective: biological mechanisms. Proc Nutr Soc, 62**,** 129-34.

SOCIALSTYRELSEN. 2018. Statistikdatabas för hjärtinfarkter [Online]. Available at: Socialstyrelsens website https://sdb.socialstyrelsen.se [Accessed 24 September 2021].

SUWASONO, Y., SAND, S., VAHTER, M., SKERFVING, S., LIDFELDT, J., ÅKESSON, A. 2010. Benchmark dose for cadmium-induced osteoporosis in women. Toxicol Lett 197, 123-127.

SWEDISH NATIONAL BOARD OF HEALTH AND WELFARE 2020. Statistics on Myocardial infarctions 2019. Health and medical care.

THIELECKE, F. & NUGENT, A. P. 2018. Contaminants in Grain-A Major Risk for Whole Grain Safety? Nutrients, 10**,** 1213.

TINKOV, A. A., FILIPPINI, T., AJSUVAKOVA, O. P., SKALNAYA, M. G., AASETH, J., BJORKLUND, G., GATIATULINA, E. R., POPOVA, E. V., NEMERESHINA, O. N., HUANG, P. T., VINCETI, M. & SKALNY, A. V. 2018. Cadmium and atherosclerosis: A review of toxicological mechanisms and a meta-analysis of epidemiologic studies. Environ Res, 162**,** 240-260.

VAN DER FELS-KLERX, H., KLEMSDAL, S., HIETANIEMI, V., LINDBLAD, M., IOANNOU-KAKOURI, E. & VAN ASSELT, E. 2012. Mycotoxin contamination of cereal grain commodities in relation to climate in North West Europe. Food Additives & Contaminants: Part A, 29**,** 1581-1592.

WALLIN, M., BARREGARD, L., SALLSTEN, G., LUNDH, T., KARLSSON, M. K., LORENTZON, M., OHLSSON, C. & MELLSTROM, D. 2016. Low-Level Cadmium Exposure Is Associated With Decreased Bone Mineral Density and Increased Risk of Incident Fractures in Elderly Men: The MrOS Sweden Study. J Bone Miner Res, 31**,** 732-41.

WALLIN, S., GAMBACORTA, L., KOTOVA, N., LEMMING, E. W., NÄLSÉN, C., SOLFRIZZO, M. & OLSEN, M. 2015. Biomonitoring of concurrent mycotoxin exposure among adults in Sweden through urinary multi-biomarker analysis. Food and Chemical Toxicology, 83**,** 133-139.

WALLIN, S., HARDIE, L., KOTOVA, N., LEMMING, E. W., NÄLSÉN, C., RIDEFELT, P., TURNER, P., WHITE, K. & OLSEN, M. 2013. Biomonitoring study of deoxynivalenol exposure and association with typical cereal consumption in Swedish adults. World mycotoxin journal, 6**,** 439-448.

WANG, J., HASANALIEVA, G., WOOD, L., MARKELLOU, E., IVERSEN, P. O., BERNHOFT, A., SEAL, C., BARANSKI, M., VIGAR, V., ERNST, L., WILLSON, A., BARKLA, B. J., LEIFERT, C. & REMPELOS, L. 2020. Effect of wheat species (Triticum aestivum vs T. spelta), farming system (organic vs conventional) and flour type (wholegrain vs white) on composition of wheat flour; results of a retail survey in the UK and Germany – 1. Mycotoxin content. Food Chemistry, 327**,** 127011.

WARENSJÖ LEMMING, E., MONTANO MONTES, A., SCHMIDT, J., CRAMER, B., HUMPF, H.-U., MORAEUS, L. & OLSEN, M. 2020. Mycotoxins in blood and urine of Swedish adolescents—Possible associations to food intake and other background characteristics. Mycotoxin research, 36**,** 193-206.

WHO & IARC 1993. Some naturally occurring substances: food items and constituents, heterocyclic aromatic amines and mycotoxins. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, 56.

ZHANG, Y., PEI, F., FANG, Y., LI, P., ZHAO, Y., SHEN, F., ZOU, Y. & HU, Q. 2019. Comparison of concentration and health risks of 9 Fusarium mycotoxins in commercial whole wheat flour and refined wheat flour by multi-IAC-HPLC. Food Chemistry, 275**,** 763-769.

ÅKESSON, A., BERGLUND, M., SCHUTZ, A., BJELLERUP, P., BREMME, K. & VAHTER, M. 2002. Cadmium exposure in pregnancy and lactation in relation to iron status. Am J Public Health, 92**,** 284-7.

ÅKESSON, A., JULIN, B. & WOLK, A. 2008. Long-term dietary cadmium intake and postmenopausal endometrial cancer incidence: a population-based prospective cohort study. Cancer Res, 68**,** 6435-41.

Appendix 1

Literature searches to identify hazards

Searches were performed between April and June 2020 in the PubMed database with the combinations of search terms listed below. The selection of literature further assessed was made on the basis of title and summary.

Search 1:

(“Whole grain”[tiab] OR “Whole grains”[tiab] OR wholegrain[tiab] OR wholegrains[tiab] OR "Whole Grains"[Mesh]) AND ("Cadmium"[Mesh] OR cadmium [tiab] OR "Nickel"[Mesh] OR nickel[tiab] OR "Acrylamide"[Mesh] OR acrylamide[tiab])
This search identified 24 articles, but did not clearly identify additional chemicals in foods beyond those already considered. Acrylamide was identified to be of potential relevance (2 articles), but was not prioritized since data on the concentration in whole grain products, e.g. cereals, was very limited.

Search 2:

(“Whole grain”[tiab] OR “Whole grains”[tiab] OR wholegrain[tiab] OR wholegrains[tiab] OR "Whole Grains"[Mesh]) AND ("Mycotoxins"[Mesh] OR mycotoxin*[tiab] OR ochratoxin A[tiab] OR OTA [tiab] OR Deoxynivalenol [tiab] OR DON[tiab] OR 3 Ac DON[tiab] OR 15-Ac-DON[tiab] OR DON-3-glucoside [tiab] OR “T2 toxin”[tiab] OR "mycotoxin T2"[tiab])
This search yielded 39 articles, identifying several mycotoxins as a potential relevance in whole grain.

The Swedish Food Agency has food-based dietary guidelines that advises the population to choose whole grains instead of refined grains to decrease several diet-related diseases. Compared with refined grains, however, whole grain products contain more cadmium and certain other undesirable substances such as mycotoxins. In order to be able to answer whether the current recommendation on increased whole grain consumption is scientifically motivated based on existing data on both risks and benefits, a risk-benefit assessment of whole grain products is needed. This report will assist risk managers at the Swedish Food Agency to make a scientifically based decision on this issue.
