Metrix - Risk-benefit assessment of foods

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Indhold

Introduction

In April 2015 Fødevareforlig 3 regarding chemistry in food was adopted by the Danish Parliament. Fødevareforlig 3 included research projects on

- Analytical methodology for chemical screening and analyses in food surveillance,
- Strengthened risk assessment of chemicals, and
- Risk-benefit assessment of foods.

This report is for the Metrix project - Risk-benefit assessment of foods.

Additional funding has been obtained from the European Food Safety Authority (EFSA) for a risk-benefit expert workshop held in Copenhagen 2017.

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Metrix – Risk-benefit assessment of foods

1.1 Overall aim

The overall aim of the Metrix project is to quantify positive and negative health impacts of nutrients, foods and diets, which are used to perform risk-benefit assessments, calculate burden of disease estimates, and ranking of food-associated risks in Denmark

1.2 Risk ranking of food-associated hazards in Denmark

1.2.1 Aim

The overall aim of the project was to estimate the public health impact of a selected list of food-associated hazards in Denmark.

The specific objectives were:

- To develop and apply burden of disease methods to estimate the impact of a selected list of priority chemical and microbiological foodborne hazards.
- To apply methods to estimate the relative contribution of different foods for estimated burden of disease.
- To rank foodborne hazards and foods on the basis of estimate burden of disease.
- To identify and characterize groups of Danish individuals whose dietary and lifestyle patterns have high burden of disease due to exposure to foodborne chemical hazards.

1.2.2 Methods/Activities

The foodborne hazards addressed were selected on the basis of available evidence of their public health impact (i.e. reported incidence), of recent scientific studies conducted at the institute or published in peer-reviewed literature, and of the latest evidence as published in the report “DK som foregangsland”. The initial hazard list was defined upon agreement with FVST, and revised along the way on the basis of data availability and resources. From this list, case studies on chemical and microbiological hazards were implemented. The current list of hazards assessed includes seven microbiological agents and four chemical hazards (Tables 1.2.2 and 1.2.3). The burden of a fifth chemical hazard (dioxin) has been estimated, but results are not presented because the analysis will be updated with recently published data.

We estimated disease burden in terms of a composite health metric that takes into account incidence, mortality, duration and severity of all health outcomes that can occur due to exposure to the hazard, the *disability adjusted life year* (DALY). This metric is widely used in burden of disease and risk ranking studies globally.

Estimating the burden of disease of a food-associated hazard requires 1) estimating total incidence and mortality of all health outcomes of related to exposure to the chemical/hazard in the population, and 2) integrating these with data on the duration and severity of each health outcome to estimate DALYs. Methodologies to estimate the burden of chemical and microbiological hazards in foods vary, and some of the differences are explained below.

Burden of disease of chemical hazards in foods

To estimate the burden of disease of dietary exposure to chemical hazards, we applied a risk assessment approach in a model that incorporates three modules: i) the *exposure module*, where the mean daily exposure to the hazard in the population is estimated; ii) the *health outcome module*, in which the probability of occurrence of the selected health outcomes following exposure to the hazard is estimated based on dose-response models; and iii) the *DALY Module*, where the estimated incidence of the health outcomes is integrated with disease duration and disability weights to calculate the Burden of Disease (BoD) in terms of DALY's. Data were retrieved from the Danish National Survey of Diet and Physical Activity (DANSDA) (food consumption data); from food monitoring surveillance (food contamination data); from scientific literature (dose-response data; disability weights); and from national statistics (disease incidence, mortality).

Burden of disease of microbiological hazards in foods

To estimate the burden of foodborne pathogens that are notifiable in Denmark, we estimate incidence by correcting notified cases for underdiagnoses and underreporting of each disease. We re-constructed the surveillance pyramid as described by. The model consists of a set of non-pathogen specific and pathogen-specific parameters defined by probability distributions. These parameters were informed by data collected through a population-based telephone survey conducted in 2009 , by evidence from National Health Registries, or by literature review. Estimated multipliers were applied to surveillance data from 2017 (available at SSI www.ssi.dk). To estimate the burden of non-notifiable diseases, we used data from terminated surveillance or from total disease envelopes as published by WHO and the Global Burden of Disease study. Data were retrieved from public health surveillance data (number of reported vases); from scientific literature and national surveys (underreporting; disability weights; etiology proportions; probability of health outcomes); and from international data bases (mortality).

Even though all pathogens of focus can be transmitted to humans through consumption of contaminated foods, most can also be transmitted through other routes of transmission, e.g. environmental, direct contact with animals or human-to-human contact. To estimate the disease burden caused by microbiological hazards that is due to foodborne transmission, we combined total DALY estimates with food attribution proportions for each pathogen.

1.2.3 Results

From the three studied chemical hazards present in foods, we estimated that MeHg caused the highest burden of disease in Denmark (478 DALYs). Acrylamide lead to the second highest disease burden (30 DALYs). Because we estimated the disease burden that was caused by exposure to foods only, 100% of this burden is be attributed to dietary exposure.

Table 1.2.1 Estimated cases and deaths and disease burden of dietary exposure to three chemical hazards in Denmark, 2017 (mean and 95% confidence interval).

Hazard	Estimated cases	Estimated deaths	Years lived with disability (YLD)	Years of life lost (YLL)	Disability adjusted life years (DALY)	DALY/100,000
Methylmercury	335	0	477.7 [149.1-952.3]		477.7 [149.1-952.3]	10.2 [3.2-20.3]
In. Arsenic	1.58	0.38	2.06 [1.56-2.55]	3.91	5.97 [5.48-6.46]	0.11 [0.10-0.12]
Acrylamide	5.3	2.15	11.15	18.65	29.8	0.6

Among foodborne pathogens, we estimated that *Campylobacter* caused the highest burden of disease (1,709 DALYs), followed by Salmonella (492) and norovirus (485) (Table 1.2.2). Listeriosis caused 196 DALYs, the majority of which (95%) corresponding to years of life lost due to mortality (186 YLL). Despite the low number of cases, congenital toxoplasmosis was responsible for the loss of 164 years of healthy life. When focusing on the disease burden that can be attributed to contaminated foods, the ranking changed, with particularly norovirus decreasing in contribution to overall health impact (Table 1.2.3).

Table 1.2.2. Reported cases, estimated cases and deaths and disease burden of seven foodborne pathogens in Denmark, 2017 (mean and 95% confidence interval).

Hazard	Reported cases	Estimated cases	Estimated deaths	YLD	YLL	DALYs	DALYs/100,000	Ranking position
Salmonella	1,065	10,386 [8,792-12,153]	28	210 [199-222]	282	492 [481-504]	8.6 [8.4 – 8.8]	2
Campylobacter	4,231	58,141 [49,617–71,781]	56	1013 [969–1,060]	696	1709 [1,665-1,755]	29.7 [29.0 – 30.5]	1
STEC	338	10,565 [7,209-14,562]	1	30 [22 - 41]	33	63 [51 - 77]	1.1 [0.9 – 1.3]	7
Yersinia enterocolítica	354	5,019 [4,312-5,839]	5	96 [89 - 110]	64	160 [152 - 174]	2.8 [2.7 – 3.0]	6
Norovirus		185,060 [156,506-212,627]	25.9 [20.4-31.7]	128.6 (106.3-153.4)	356.3 (280.4-435.8)	485 [398-573.1]	8.6 [7.0-10.1]	3
Congenital toxoplasmosis	-	10 [8-12]	1 [1-2]	53 [32-77]	112 [81-153]	165 [126-222]	-	5
Listeriosis	58	58	12	14.2 [11.4-16.9]	186.4	196 [193.5-198.5]	3.4 [3.4-3.5]	4

Table 1.2.3. Total disease burden and food-associated disease burden caused by seven foodborne pathogens in Denmark, 2017.

Hazard	Total DALY	Proportion Foodborne*	Foodborne DALY	Ranking position
Salmonella	492 [481- 504]	76%	374	2
Campylobacter	1709 [1,665-1,755]	76%	1299	1
STEC	63 [51 - 77]	60%	38	7
Yersinia enterocolítica	160 [152 - 174]	100%	160	4
Norovirus	485 [398-573.1]	18%	86	6
Congenital toxoplasmosis	164 [126-212]	61%	100	5
Listeriosis	196 [193.5-198.5]	100%	196	3

*Hald et al., 2016.

1.2.4 Discussion

Estimating the burden of disease caused by chemical and microbial hazards has different requirements and challenges, the latter being mostly linked to estimating the incidence and mortality of disease. These are for example linked to the type of health outcomes that exposure leads to (i.e. acute or chronic), to the availability of surveillance and epidemiological evidence, and to knowledge of the presence and effects of hazards in foods.

We concluded that, among the four chemical hazards studied, MeHg caused the highest burden in the population. The foods contributing to the estimated DALY estimated varied for each pathogen (results not shown).

Among foodborne pathogens, *Campylobacter* and *Salmonella* lead the ranking in burden of disease and estimated incidence. Even though the highest estimated incidence was for norovirus, the disease burden that can be attributed to contaminated foods was low because severity and duration of disease are low, and because a small fraction of cases are caused by ingestion of contaminated foods (human-to-human transmission playing a major role). Some diseases with low incidence in the population, specifically listeriosis and congenital toxoplasmosis) had a substantial burden of disease because disease outcomes are very severe.

Comparing disease burden of chemicals and pathogens is challenging. Reasons for this include the fact that they have very different health outcomes, and that there are diverse levels of strength of evidence for the two types of hazards. Furthermore, we focused only on health impact (as measured in DALYs), but a risk ranking exercise should be a complex integration of various other indicators, including e.g. economic impact and the potential for and type of interventions.

One of the major limitations encountered was on estimating the burden of disease of chemicals, which is challenging in many ways. First, establishing the link between exposure to a chemical

hazard and the development of disease is difficult because the health outcomes may not observed for years following exposure. We applied a risk assessment approach, in which we estimated incidence of disease due to exposure by combining current exposure with available dose-response data. The latter are available from animal studies or epidemiological evidence, and are a large source of uncertainty. However, for most chemicals we were either not able to measure this uncertainty, or could measure it partially. As an example, when estimating the disease burden due to exposure to Cd, I-As and Acrylamide, uncertainty in dose-response was not quantified. Second, consumers are exposed to multiple chemical hazards continuously, and exposure assessments need to account for long-time exposure through foods and other sources and link this with the probability of adverse health effects. Third, exposure to multiple chemicals with similar health effects may potentially lead to synergistic effects. Lastly, human data linking exposure to effect (i.e. dose-response) are often lacking, and estimations typically need to rely on animal studies.

Several improvements and further developments are planned for the next three years under the Metrix project.

1.2.5 Conclusions

The approaches developed allow for estimating the public health impact of food-associated hazards in the population, as well as the relative contribution of different foods for this disease burden. These will be useful for establishing priorities for food safety interventions aimed at reducing the risk of disease due to chemical and microbiological hazards in foods. Further developments of these methods and assessment of more food-associated hazards will allow for a more complete risk ranking exercise.

1.3 Risk-benefit assessment - food substitutions

Risk-benefit assessment (RBA) of foods is a tool used for weighting the adverse and beneficial health effects associated with food consumption. RBA offers support to policy makers by providing evidence on the overall health impact of e.g. dietary interventions or food policies, and thus can provide guidance for public health promotion. So far, most existing RBAs have been conducted by only considering one food in isolation from the whole diet. However, the change in consumption of one food will likely change the consumption of other foods in the diet, which may influence human health. Only very few RBAs have accounted for substitution of foods; most of these compared exposures to nutrients and contaminants to established health-based guidance values and dietary reference values, respectively, without accounting for the overall health impact in terms of morbidity and mortality of the associated diseases.

1.3.1 Aim

The overall aim was to develop an approach for integrating food substitutions in RBA that allows for the quantification of the associated long-term health impact. Case studies based on the Danish food-based dietary guidelines were conducted to fulfill this aim.

1.3.2 Methods/Activities

The health impact of substituting red and processed meat by fish to reach the recommended intake of fish (350 g/week) in the Danish adult diet was investigated in two case studies. Two different approaches to model the substitution were taken. The first case study[1] based the substitution on a deterministic approach, assuming the same substitution behavior across the Danish population. The influence of the choice of fish species consumed on the overall health impact was investigated in four alternative scenarios, assuming also a change in the fish species consumed before substitution.

In order to get more detailed insight in which subgroups will experience a health loss and a health gain, respectively, the variability in the overall health impact was assessed in the second case study[2] investigating the same substitution as the first case study. Variability between individual substitution behaviors was simulated using a probabilistic approach. In order to reflect only between-individual variability in the distribution of long-term intakes before and after the substitution, without the day-to-day variability for each individual, a model to adjust intake differences for within-individual variability was proposed. The approach taken for the substitution and modeling of long-term intake differences allowed for a quantification of the health impact at the individual level to reflect variability in the overall health impact of the theoretical intervention.

1.3.3 Results

The results of the first case study showed that the overall health impact of substituting red and processed meat by fish varies depending on the fish species consumed. The largest health gain

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[1] Sofie Theresa Thomsen, Sara Monteiro Pires, Brecht Devleesschauwer, Morten Poulsen, Sisse Fagt, Karin Hess Ygil, Rikke Andersen, Investigating the risk-benefit balance of substituting red and processed meat with fish in a Danish diet, Food and Chemical Toxicology, Volume 120, 2018, Pages 50-63, https://doi.org/10.1016/j.fct.2018.06.063. (http://www.sciencedirect.com/science/article/pii/S027869151830437X)

[2] Sofie Theresa Thomsen, Waldo de Boer, Sara M. Pires, Brecht Devleesschauwer, Sisse Fagt, Rikke Andersen, Morten Poulsen, Hilko van der Voet, A probabilistic approach for risk-benefit assessment of food substitutions: A case study on substituting meat by fish, Food and Chemical Toxicology, Volume 126, 2019, Pages 79-96, https://doi.org/10.1016/j.fct.2019.02.018. (URL: http://www.sciencedirect.com/science/article/pii/S0278691519300699)

was observed when all the fish consumed was either a mix of fatty and lean fish (according to average preferences in Denmark) or only fatty fish. A smaller health gain was estimated when only consuming lean fish, while a marked health loss was estimated when all fish consumed was tuna. Women in the childbearing age were identified as a particularly sensitive subgroup based on the estimated health impact of maternal fish consumption on the neurodevelopment of unborn children.

The substitution model proposed in the first case study did not account for variability in substitution behaviors in the population. The variability in the final health outcome was not assessed either. Meanwhile, these limitations were addressed in the second case study.

The results of the second case study showed that large variations exist in the overall health impact of substituting red and processed meat by fish in the Danish adult population. Elderly, in particular men (> 50 years of age), experienced the highest health gain, along with women in the child-bearing age (in particular those between 25 and 40 years of age), who were assigned the health impact experienced by their yet unborn children. However, a small fraction of these young women were assigned an overall health loss, primarily due to the adverse effects of methyl mercury on fetal neurodevelopment.

1.3.4 Discussion

The two case studies proposed methods to integrate food substitution in RBA. Both the deterministic and the probabilistic substitution models suggest approaches to account for substitution of foods, and the choice of model will depend on which questions need be answered. The deterministic substitution model is valuable for defining extreme or “worst-case” scenarios, whereas the probabilistic substitution model is useful for investigating the variability in substitution behavior and the resulting health impact to identify sensitive subgroups in the population. We found that the overall health impact of the change in consumption of one food may depend on which other foods are changed as a consequence, stressing the need for accounting for substitution in RBA.

Challenges related to the integration of substitution in RBA remain. The estimates obtained from RBA are associated with uncertainty. Dose-response models were identified as a particular source of the quantified uncertainty in the RBA studies conducted in this thesis. Uncertainties associated with the choice of data for the dose-response modeling are difficult to quantify but contributes to the overall uncertainty of the estimated health impact. The implications of the choice of data to model the association between intake of a food or food component and a health effect were also investigated. Large variation between dose-response functions based on data associating a health effect with either an intake of a food component, a non-specified substitution of a food, or a specified substitution between foods was illustrated.

By estimating the health impact only based on the effects associated with the intake of a food component, the potential impact of the food matrix on the diet-disease association is neglected, while calculations based on association measures for non-specified substitutions ignore underlying food substitutions. When not specified in the statistical analysis of observational studies, it is unclear which substitution is reflected in the association measures and thus in the results of RBAs, building on these association measures. Furthermore, the health impact estimated in RBAs of food substitutions may in fact be a mixture of food substitutions, including other substitutions than that investigated.

1.3.5 Conclusions

In conclusion, two different methods to model substitution were proposed. A deterministic substitution model, assuming the same substitution behavior across the population, and a probabilistic substitution, which accounted for variability in substitution behaviors, were developed. Both models presented limitations and advantages, and the choice of approach for modeling substitution depends on the RBA question.

The largest health gain was observed when all the fish consumed was either a mix of fatty and lean fish (according to average preferences in Denmark) or only fatty fish. A smaller health gain was estimated when only consuming lean fish, while a marked health loss was estimated when all fish consumed was tuna. The health impact was found to vary between subgroups, with the highest health gain observed among women in the childbearing age and the older generations, mainly men. An overall health loss was estimated for a small proportion of women in the childbearing age due to adverse effects of chemical exposures that would be experienced by their unborn children. Our results suggest a need for targeted public health guidance.

Scenario analyses should be encouraged when different dose-response data with sufficient strength of evidence are available. Assumptions and limitations of the epidemiological study behind the dose-response data should be acknowledged and communicated along with the final results. Finally, the need for specification of food substitution in human observational studies was emphasized.

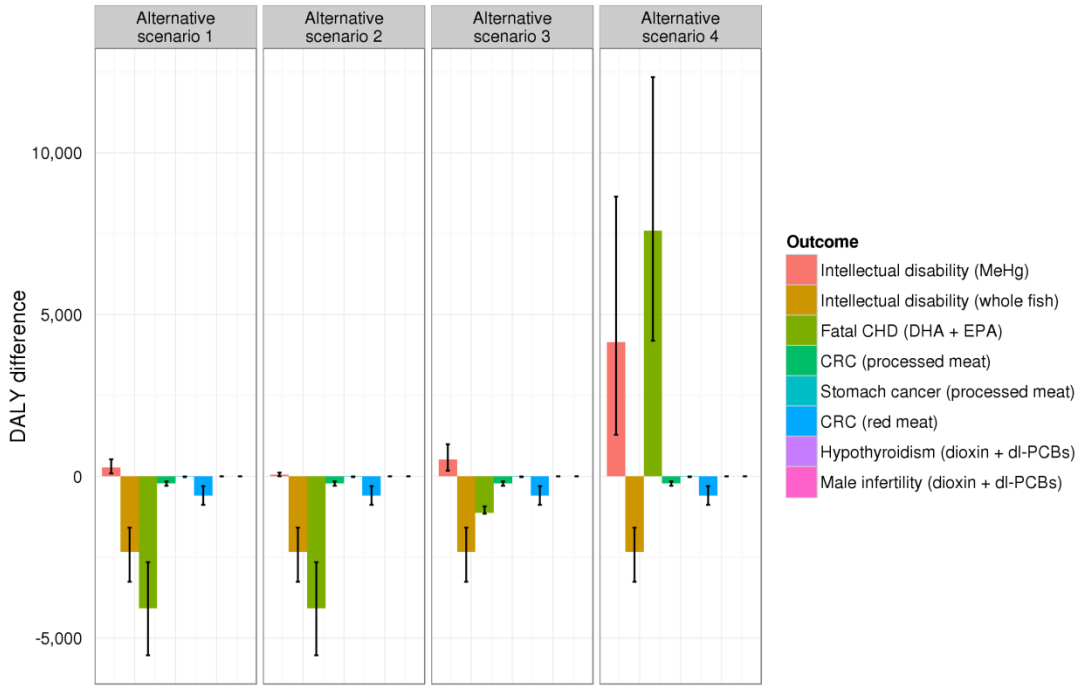

Fig 1.3.1. Difference in Disability-Adjusted Life Years (DALYs) by scenario and outcome. Contribution of each health outcome to the overall DALY difference estimates for each alternative scenario for the total Danish adult population (≥ 15 years; 4.7 million individuals). Each bar represents the health impact of the substitutions on individual health effects. Error bars indicate 95% uncertainty intervals.
Abbreviations: CRC: colorectal cancer; DALY: disability-adjusted life years; DHA: docosahexaenoic acid; dl-PCB: dioxin-like polychlorinated biphenyl; DW: disability weight; EPA: eicosapentaenoic acid; MeHg: methyl mercury.

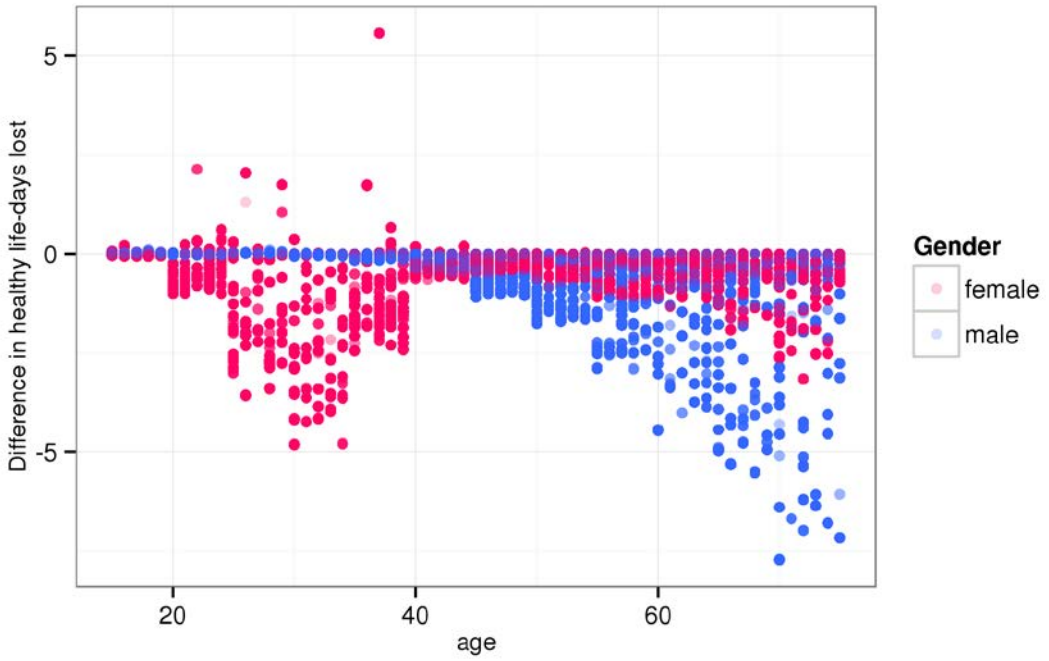

Figure 1.3.2 Total individual differences in healthy life-days lost by age and sex for the 100,000 simulated individuals. The individual health impact is expressed as the estimated individual difference in healthy lifedays lost between the reference and alternative scenario. Red dots represent women and blue dots represent men. Negative differences imply a health gain and positive differences imply a health loss. Age is given in years.

1.4 Risk-benefit assessment - Health impact of substituting brown for polished rice in the Danish population

1.4.1 Aim

Wholegrains contain a range of vitamins and minerals, are an important source of dietary fiber and consumption is associated with risk reduction of non-communicable diseases, including type 2 diabetes (T2DM), cardiovascular disease (CVD) and colorectal cancer (CRC). Therefore, choosing wholegrain products over refined grain products is recommended in the Danish food-based dietary guidelines (FBDG) in order to reach a daily intake of 75 g wholegrain per 10 MJ as a part of a healthy diet. Rice is a cereal and can be consumed either as wholegrain (brown rice) or refined (white rice); following the Danish FBDG, white rice should therefore be replaced by brown in a diet to reduce risk of disease. However, brown rice may also be a source of inorganic arsenic (iAs) specifically present in the germ and bran of the rice grain. IAs has by the International Agency for Research on Cancer (IARC) been classified as carcinogenic to humans. The risk of cancer due to iAs in rice and other food products including water has been assessed previously, but has never been assessed in comparison to potential beneficial health effects of brown rice.

The primary aim of this study was to quantify the health impact, in terms of DALY, of substituting white rice consumption by brown rice in the average and high-intake Danish consumers. As a secondary aim, we evaluated the impact on disease risk depending on effect sizes derived via the food (i.e. rice) consumed as a whole or via the individual food components (i.e. fiber and iAs). We evaluated the sensitivity of the model due to the uncertainty of the dose response relationship for iAs and of the evidence of effect of fiber on risk of CVD.

1.4.2 Methods/Activities

In order to assess the health impact of substituting brown for white rice in the average and high intake Danish rice consumers, we investigated the following four scenarios:

1) Changing the current daily mean consumption of white and brown rice to 100% brown rice
2) Changing the current daily mean consumption of white and brown rice to 100% polished rice
3) Changing the current daily consumption of the 95th percentile (P95) of white and brown rice to 100% brown rice
4) Changing the current daily consumption of the 95th percentile (P95) of white and brown rice to 100% white rice

As beneficial and hazardous compounds in rice we identified cereal fiber and IAs, respectively. Through systematic literature reviews we chose to account for the health effects of which convincing evidence for a cause effect relationship was found, shown in figure 1.4.1 The amount of rice consumed in the Danish population was obtained from the Danish National Survey on Diet and Physical Activity (DANSDA). The relation between exposure and the associated health effect was described by a dose-response relationship, identified in the literature.

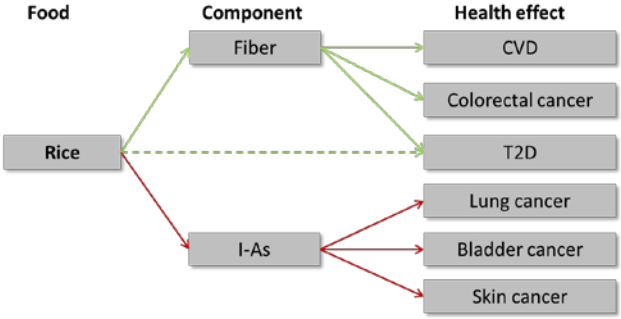

Figure 1.4.1 Conceptual overview of the risk benefit assessment of rice. Full arrows represent the connection between the food via food components and associated health effects selected to be included in the model. Dashed arrow represents the direct association between the food and health effects. Green arrows indicate beneficial health effects; red arrows indicate adverse health effects. I-As = inorganic arsenic; CVD = cardiovascular disease.

1.4.3 Results

Several dose-response relationship has in the literature been applied to characterize the risk of the different cancers due to exposure to iAs. We therefore evaluated the impact of the different relationships. The DALY per 100,000 individuals attributed to iAs from rice in each scenario showed significant differences between reference and alternative scenarios per dose response relationship for inorganic arsenic exposure and lung, bladder or skin cancer. In the risk benefit assessment, we apply a conservative approach for iAs and use the most conservative dose response function for each cancer.

The health impact of substituting white rice by brown rice per health effect calculated as the DALY difference per 100,000 Danish inhabitants between reference and alternative scenarios per health effect showed significant difference in the overall health impact by the summed DALY from each health effect. The DALY calculations were based on the most conservative dose response relationships between inorganic arsenic and health effects for lung (Ferreccio, 2000), skin (Chiou, 2001) and bladder cancer (Morales, 2001).

1.4.4 Discussion

Overall, we found a beneficial health impact of substituting white rice by brown in the average and high-intake Danish consumers. The model is, however, sensitive to the dose response relationships used and health effects accounted for. The evidence on the relation between fiber and CVD is not convincing and we evaluated the overall health impact if CVD was excluded. We still found an overall health benefit from the substitution, but not of the same magnitude. It should be mentioned that it is unlikely that rice fiber is a prominent contributor to the cereal fiber studied in cohort studies, which might have an impact on the effect sizes. By characterizing the beneficial effect on T2DM using evidence on rice as a whole consumed results in a larger overall health benefit than when only the effect of fiber is considered. This highlights the food matrix's impact on the disease relation compared to when single nutrients are considered. The exposure to iAs when high consumers substitute to 100% brown rice leads to a margin of exposure of approx. 2 - 50 using the lower and higher level of EFSAs $BMDL_{0.1}$ range, respectively. As brown rice is only a minor contributor to the wholegrain consumption in the diet of both the average and high intake consumers, it is therefore relevant to consider if wholegrain

should primarily come from other sources than rice in order to limit exposure to iAs, despite the overall beneficial health impact found in this study.

1.4.5 Conclusions

We found an overall beneficial health impact by substituting white rice by brown in both the average and high intake Danish consumers. However, the margin of exposure of iAs is very small, why it should be considered whether wholegrain should primarily come from other sources than brown rice, despite the beneficial effects.

1.5 Risk-benefit assessment - linseed intake in the Danish population

1.5.1 Aim

A quantitative risk-benefit assessment is in-progress to evaluate the overall health impact of consumption of whole linseeds in the Danish adult population.

1.5.2 Methods/Activities

Based on epidemiological evidence, potential health effects associated with intake of these different components contained in whole linseeds were identified (Figure 1.5.1). These included fiber, α-linolenic acid and cadmium. We applied estimates for the identified dose-response relationship between intake of these components and chronic health effects.

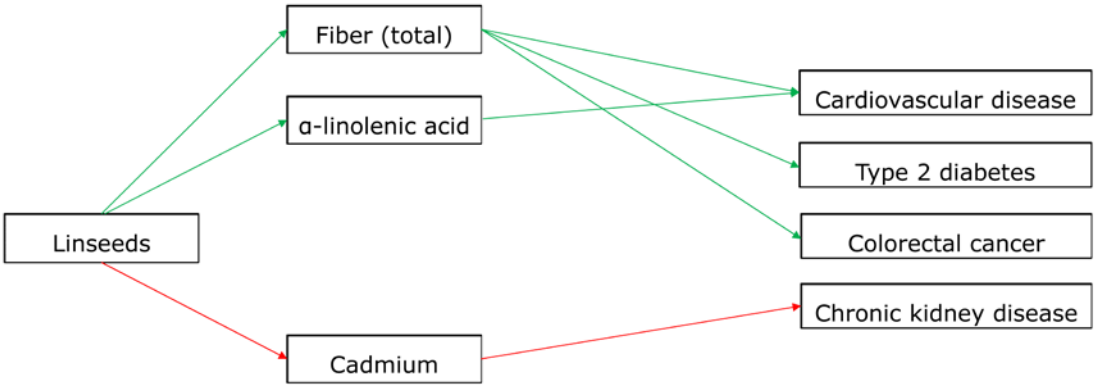

Figure 1.5.1. Overview of identification of potential chronic health effects related to exposure to specific components contained in linseeds. The green lines indicate beneficial health effects, whereas the red lines indicate adverse health effects.

The current intake of linseeds was compared with different scenarios reflecting consumers with different eating patterns leading to moderate or very high intakes of whole linseeds. The defined intake scenarios ranged from 1.4 g/d (current intake) to 45 g/d (5 tablespoons). The calculation of the current intake of linseeds was based on estimated exposure through intake of bread by combining Danish dietary surveys 2011-2015 data (7-day food records) with 2015 sale data from Gfk ConsumerScan. Concentration data on fiber, α-linolenic acid and cadmium (maximal value) was obtained from Frida Food data. For cadmium, the estimation included background exposure data (maximal value) obtained from the Chemical contaminants 2004-2011 report that was added to the estimated cadmium exposure from linseeds.

Scenario	Intake description	Linseeds (g/d)
Reference (current intake)	50th percentile for intake of bread with and without seeds	1.5
1	97.5th percentile for intake of bread with and without seeds	4.1
2	97.5th percentile for intake of bread with seed	7.1
3	97.5th percentile intake of bread with seed + ½ tablespoon	11.6
4	97.5th percentile intake of bread with seed + 1 tablespoon	16.1
5	2 tablespoons	18.0
6	3 tablespoons	27.0
7	4 tablespoons	36.0
8	5 tablespoons	45.0

* 1 tablespoon of linseeds = 9 g

The quantitative assessment was performed by weighting risks and benefits using a composite health measure, Disability Adjusted-Life-Years (DALYs). The difference in DALYs for the specified scenarios compared with current estimated intake (reference intake) was calculated as follows: DALY difference = DALY (alternative scenario) – DALY (reference intake).
The calculations were made for the Danish population between 15 and 75 years of age.

Table 2. Concentration of nutrients and contaminants in linseeds.

	Concentration data	
Compound	**Concentration**	**Data source**
Fiber	30.4 g/100 g	Finland 2017[b]
ALA	25 g/100 g[a]	Finland 2017[b]
Cadmium	0.21 mg/kg (min: 0.10 mg/kg, max: 0.52 mg/kg)	Finland 2017[b]
Cyanide	300 mg/kg (min: 140 mg/kg, max: 330 mg/kg)	Control Project Report, Denmark 2014

Abbreviations: ALA: alpha-linolenic acid; bw: body weight;
[a] The percentage of total fatty acids in linseeds was 58%.
[b] Oil Seed Mapping and Control project.

1.5.3 Results/Discussion/Conclusion

Preliminary results indicated that intake of linseeds from bread seems to have a slight beneficial effect in the general Danish adult population. For higher intake levels of whole linseed, the risk-benefit balance still is in the beneficial direction. At higher intake levels of linseed there are some uncertainties related to the calculations and uncertainties related to the absorption of the substances from the whole seed. Since the high intake scenarios are extrapolating beyond the observable intake range, the beneficial effect may be overestimated, as the dose-response relations due to biological plausible reasons could be expected to level off.

Regarding absorption, it is assumed that all fiber, α-linolenic acid and cadmium in the linseeds are absorbed. However, data from humans indicate that the absorption of cadmium from the diet is relatively low (3–5 %). Similarly, in sunflower seeds, data suggest that only about 10% of the cadmium is absorbed. A low absorption rate probably also account for α-linolenic acid in linseeds.
Even though, high intake of linseeds had a beneficial health outcome in the RBA, fiber, and α-linolenic acid accounting for the beneficial effects can also be obtained from other foods, thereby avoiding the cadmium present in linseeds.

A manuscript based on these results is under preparation and will be submitted to a peer-reviewed scientific journal.

1.6 Development of a method to optimize personalized fish intake recommendations

1.6.1 Aim

The aim is to develop methods for generating food-based personalized dietary advice. The research was directed at the application of mathematical optimization techniques for different challenges regarding this topic and fish intake in Denmark was used as a case study. Three specific objectives were formulated to achieve the aim:

- To develop a model for generating personalized fish intake recommendations
- To analyze the effect of including individual variation in background exposure when modeling personalized fish intake recommendations
- To develop a model for generating a trade-off curve between deviation from preference and cost for optimized personalized intake recommendations

1.6.2 Methods/Activities

Mathematical optimization techniques are applied for generating personalized fish intake recommendations that account for individual dietary patterns, a set of pre-defined health related criteria, and optionally cost. Mathematical optimization involves finding the minimum of an objective function subject to a set of constraints. The constraints represent requirements that limit the candidate choices of the problem and the objective function determines the best choice among feasible candidates. Model constraints of our models included recommendations for eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and vitamin D and tolerable levels for methyl mercury, dioxins, and polychlorinated biphenyls (dl-PCBs). The study population was 3,016 Danish adults from the Danish National survey of Diet and Physical Activity (DANSDA). The outcome is described in three papers:

- Paper A. Use of mathematical optimization models to derive healthy and safe fish intake (published)
- Paper B. Personalized fish intake recommendations: the effect of background exposure on optimization (published)
- Paper C. Optimizing healthy and safe fish intake recommendations: a trade-off between personal preference and cost (under revision)

An overview of the model of the three studies is provided in Figure 1.6.1

	Paper A	Paper B	Paper C
Objective function	Minimize deviation from preference		Minimize deviation from preference and cost *or* cost
Constraints	EPA+DHA, vitamin D, methyl mercury, dioxins+dl-PCBs		
Background Exposure	Estimated Averages	Individual values Scenario analysis	Individual values
New species in advice	Allowed *or* not allowed	Allowed *or* not allowed	Allowed
Study population	3,016 Danish adults from DANSDA		

Figure 1.6.1 Overview of the model of the three studies

In Paper A and B, personalized fish intake advice is obtained by minimizing the deviation from current observed fish intake subject to the constraints. This approach generates recommendations that are as close as possible to the individuals' current observed consumption. Such advice may be more relevant and achievable for the individuals as compared to advice that deviate more from personal preferences. Background exposure needs to be included in the modeling because fish may not be the only source of the considered nutrients and contaminates. In Paper B, the effect of including individual variation in background exposure was analyzed through a scenario analysis with 24 background exposure scenarios. The background exposure sources included were foods other than fish, vitamin D supplements, sun, and air. In Paper C, the model minimized deviation from preference and cost simultaneously, with different relative importance of the cost. Hence, individual optimal trade-off curves between deviation from personal preference and cost could be generated.

The idea behind optimization of fish intake is not to suggest that existing general food-based dietary guidelines should be replaced in any way, but rather to provide methods for developing compliments or alternatives to such population-based advice.

1.6.3 Results

The intake of 350 g fish/week of which 200 g should be fatty fish, i.e., the Danish official food-based dietary guidelines for fish, is in our model shown to be healthy and not harmful, according to the model constraints. However, following this advice may for individuals require large behavior changes, which may lead to lack of compliance. This is illustrated in figure 1.6.2. The results are sensitive to variation in background exposure, especially the background exposure of vitamin D, which can be provided by several sources, i.e., foods, supplements, and sun. This is illustrated in Figure 1.6.3. For a winter scenario, when the supplement intake data is excluded, the individuals who reported an intake of vitamin D supplements should be recommended to increase their fish intake a lot more.

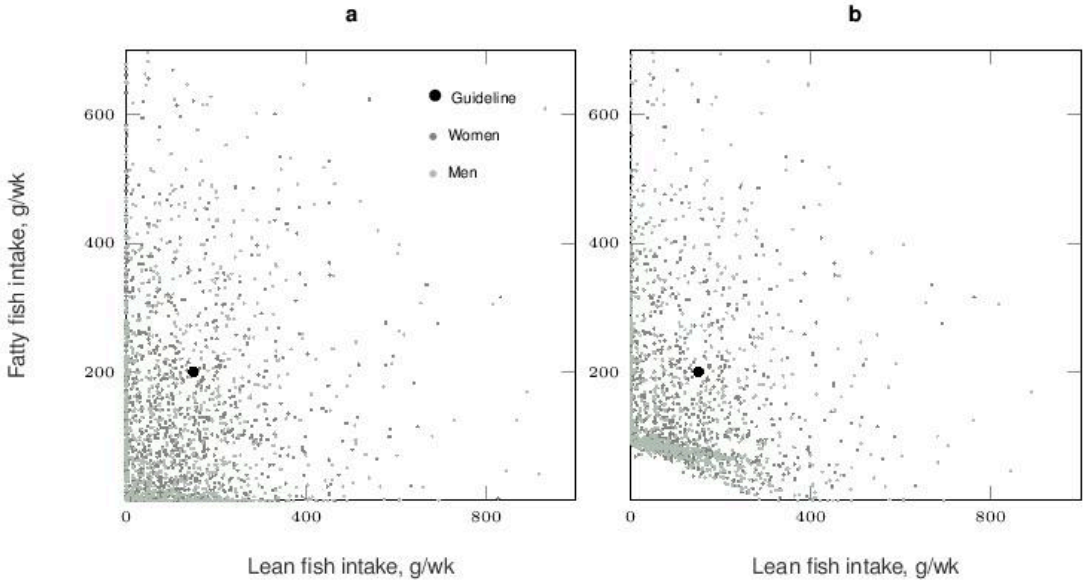

Figure 1.6.2. Observed reported intake of lean and fatty fish for 3,016 individuals from DANSDA (1,552 women and 1,464 men) **(a)** and modelled recommended fish intake with the baseline background exposure scenario (some vitamin D provided by the sun, individual data on background intakes/exposure to the nutrients/constraints, and individual vitamin D supplement data) **(b).**

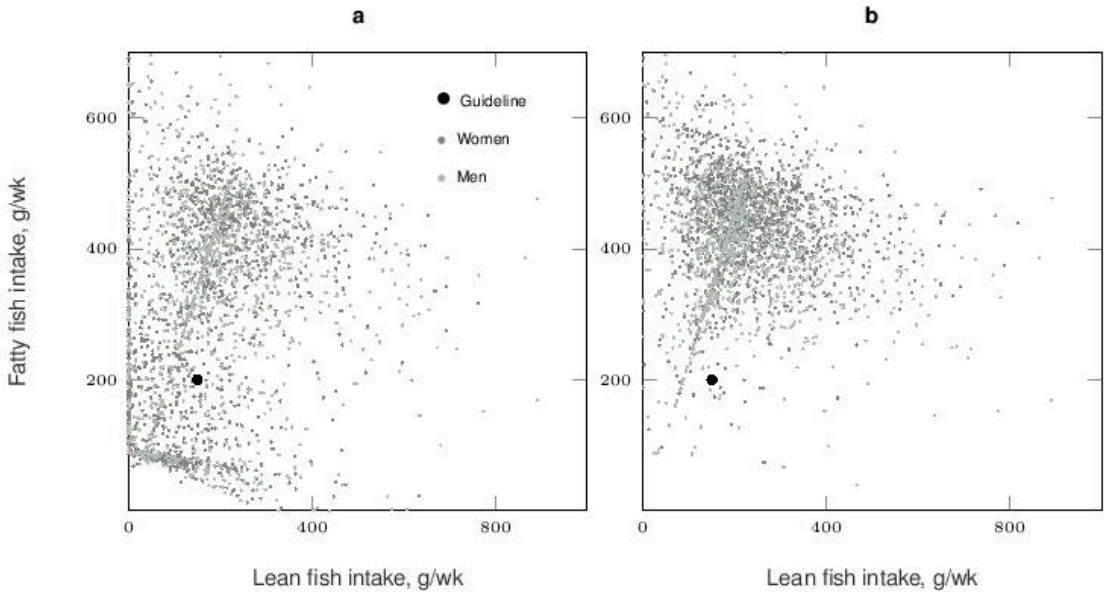

Figure 1.6.3. Modelled recommended fish intake for with the winter scenario (no vitamin D provided by the sun, individual data on background intakes/exposure to the nutrients/constraints, and individual vitamin D supplement data) **(a)** and the winter scenario without vitamin D supplements **(b).**

1.6.4 Discussion

The model can be extended to other nutrients, contaminants, and foods, and utilized to provide recommendations that are adapted to individuals. By minimizing the need for large and ultimately unrealistic changes in behavior, our hypothesis is that this approach may have the potential to increase compliance with guidelines. A further development and expansion of this approach may therefore have an impact on the promotion of health and prevention of disease in

populations. The results of this method should be applied in a real-life setting in order to validate their impact. In this paper, we assume that the personalized dietary recommendations deviating as little as possible from current consumption will have higher adherence than general FBDG, but it is not verified. Exploring this would require knowledge from other research fields.

1.6.5 Conclusions

In conclusion, it was shown that mathematical optimization, specifically quadratic programming, can be used to derive achievable personalized recommended fish intakes that deviate as little as close as possible from individual observed consumption and ensure a safe and healthy fish consumption pattern. The method also be expanded to consider cost of fish intake and individual optimal trade-off curves between observed fish intake and cost of fish can be generated.

1.7 Overall discussion

RBA builds on the risk assessment framework, which is a scientific process that includes the four steps: hazard identification, hazard characterization (dose-response assessment), exposure assessment, and risk characterization. In RBA, a parallel process for characterizing benefits is included and an additional fifth step is introduced, which integrate risks and benefits.

In the Metrix project, disease burden for a number of food associated risks in Denmark have been quantified and risk-benefit assessment have been performed for a few specific foods. In connection with this work the following models and methods have been developed: a model to estimate the disease burden of chemicals, an optimization method to calculate the optimal intake of foods, and a substitution model that can be used to assess the health impact of e.g. different diets. These new methods and models will give the food authority tools that can be used to prioritise health intervention and thereby lead to improved food safety.
The outcome of the specific risk-benefit assessments performed in this project showed in general that the beneficial nutritional effects outweighed the adverse effect arising from contaminants. Even though the beneficial effects seemed to dominate for the foods assessed, the intake of contaminants at high intake levels are not negligible. It could therefore, for each food be considered, whether the beneficial compounds present could be obtained through intake via other food sources that do not contain these contaminants. However, such other food may also contain contaminants that raise additional health concern.

As in food risk assessment, the data and models used in risk-benefit assessment are always associated with uncertainty, related to missing data, restrictions in the data, representativeness of the data and modelling assumptions. This uncertainty is reflected in the assessment done, implying uncertainty about the risk-benefit balance and uncertainty in the estimated health impact. In our risk benefit assessments, uncertainty is usually addressed by statistical analysis of the data and scenario analyses. These scenario analysis compare different modelling assumptions and/or best- and worst-case scenarios. The uncertainty analysis gives insight in the importance of different sources of uncertainty, and allows risk managers to take the uncertainty of the impact of risk management decisions into account.
In international food safety risk analysis, uncertainty currently gains increasing attention, as exemplified by the guidelines for uncertainty assessment recently published by EFSA and a workshop on Uncertainty in risk assessments, organised by BfR and EFSA (Berlin, feb 2019). We aim to take advantage of these recent developments in our future risk benefit assessment through our international collaboration and involvement in EFSA.

1.8 Overall conclusions

In the Metrix project, disease burden for a number of food associated risks in Denmark have been quantified and risk-benefit assessment have been performed for specific foods. The implementation of these new methods and models will give the food authority tools that can be used to prioritise health intervention and thereby lead to improved food safety.

1.9 Perspectives

The models and methods developed in the Metrix project during the project has been used to assess a number of specific foods and food associated risks. These methods and models are however generic and can be used to assess a range of other foods and food risks. The methods and models have been described in peer-reviewed papers and have led to a number of

international collaborations. As a consequence risk-benefit projects have been taken up in a number of other European countries.
Metrix has also collaborated with EFSA on RBA, which has led to one sponsored workshop, a summer school on RBA, one EU FORA fellow working at DTU with RBA and two granted EFSA projects within RBA. EFSA consider RBA as one of their priority areas.

Dissemination

The work performed within the Metrix project has been published in a number of peer-reviewed paper (see references). More papers will be submitted during the next months. The Metrix project and results obtained herein has be presented more than 20 times at national and international meetings, workshops and conferences.

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(Results from the research projects can be found in the published papers below. Publications from Metrix are in bold)

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