

Estimation of micronutrient intake distributions:

Development of methods to support food
and nutrition policy making

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Thesis

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ABSTRACT

Introduction

Adequate and safe micronutrient intake is important. Both insufficient and excessive intakes should be prevented as these can be associated with negative health effects. Therefore, the population intake distribution will ideally lay between insufficient and excessive intakes. For the development and evaluation of nutrition and food policy a good estimation of dietary micronutrient intake is of great importance.

Aim

Three challenges were addressed to improve the estimation of population micronutrient intake distributions: 1) how to estimate current habitual micronutrient intake when (detailed) data are lacking or data from different sources should be combined, 2) how to predict future intakes in order to support policy making, and 3) how to estimate a maximum safe fortification level per food item. The aim of this PhD-thesis is to further develop and apply statistical models which can cope with these challenges.

Methods & Results

Data from the Dutch National Food Consumption Surveys (DNFCSs) were used to develop and apply statistical models which can cope with the defined challenges. In addition, data from the Dutch food composition database (NEVO) and the Dutch dietary supplement database (NES) were used.

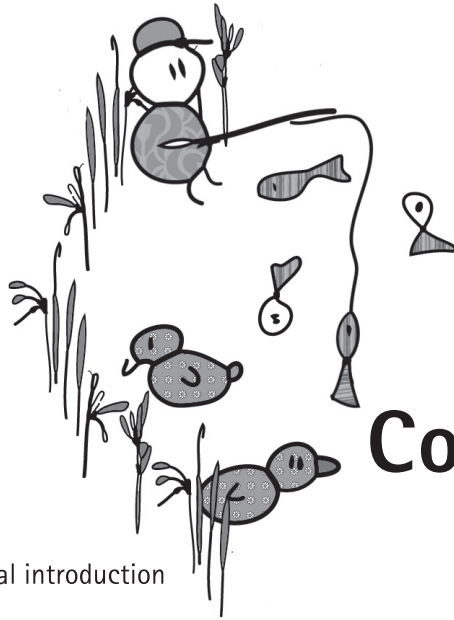
Three main methodological improvements have been made. First, the combination of a deterministic approach with probabilistic approaches to be able to take into account uncertainty and variability were needed. This method was applied to estimate habitual iodine and salt intake distributions. From DNFCSs no detailed information was available on the discretionary use of (iodized) salt and no up to date information was available on the use of iodized salt in industrially processed foods. Estimates of the proportion of the population discretionarily using (iodized) salt and the proportion of industrially processed foods applying iodized salt were obtained from other data sources. The model accurately estimates habitual iodine and salt intake distributions when compared with studies measuring urinary iodine and sodium excretion. Additionally a framework was developed to simulate the habitual intake distribution for potential scenarios of future fortification strategies. Within this framework, deterministic and probabilistic approaches were combined when uncertainty or variability had to be taken into account. This framework was illustrated by the estimation of habitual folate-equivalent intake for different scenarios of mandatory or voluntary fortification with folic acid. Further this framework was applied to estimate the habitual iodine intake for several potential changes in the Dutch iodine policy and also for several scenarios of salt reduction strategies.

A second methodological improvement was the development of a new statistical model to estimate habitual total micronutrient intake aggregated from food and dietary supplements. Within this 3-part model, habitual intake is estimated separately for a) intake from food for non-users of dietary supplements, b) intake from food for users of dietary supplements, and c) intake from dietary supplements for users only. Habitual total intake for the whole population was obtained by combination of the three separate habitual intake distributions ('first shrink then add'). This 3-part model was illustrated by vitamin D intake for young children. With a more simple 'first add then shrink' approach the estimation of habitual total vitamin D intake distribution may give inconsistent results for the distribution of intake from foods and dietary supplements combined as compared to the intake from food only. In addition, this more simple approach may not be able to cope with multi modal distributions. With the newly developed model this inconsistency problem was solved and the multi-modal shape of the distribution as observed in the 'raw' data was preserved.

Third, a model calculating the maximum safe fortification level per 100 kcal of a food was developed for the Dutch situation. By considering the tolerable upper intake level and reasonable high micronutrient intakes from food and dietary supplements, the 'free space' for voluntary fortification was calculated. This amount was divided over the amount of energy intake that can and may be fortified. The model was applied to derive safe maximum fortification levels for vitamin A, D, and folic acid. Based on these results the risk manager decided to legally allow voluntary fortification with vitamin D and folic acid up to a maximum level of 4.5 and 100 µg/100 kcal respectively.

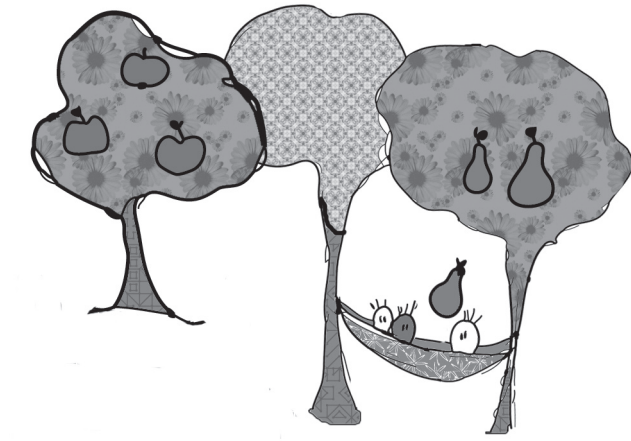
Conclusion

The methodological improvements have resulted in higher accuracy for estimations of habitual intake distributions, which are essential for nutritional and food policy making. Furthermore, scenario analyses provide (under specific conditions) quantitative insight into proposed changes or areas such as maximum safe fortification levels. Several results and methods described are currently being used in research to assist Dutch and European food and nutrition policy making, which shows these methodologies are of immediate value to the practice of policy development and support.



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1

General introduction

Why assessing the intake of micronutrients

Micronutrients (vitamins and dietary minerals) are essential in small amounts for growth, development and maintenance of the human body throughout life. Vitamins are organic compounds that the human body cannot synthesize itself, except for vitamin D, and should be obtained from the diet in adequate amounts, similar as dietary minerals (Stipanuk, 2000).

Adequate and safe micronutrient intake is important. Both insufficient and excessive intakes should be prevented as they can be associated with negative effects on health. For most micronutrients the harmful health effects are due to chronic rather than acute too low or too high intakes. The type of adverse health effects and the seriousness depend on the specific micronutrient, the dosage, and the life stage of the subject (e.g. infants, elderly, pregnant women). Ideally, the population micronutrient intake distribution lies between insufficient and excessive intakes (Health Council, 2009; IOM, 2000b). However, in practice part of the population may have too low or too high intakes (Figure 1.1).

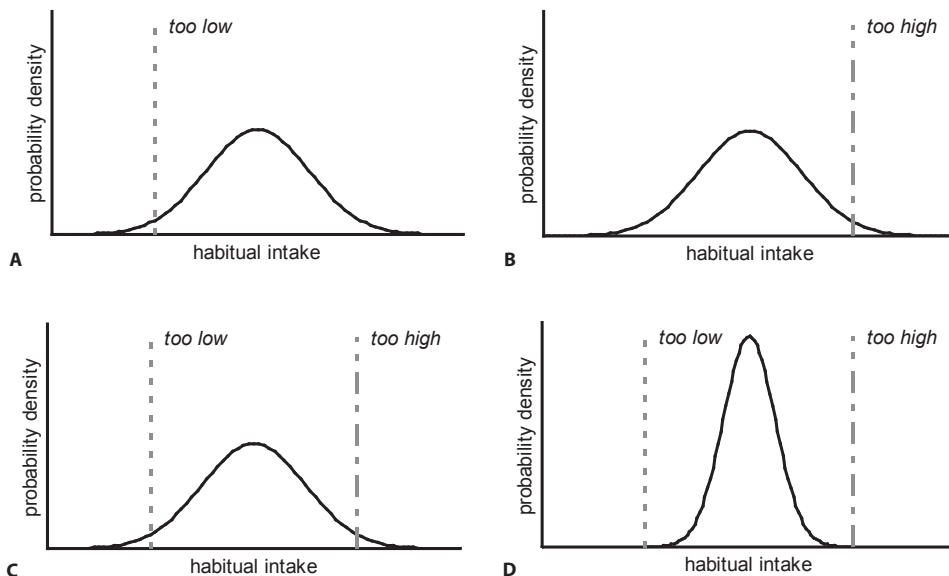


Figure 1.1 Overview of population habitual intake distributions and the evaluation of too low and too high intakes. **A:** part of the population has too low intakes; **B:** part of the population at risk of too high intakes; **C:** part of the population has too low intakes, other part at risk of too high intakes; **D:** population with adequate and safe intake.

It is the role of the (national) authorities to protect public health (Allen *et al.*, 2006). Nutrition policy should result in most of the population having adequate micronutrient intakes, without the risk of excessive intakes. To be able to evaluate whether the population intake is adequate and safe, several (inter)national expert committees, such as the Health Council of The Netherlands, the European Food Safety Authority and the USA Institute of Medicine have set population reference intakes and tolerable upper intake levels (UL).

Research bodies estimate the population micronutrient intake distributions using data from national food consumption surveys and compare these with the dietary reference values and tolerable upper intake levels. It is an ethical issue for risk managers to deem what proportion of the population outside the recommended intake levels is acceptable. If the estimated proportion of the population with insufficient or excessive intakes is higher than the a priori defined acceptable proportion, it may suggest there is a public health issue. This could require amendment in public health policy or further investigation to ensure there aren't alternative explanations e.g. overly conservative reference values or methods being employed in dietary assessment are invalid. Additional studies on e.g. nutritional status or observations of clinical manifestations of insufficient or excessive intakes are valuable.

Worldwide, expert committees identify potential bottlenecks in the micronutrient intake for their specific country based on the scientific evidence available. The potential problems with insufficient or excessive intakes differ between countries due to differences in e.g. dietary patterns or food supplies. Furthermore, dietary patterns and food supply are not static and potential inadequacy may appear or disappear in time. In Western countries similar potential bottlenecks in micronutrient intake are identified, for example vitamin D, folate, iodine, and salt ((Health Council, 2000b; 2008; b; c; 2009; Elmadfa, 2009); and references within these). Especially for those micronutrients it is relevant to assess the intake distribution validly.

There are different approaches correcting insufficient or excessive intakes. Besides advice or education to improve the diet according to the healthy diet guidelines (Health Council, 2006), specific subpopulations can be advised to take or avoid dietary supplements (also referred to as food supplements), and foods can be fortified or reformulated by food manufacturers on a mandatory or voluntary basis. An example of fortification is the addition of iodine to salt. The reduction of sodium content in processed foods is an example of food reformulation. Specific subpopulations at risk of inadequate intake of specific micronutrients are encouraged to increase their intake through consumption of dietary supplements or fortified foods, in addition to a varied diet. In the Netherlands it is advised to increase the vitamin D intake for young children, the elderly, those with dark skin colour and

those with inadequate exposure to sunlight. Women attempting to conceive are advised to increase folic acid intake (Health Council, 2008a; b). Nowadays many different types of fortified foods and over the counter dietary supplements are available. Although this may result in improvement in those with insufficient intake from the regular diet, others may be at risk of exceeding safe intake levels due to aggregation from different sources.

To ensure safety of all consumers and also to ensure that target populations benefit from the fortification or supplementation, it is advised to regulate all forms of fortification (Allen *et al.*, 2006) and supplementation (Anonymous, 2002a). For these purposes, it is essential to have an insight into the total micronutrient intake distribution of the population from all dietary sources. Additionally, insight into the proportion of the (sub)population at risk of insufficient or excessive intakes is required.

Food fortification and supplementation in The Netherlands – starting point

Micronutrients are added to foods in order to restore losses due to production processes or to increase the amount to make it nutritionally comparable to a substitute food. An example of restoration is the addition of micronutrients to 'ready- to-eat' meals to the value of the non-prepared foods compensating for losses during the meal preparation. A well known example of substitution is the addition of vitamin A and D to (low-fat) margarine making it nutritionally similar to butter. Additionally, there is a long history of food fortification being employed to prevent classic deficiency diseases, such as the addition of iodine to salt. Fortified foods are becoming more and more available worldwide for use in the prevention of chronic diseases, as well as improving health outside the scope of classic deficiency diseases (Park *et al.*, 2001).

Fortification may be mandatory or voluntary. When authorities legally obligate food manufacturers to fortify specific foods with specific micronutrients it is referred to as mandatory fortification. Throughout the world micronutrients such as iodine, vitamin A, iron, and increasingly folic acid are fortified on a mandatory basis. (Allen *et al.*, 2006; Flynn *et al.*, 2009). In The Netherlands there is currently no mandatory fortification practice (Flynn *et al.*, 2009).

In voluntary fortification, food manufacturers are allowed, though not obligated, to fortify their foods with micronutrients. This type of fortification is generally market-driven within the limits of the policies set by the authorities. In some countries, including The Netherlands, the voluntary fortification of specific micronutrients in specific foods is encouraged instead of enforcing mandatory fortification (Allen *et*

al., 2006). In The Netherlands, agreements are in place with bakeries to fortify their bread with iodine (iodized salt) and with (low-fat) margarine producers to fortify (low-fat) margarine with vitamin A and D (Anonymous, 2008; Kraak, 2004). In the Dutch Commodity Act it is regulated that fortification (excluding restoration and substitution) with vitamin A (retinol), vitamin D, synthetic folic acid, selenium, copper, and zinc is prohibited due to the small range between the nutritional recommendations and the tolerable upper intake level. Additionally fortification with these foods is not regarded as nutritionally essential (Anonymous, 1996). For other micronutrients it is regulated that these may be applied in food fortification in amounts that a normal daily portion would deliver at least 15% and at maximum 100% of the recommended daily allowance (Anonymous, 1996). Currently, European legislation is in preparation in which minimal and maximum levels of vitamins and minerals added to foods will be regulated (Anonymous, 2006).

The market for over the counter dietary supplements is increasing (Bailey *et al.*, 2011; Briefel *et al.*, 2004; Ocké *et al.*, 2005a). For users of dietary supplements, these are major sources of their micronutrient intake (Flynn *et al.*, 2009). In general, adherence to guidelines of a healthy diet should provide adequate amounts of micronutrients (Health Council, 2006). However for some micronutrients, such as vitamin D and folic acid, the Dutch Health Council advised specific subpopulations to use specific dietary supplements (Health Council, 2008a; b). In addition to advice for specific subpopulations, the amounts and chemical form of a micronutrient permitted in dietary supplements are regulated (Anonymous, 1994; 2003). For vitamin A and D a maximum daily dose amount is set, which depends on life stage (Anonymous, 1996.) For other micronutrients, maximum daily dose amounts will be set in European legislation (Anonymous, 2002a).

Evaluation of insufficient or excessive intakes – state of the art

Dietary intake assessment

Different methods are available to assess dietary intake. Choosing which method to apply depends on the aim of the study, the study population, and the budget available. Some methods will give insight into the availability of foods rather than actual individual food consumption; e.g. food balance sheets and household purchase data. Such data is not based on the intake of individuals and therefore the proportion of the population with inadequate micronutrient intakes cannot be estimated. In general, four methods measuring individual food consumption are available: dietary record,

24-hr recall, dietary history, and food frequency questionnaire (FFQ) (Van Staveren *et al.*, 2006). The dietary history method is time consuming and expensive and therefore not often used in (National) Food Consumption Surveys. Both dietary history and FFQ measure dietary intake over a timeframe longer than 1 day e.g. the previous week, previous month or previous year, so they estimate habitual intake (also referred to as usual intake) over a defined reference period. Due to the limited number of foods included in FFQs, quantification of the absolute intake is not considered sufficiently valid. This makes a FFQ as a single method a poor tool for estimation of the proportion of the population with inadequate intakes. A dietary record and a 24-hr recall measure the actual intake on one or more days. In order to estimate the distribution of the habitual intake of a population independent repeated dietary records or 24-hr recalls are required in combination with statistical models (see below) (Carriquiry, 2003). Both 24-hr recall and dietary record have their own advantages and disadvantages. Dietary records are more demanding of a survey participant compared with 24-hr recalls and as the dietary intake has to be recorded immediately this may influence actual consumption. On the other hand, 24-hr recalls rely on the memory of participants and may therefore be not suitable for some subpopulations, e.g. young children. There may also be an impact on estimation of portion sizes (Van Staveren *et al.*, 2006). Internationally, the 24-hr recall is regarded as the preferred method for the general population, excluding young children (Brussaard *et al.*, 2002; EFSA, 2009). As the micronutrient composition of fortified foods may vary significantly from their non-fortified counterparts, detailed information on the type of food consumed should be collected with the dietary assessment (EFSA, 2009). Further, to estimate infrequently consumed foods or food groups, an additional food propensity questionnaire is required (Carriquiry, 2003; EFSA, 2009; Tooze *et al.*, 2006). In order to estimate the

Box 1.1 Dutch National Food Consumption Survey (www.rivm.nl/vcp)

	Time period	Population	Method	Days
DNFCS-1	April 1987 - March 1988	1-85 yr	Food diary	2 consecutive days
DNFCS-2	January - December 1992	1-92 yr	Food diary	2 consecutive days
DNFCS-3	April 1997 - March 1998	1-97 yr	Food diary	2 consecutive days
DNFCS-2003	October - December 2003	19-30 yr	24-hr recall	2 independent days (8-13 d apart)
DNFCS 2005-2006	October 2005 - November 2006	2-6 yr	Food diary	2 independent days (8-13 d apart)
DNFCS-2007-2010	March 2007 - April 2010	7-69 yr	24-hr recall	2 independent days (ca. 4 weeks apart)

total micronutrient intake, detailed information on the use of dietary supplements should also be assessed (EFSA, 2009). For the dietary assessment methods applied in the Dutch National Food Consumption Survey (DNFCS) system see Box 1.1. Advances in science, e.g. about the habitual intake distribution, resulted in several changes in the dietary assessment method over years.

Estimation of (micro)nutrient intake

From estimates of food consumption, micronutrient intake can be estimated. This requires food composition data. Many countries, including The Netherlands (www.rivm.nl/nevo), have national food composition databases that contain information on the nutritional composition of foods. These databases often do not include all foods available in a specific country, but for feasibility reasons (there is a large turnover each year), only have composition data of foods that are regularly consumed by the population and deliver a large part of energy or nutrient intake. Furthermore for most foods listed, the values will be an average composition make up for many versions of the same food, e.g. average values for a number of brands of one product or the same foods produced from different regions.

To estimate the micronutrient intake from dietary supplements, their composition is required as well. In The Netherlands, the Dutch Supplement Database (NES) is available (Buurma-Rethans *et al.*, 2008). The supplement composition in this database is based on the information on the label, rather than analytical measurements. There are however studies suggesting overages (Consumentenbond, 2011; Dwyer *et al.*, 2007; Roseland *et al.*, 2008). Due to for instance the high turnover of dietary supplements on the market and the frequent changes in composition, it is a challenge to keep dietary supplement databases up to date.

Estimation of habitual intake from short term measurements

Most health effects of micronutrient intakes are chronic rather than acute. Therefore, insight into the long-term intake is required to quantify the proportion of the population with insufficient or excessive intakes. The detailed information required to estimate the proportion of these groups is often obtained from repeated short-term measurements, rather than long-term measurements. Due to repeated short-term data collection, this data contains the variation between persons, which is of interest, but it also contains day-to-day variation within the same individual. Habitual intake is defined as the long-term average daily intake by an individual and is also referred to as usual intake (Carriquiry, 2003). Habitual intake can be estimated from repeated independent short-term measures applying statistical correction for the within-person

variation (i.e. day-to-day variation). Several methods are available (Dodd *et al.*, 2006; Hoffmann *et al.*, 2002; Nusser *et al.*, 1996; Tooze *et al.*, 2006). In general, a) the population nutrient distribution is transformed to a more or less normal distribution, b) the within-person variation is estimated and the total variation is corrected for this within-person variation, and c) the corrected data is transformed back to the original scale. The result is a narrower distribution as (part of) the within-person variation is removed. The methods assume that the mean or median of the distribution should remain similar before and after correction for within-person variation, whereas both tails of the distribution change. For estimation of the proportion of the population with insufficient or excessive intakes the tails of the distribution are very important. If data as observed are used without correction for within-person variation, the population intake distribution is wider and therefore the estimated proportion of the population with insufficient or at risk of excessive intakes will be biased.

For episodically consumed foods, a one-time repeated short-term measurement is not adequate to estimate the habitual intake. Combining the data of the repeated short-term measurements with data from a food propensity questionnaire (FPQ) could improve the estimation as the probability to use such episodically consumed food can be estimated more accurately (EFSA, 2009; Tooze *et al.*, 2006).

Nutritional reference values for micronutrients

Several (inter)national institutes have established nutritional reference intakes for micronutrients, based on the state-of-the-art scientific evidence (examples are: (Health Council, 2000a; 2003; IOM, 2000a; 2001; 2004; 2010; SCF/NDA, 2006). Generally, human studies are preferred over animal studies and *in vitro* studies to derive nutritional reference values. Intervention studies to study nutrient deficiencies are generally presumed not ethical though an exception could be made if for instance a specific population intake is below the proposed optimum level to prevent deficiency. As studies determining the intake level at which deficiency appears are scarce, reference intakes are generally based on other types of research. For instance, 1) summation of the nutrient amounts that determine the requirement: losses and additional needs for growth and development together with bioavailability of the nutrient, 2) nutrient intake and relation with biochemical parameter of nutritional status, 3) nutrient intake and association with risk of chronic disease, and 4) mean intake of the population if no deficiency is reported. If a quantitative dose-effect relation is available the estimated average requirement (EAR) can be established (Figure 1.2). The EAR is defined as the (estimated) average of the distribution of intake requirements needed to fulfill the physiological needs of the population. If the variation in requirements between individuals is known a recommended daily allowance (RDA) can be set (i.e. $EAR + 2*SD$).

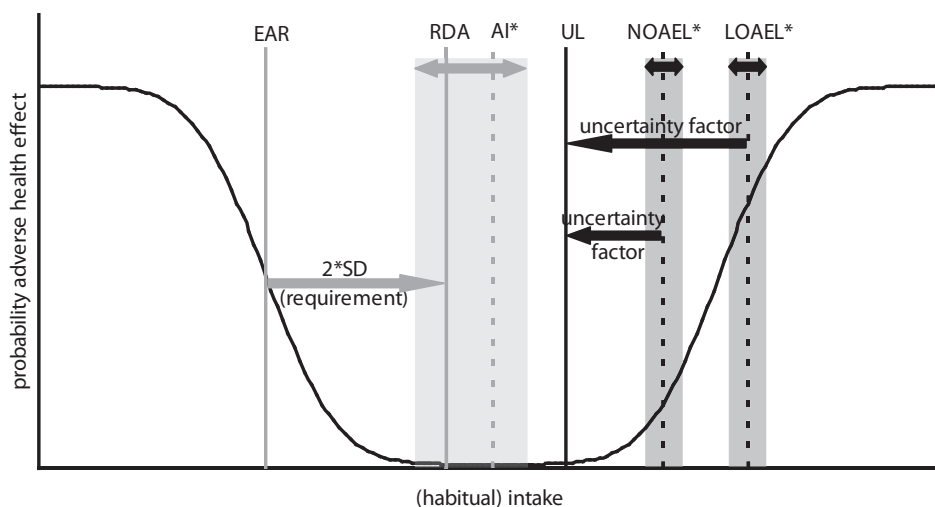


Figure 1.2 Schematic overview of the relationship between (habitual) intake and probability of adverse health effects including the different nutritional reference intakes. * AI, NOAEL and LOAEL do not have exact relation with requirement (or intake); therefore the lines are dashed and surrounded by a shaded area. EAR: estimated average requirement; RDA: recommended daily allowance; AI: adequate intake; UL: tolerable upper intake level; NOAEL: no observed adverse effect level; LOAEL: lowest observed adverse effect level; SD: standard deviation.

The RDA is a level of intake which is adequate for a large portion of the population. If detailed (quantitative) research information is lacking no EAR or RDA can be set, instead an adequate intake (AI) is set. Generally, an AI is proposed to be the lowest amount of a nutrient estimated to be sufficient for the whole population. An AI is assumed to be higher than the RDA if that could be derived (Health Council, 2001; IOM, 2000b). The nutritional reference values for low intake are not harmonized, therefore types of values other than those explained above, as well as other terminology are present. However, in this PhD-thesis the terminologies as used by the Dutch Health Council and USA Institute of Medicine are used.

A reference to evaluate high intakes is the tolerable upper intake level (UL). This is not a recommended intake level, but an estimation of the amount of intake below which the risk of adverse health effects is unlikely (Figure 1.2) (IOM, 2000b; SCF/ NDA, 2006). Sufficient data is needed to derive a no-observed adverse effect level (NOAEL) or instead a lowest-observed adverse effect level (LOAEL) and derive an UL. If more adverse health effects appear, the health effect with the lowest NOAEL, the critical endpoint, will be the basis of the derivation of the UL. Uncertainty associated with extrapolation

of the research results to the general population and variation in susceptibility between individuals are taken into account applying an uncertainty factor. With large uncertainty, the uncertainty factor will be higher and as a consequence the lower the UL will be. However, for risk managers the UL of a nutrient should never be lower than the recommended intake (Health Council, 2001; IOM, 2000b; SCF/NDA, 2006). Adverse health effects of high nutrient intakes are mostly based on scarce observational human studies and animal studies. Similar to studying the amount to prevent nutrient deficiency, human intervention studies to the adverse effects of excessive intakes are considered unethical (Health Council, 2001).

The nutritional recommendations are generally established for a healthy population and within this population for different life stages. If a nutritional recommendation cannot be established for a specific subpopulation based on scientific evidence, the recommendation may be derived by extrapolation from other subpopulations based on e.g. weight or metabolic weight (i.e. $\text{weight}^{0.75}$) and/or allowing for growth (Health Council, 2001; IOM, 2000b; SCF/NDA, 2006).

Evaluation of population micronutrient intake

The most straightforward way to evaluate the adequacy of the population micronutrient intake would be to compare for each individual the habitual micronutrient intake with the individual requirement or individual highest level at which no adverse health effects will appear. In theory, the proportion of the population with insufficient or excessive intakes will be shown by counting the subjects with habitual intakes below their requirements or above their individual NOAEL, and dividing this count by the number of individuals in the total population (Carrquiry, 1999; IOM, 2000b). However, information on the individual requirement or individual NOAEL is not available and other methods are needed. For the evaluation of the micronutrient intake in populations the EAR and UL are the most appropriate nutritional references to quantify a potential health problem. Although there might be discussion on the currently set EARs, AIs, and ULs, in the studies included in this PhD-thesis we take them as currently set.

Evaluation of insufficient intakes using the EAR

The population habitual micronutrient intake can be compared with the EAR to evaluate insufficient intakes (Carrquiry, 1999; IOM, 2000b). The proportion of the population with intakes below the EAR is, under some assumptions (Carrquiry, 1999), an estimation of the proportion of individuals in the population which have intakes below their individual requirements (Figure 1.1). This method is known as the EAR cut-point method (IOM, 2000b). Alternatively and under slightly more relaxed assumptions, the

probability approach could be applied. For both methods, the intake and requirement must be independent. In the probability approach the estimated population habitual intake distribution is combined with the distribution of requirements in a population using Monte Carlo simulation. For many iterations values from the habitual intake distribution are compared with values from the requirement distributions to estimate the proportion with intakes below the requirement (Carriquiry, 1999; IOM, 2000b; NRC, 1986). The probability approach requires a detailed description of the population distribution of requirements, such detailed data is generally lacking. Adopting a different type of distribution for the requirement may have considerable impact on the results.

If the EAR is not available, an AI can be used to evaluate the population intake qualitatively. The proportion of the population with intakes below the AI is not valuable for quantifying the prevalence of insufficient intakes, as for most individuals in a population, the AI is higher than their individual requirement. If the mean population intake is above the AI it can be stated that the prevalence of insufficient intake is likely to be 'low'. However, if the mean population intake is below the AI no statement on the prevalence of insufficient intakes can be made (IOM, 2000b).

Evaluation of high intakes using the UL

Habitual intakes above the UL cannot be considered immediately as unsafe, as the UL is the amount of (habitual) intake for which adverse health effects are unlikely to appear (Carriquiry *et al.*, 2006; SCF/NDA, 2006). Similar to the reference intakes concerning low intake, the highest amounts for which adverse health effects are unlikely may vary within the population and is a distribution rather than a point estimate. In addition, the relationship between the adverse health effect and the micronutrient can be described as a dose-response curve. Such dose-response curves are not available for most micronutrients (Carriquiry *et al.*, 2006). The proportion of the population with intakes above the UL is not equal to the proportion of the population with adverse health effects due to excessive intakes (Figure 1.2). Carriquiry and Camano-Garcia propose to only state that the proportion of the population with habitual intake below the UL is very likely to have no adverse health effects due to excessive intake (Carriquiry *et al.*, 2006).

How to ensure safe voluntary food fortification and supplementation

In general, the total intake of a micronutrient from different sources should be safe for a population. So the total intake of a micronutrient from basic foods (excluding voluntary fortification; also referred to as background diet), voluntary fortified foods and dietary supplements should be below the level at which adverse health

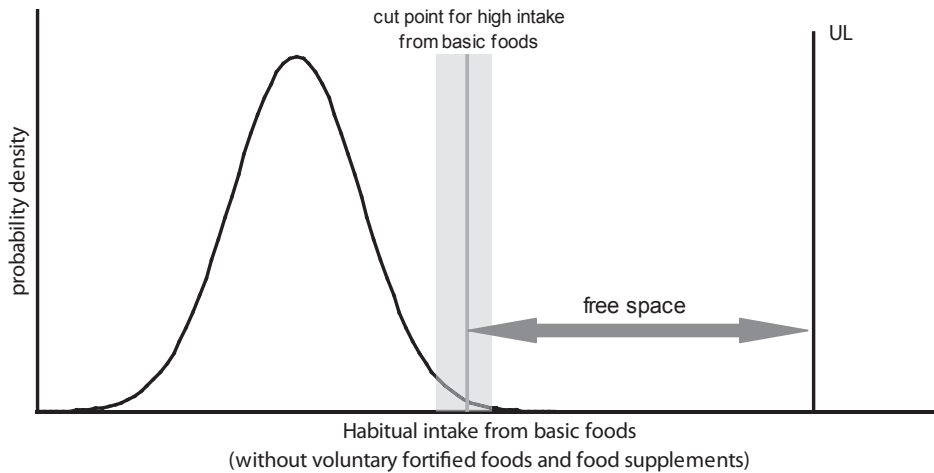


Figure 1.3 Schematic overview of the general principle of the 'free space' that is available for intake from voluntary fortified foods and dietary supplements. UL = tolerable upper intake level. Cut-off point for high intake from basic foods is not fixed but should be determined by a risk manager, indicated by the shaded area surrounding the line.

effects may appear. Several calculation models are published estimating a safe maximum amount of micronutrients for voluntary food fortification and/or dietary supplements (Domke *et al.*, 2004a; b; Flynn *et al.*, 2003; Rasmussen *et al.*, 2005). The principle of these methods is similar (Figure 1.3). The first step in this process is to determine whether the current micronutrient intake from basic foods is below the UL; the degree to which this occurs is the so called 'free space' which could be filled with intakes from voluntary fortified foods or dietary supplements. In the published models the 'free space' is the difference between the UL and the intake at the 95th percentile of the distribution (Flynn *et al.*, 2003; Rasmussen *et al.*, 2005) The intake at other percentiles can also be used. The next step is to decide how to divide this free space over voluntary fortified foods and dietary supplements. This can vary from assignment of 100% of the free space to voluntary fortification to assignment of 100% of the free space to dietary supplements. It should then be decided how to divide the free space over the foods that will be voluntary fortified with a specific micronutrient, for instance a specific maximum dose per 100 g, 100 kcal, or portion size. This requires insight into the consumption pattern of food, in addition to habitual nutrient intake from all foods.

Challenges in estimating micronutrient intake distributions and study aims

For both the evaluation of current dietary policies and for the development of new policies, information on the habitual nutrient intake distribution is required. This may be a current nutrient intake distribution, which can be estimated directly from a national food consumption survey, or a potential future nutrient intake distribution, which could be estimated from different scenarios. Information on the habitual nutrient intake distributions could assist policy makers in their handling in specific situations and with regulation of adequate and safe population intakes.

In this general introduction a commonly used (deterministic) approach to estimate population micronutrient intake is described. This approach is not always appropriate and several challenges can be identified (Table 1.1). These challenges are aggregated to three research questions based upon issues which have arisen in the food and nutrition policy field: 1) how to estimate current habitual micronutrient intake when (detailed) data are lacking or data from different sources should be combined, 2) how to predict future intakes in order to support policy making, and 3) how to estimate a maximum safe fortification level per food item. The aim of this thesis is to further develop and apply statistical models to estimate micronutrient intake distributions which can cope with these challenges and provide solutions for the three questions. The examples and micronutrients in this thesis were chosen based on the need to improve estimates of intake distributions from a policy making point of view. Below the identified challenges and the outline of this thesis are described.

Policy decisions regarding mandatory or voluntary micronutrient fortification may influence the population micronutrient intake. The ultimate goal is that the intake will be improved and become adequate in a larger part of the population while avoiding risk of excessive population intakes. Insight into the possible changes in population intake distributions prior to the actual change in policy is important. This prior insight requires modeling of potential *future* changes in food composition and in the resulting population intake of micronutrients. In **Chapter 2**, a general framework for estimating the population micronutrient intake distribution for scenarios of potential future mandatory or voluntary fortification strategies is described. This general framework is applied in **Chapter 3** to estimate the impact of changes in the iodine policy on the habitual iodine intake distribution and in **Chapter 4** to estimate the impact of salt reduction (food reformulation) on both sodium and iodine intake distributions.

There are also challenges in estimating population current micronutrient intakes. For some micronutrients not all sources of dietary intake are always included in food consumption surveys. An example is the use of (iodized) salt during cooking and for seasoning (discretionary use) and use of dietary supplements. Discretionary salt is a

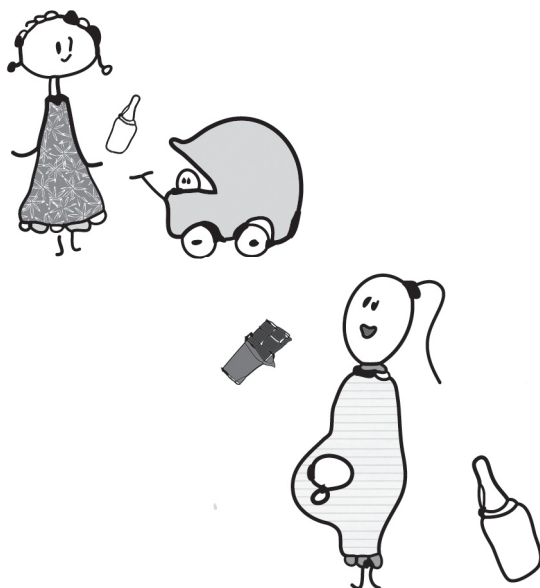
Table 1.1 Challenges in estimation and prediction of habitual population micronutrient intakes and regulation of safe fortification

Chapter	Nutrient	Policy questions		
		Estimation current intake	Prediction future intake	Regulation safe fortification
2	Folate/folic acid		What foods fortified What fortification level Who will use fortified foods	
3	Iodine	(Detailed) data lacking on sources of intake (e.g. kitchen salt, supplements)	What foods contain iodized salt under changed policy	
4	Iodine, salt	(Detailed) data lacking on sources of intake (e.g. kitchen salt, supplements)	What foods contain iodized salt under changed policy	
5	Vitamin D	Combine different data sources Combine separate estimations of intake distributions from food and dietary supplements		
6	Vitamin A, D, folic acid			What part of the food supply will be fortified How to set max fortification level for whole population Who to protect
7	Folic acid	Lack of recent food consumption data		

very important source of sodium and iodine intake and neglecting this source will largely underestimate these intakes. In **Chapter 3** a model combining a deterministic approach with probabilistic approaches is developed in which a) data from other sources than the food consumption survey, b) several assumptions, and c) uncertainty and variability are taken into account to estimate the habitual total iodine intake distribution from all sources (including discretionary salt and dietary supplements). The same model is applied in **Chapter 4** to estimate total sodium and iodine intake for scenarios of salt reduction.

In addition to food fortification, dietary supplements may also substantially contribute to micronutrient intake. Therefore it is important to take this source into account when estimating the habitual total micronutrient intake distribution. The methods currently used for estimating the habitual total micronutrient intake do not take into account differences in within-person and between-person variability between the micronutrient intake from foods and dietary supplements. Neglecting these differences may result in invalid estimates of population micronutrient intake distributions and as a consequence lead to biased estimations of the proportion of the population with insufficient or excessive intakes. A model is developed to estimate habitual total micronutrient intake, taking into account the potential differences in within-person and between-person variability (**Chapter 5**).

Chapters 2-5 focus upon the estimation of the habitual micronutrient intake distribution, prediction of possible future intake distributions, and the evaluation of these distributions against population reference intakes and tolerable upper intake levels. Such intake distributions can also be used as input in statistical models. One example is modeling the maximum safe fortification level of a micronutrient in order to protect the population from excessive intakes from all sources (**Chapter 6**). Several assumptions have to be made in such models, for example about future use of voluntary fortified foods. To ensure safe population intakes these assumptions have to be evaluated after the policy comes into effect. Results of evaluation studies will show the actual change in dietary intake after implementing a new food or nutrition policy. Additionally, it may show that some of the assumptions were not correct and that new or adapted policies are required. In **Chapter 7** an evaluation study for maximum safe levels for voluntary fortification is described. In **Chapter 8** a summary of the main methodological developments described in this thesis is presented. In addition, the findings from this PhD-thesis are discussed in a larger perspective, together with remaining challenges and needs for future improvements or developments.



2

Framework for intake simulation of functional ingredients

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Abstract

Objective: To create a general framework for the simulation of intakes from mandatory or voluntary fortification, which will make outcomes of simulation studies more comparable and give insight on uncertainties.

Design: A general framework was developed based on methods used in already published case studies of mandatory fortification. The framework was extended to be suitable for the simulation of voluntary fortification. Case studies of folic acid fortification were used to illustrate the general framework.

Results: The developed framework consists of six steps. First, the definition of the fortification strategy (step 1), followed by the identification of potential carrier products (step 2), and the definition of fortification levels or ranges (step 3). Thereafter, virtual food/dietary supplement composition data are created (step 4) and food/dietary supplement consumption data are required (step 5). Finally, the intake of the functional ingredient from functional foods, other foods and dietary supplements is calculated during the simulation resulting in total habitual intake distributions (step 6).

Conclusions: Simulation of both mandatory and voluntary folic acid fortification in The Netherlands showed that the general framework is applicable. Also with incomplete data or data from different sources, the (habitual) intake distributions can be estimated using assumptions, statistical procedures or probabilistic modeling approaches. It is important that the simulation procedure is described well, so that an insight on uncertainties and knowledge gaps to be filled is given.

Introduction

Originally, the purpose of adding micronutrients to foods and using supplements was to prevent deficiency diseases. Nowadays, there is an additional health focus: the prevention of chronic diseases (Park *et al.*, 2001). Also, it is claimed that the addition of other bio-active ingredients to foods and supplements, like phytosterols, will help to improve health. As a consequence, consumers are currently exposed to higher amounts and different ratios of micronutrients and to a range of new ingredients compared to earlier times. Because of international changes in and harmonization of fortification policies and the ongoing introduction of new functional foods, the exposure to these ingredients will remain subject to change.

Authorities can influence the intake of functional ingredients from fortified foods by regulating either mandatory or voluntary fortification programs. In mandatory fortification, all selected products are required to be fortified with certain amounts of a functional ingredient. In voluntary fortification, manufacturers are permitted to fortify (selected) products, but this is not compulsory. For a governmental policy on fortification, it is important to have insights in the current population intake distributions to identify potential nutritional problems and to compare current intakes with any expected intake changes. Calculation of the expected future population intake distribution after fortification is useful for several reasons; to gain insights into the impact of potential decisions of policy-makers and to determine which policy will result in the desired or most optimal effect. At this moment, some specific case studies have been published in which the intake of fortified foods or functional ingredients is simulated (Bausch-Goldbohm *et al.*, 1995; Brussaard *et al.*, 1995; Burger *et al.*, 2004; Firth *et al.*, 1998; Green *et al.*, 2003; Johnson-Down *et al.*, 2003; Kuhlmann *et al.*, 2005; Raulio *et al.*, 2001; Suojanen *et al.*, 2002). These case studies had different goals, but all of them simulated mandatory fortification. Although these studies had more or less similar methodologies, a uniform framework to simulate the intake of functional ingredients, from fortified foods, other foods and dietary supplements, was not used.

A simulation framework to assess intake is required to perform uniform and systematic comparisons of different exposure scenarios and eventually benefit-risk evaluations. Such a uniform framework will provide a systematic insight on the effect of different food policies and may help policy-makers to choose the most optimal scenario based on quantitative results. In addition, using a uniform framework will make possible the comparison between different policies, studies and countries. The use of a uniform framework will also give insight in uncertainties in the simulation, for instance, caused by lack of data or assumptions made. In this Chapter, we describe such a framework that will be applicable for many functional ingredients. Of course, because of the

enormous variability in functional ingredients, at some points different strategies may be followed, examples of which will be presented. Our framework is illustrated by simulation of both mandatory and voluntary folic acid fortification.

General methodology

Our general framework for the simulation of the intake of functional ingredients at a population level consists of six steps (Figure 2.1). We will first outline each step and then illustrate the process with simulations of folic acid fortification.

Fortification strategy (step 1)

Authorities may influence the intake of functional ingredients by the population through various strategies: (1) promote supplementation, (2) mandatory fortification or (3) voluntary fortification. The fortification strategy chosen depends on, among others, the current intake distribution of the population, the proportion of subjects with an inadequate and/or excessive intake and the desired intake distribution. In addition, factors such as costs and enforcement will also influence the choice of a final strategy.

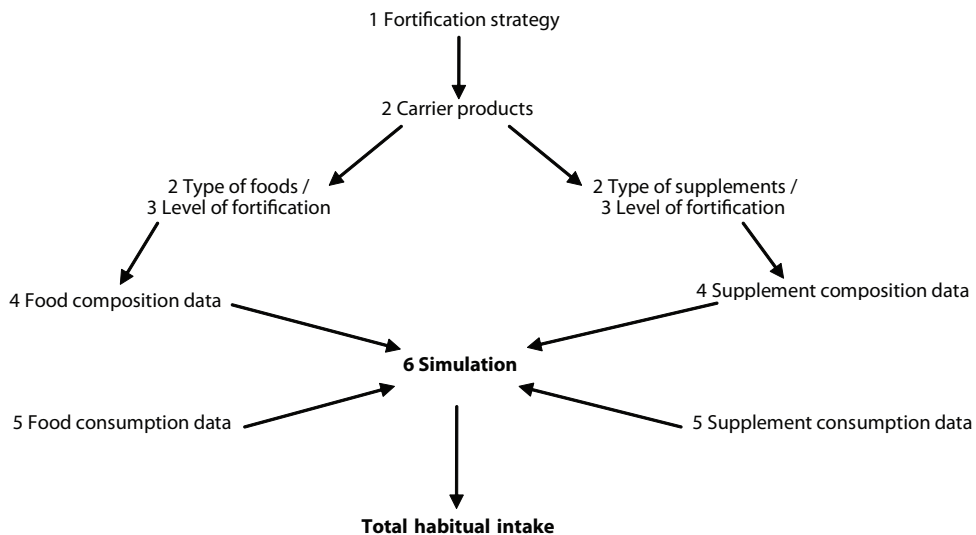


Figure 2.1 Systematic framework for the simulation of intake of functional ingredients.

Carrier products: type of foods and/or supplements (step 2)

Next, carrier products need to be selected. In principle, both foods and supplements can be used as carrier products. In the case of mandatory fortification, the target population is a large part of the total population. Therefore, the food(s) chosen should be consumed frequently and by a large proportion of the population. For this reason, supplements are considered not suitable (Millen *et al.*, 2004; Ocké *et al.*, 2005a), while staple foods appear to be a good choice.

For voluntary fortification, both foods and supplements can be carrier products. In theory, all foods that technically can be fortified may be a carrier product. However, authorities may select specific products that may or may not be fortified. An example of the latter are alcoholic beverages. Factors like consumer awareness, price and health focus will influence the degree of intake. For both mandatory and voluntary fortification approaches, international experiences (Bausch-Goldbohm *et al.*, 1995; Burger *et al.*, 2004), scientific studies with fortified foods (De Jong *et al.*, 2005), but also existing/requested (inter)national permissions (De Jong *et al.*, 2004; Suojanen *et al.*, 2002) can be used to select the carrier products. Besides, current consumption distributions of foods can help to choose carrier products that are for example consumed mainly by the target population (Green *et al.*, 2003).

Level of fortification (step 3)

Next, fortification levels have to be chosen. These levels may be adopted from international fortification experiences or from levels used in scientific studies. If the aim is to increase the intake in a (sub)population to reach a certain level, the known difference between current intake and desired intake may be used to calculate potential fortification levels (Bausch-Goldbohm *et al.*, 1995). Moreover, (inter)national regulations about the minimum level of the functional ingredient to carry a claim on the product (Johnson-Down *et al.*, 2003), but also (inter)national set maximum levels for fortification (Flynn *et al.*, 2003; Rasmussen *et al.*, 2005) or existing/requested (inter)national permissions (De Jong *et al.*, 2004; Suojanen *et al.*, 2002) may be useful. If previous experience is not available, the choice of fortification levels has to be based on the best educated guess. In practice, this will mean that with 'trial- and-error', levels are chosen to get close to the aim.

Important factors herein are consumption pattern, current intake distribution of the functional ingredient, and if available, the margin between the recommended intake and the tolerable upper intake level (UL).

Food and supplement composition data (step 4)

In order to simulate the intake of functional ingredients, the current composition of the carrier products should be virtually replaced by the composition after fortification. In many countries, national food composition tables are available (NEVO, 2001; Deharveng *et al.*, 1999). However, some specific compounds are not (completely) covered by these tables. The missing composition might be estimated using data from foreign countries, from additional analytical analyses, recipe calculations or from information obtained from experts or manufacturers. Sometimes the functional ingredient is not part of the background (i.e. unfortified) diet. In that case, the functional ingredient should be added to the food composition table to create the virtual food composition. Supplement composition data are difficult to obtain. Nevertheless, such data are important for the calculation of the total intake of functional ingredients from different sources (WHO, 2006).

Food and supplement consumption data (step 5)

Because adverse health effects are often the result of a chronic inadequate or excessive intake, long-term exposure is usually of interest. Consequently, habitual (also referred to as usual) intakes should be estimated. Several methodologies are available to assess food and supplement consumption (Gibson, 2005). Long-term methods can be used to assess habitual intake of foods or food groups and when the amount consumed is known, also the habitual intake of nutrients can be used (Gibson, 2005). Short-term methods will give information about actual intakes and can only be used to estimate habitual nutrient intake by statistical correction for day-to-day (i.e. within-person) variation (Hoffmann *et al.*, 2002; NRC, 1986; Nusser *et al.*, 1996; Slob, 1993; 2006). This day-to-day variation depends on the nutrient, the population under study and seasonal variation in consumption (Basiotis *et al.*, 1987). Consumption data of representative samples of the whole population should be available to extrapolate the results to a population level. However, sample sizes used in national food consumption surveys are often too small to estimate habitual intake of (a) products consumed by only a small subpopulation or (b) products consumed infrequently (Carriquiry, 2003).

Simulation of total habitual intake (step 6)

The next step is simulation of fortification with the functional ingredient. One should remember that functional ingredients can be either the natural substances or their chemical equivalents, which may have different characteristics, e.g. difference in bioavailability. Therefore, ingredient-specific adaptations of the procedure may be necessary.

In the optimal situation, consumption of food and supplements is measured at the same time, in the same representative population (large enough sample size), and with similar methods. In that case, the simulated total habitual intake of the functional ingredient can be estimated by adding up the habitual intake from different sources per individual. However, this 'straightforward' approach is often not possible due to lacking data and a small sample size (Ocké *et al.*, 2005a; b). In those cases, total habitual intake needs to be estimated based on data measured at different periods, in different study populations, with different methods, or even with some specific data lacking. In the literature, several approaches have been suggested to deal with this less optimal situation (Lewis *et al.*, 1999; WHO, 2006). Probabilistic modeling can be used to estimate the total intake of a functional ingredient by combining the intake originating from long-term and short-term methods or from different study populations. Also, if some of the data are unknown, probabilistic modeling can be used to calculate the total habitual intake by imputation of the missing data (Gibney *et al.*, 2004; 2003; Vose, 2000).

Simulation of mandatory fortification

For the simulation of mandatory fortification, all counterparts of the carrier product(s) will be replaced by virtually fortified products. The virtual food composition data will be combined with the consumption data to calculate the intake of the functional ingredient (i.e. sum of consumed amount x functional ingredient concentration).

Simulation of voluntary fortification

In the simulation of voluntary fortification, virtual new food composition data cannot be created as 'straightforward' as described for mandatory fortification, as there are more uncertainties. First of all, it is unknown what the manufacturers will do, e.g. what proportion of carrier product(s) will be fortified and at what fortification level? In voluntary fortification, the fortification levels are more likely to vary compared to mandatory fortification. Secondly, little is known about consumers' behavior when there is a choice between fortified and unfortified products. The proportion of consumers can be estimated from available (inter)national consumption data, market shares or empirically when no data are available. Thirdly, there are practical problems to perform the simulation because the required data need to be very detailed which is often not the case. Brand-specific consumption data may not be available, and sample sizes in surveys are usually too small to get a representative sample of the consumers of specific or infrequently consumed products. Besides, when short-term methods are used, many participants may not consume these voluntary fortified products at all during the survey, but may not represent true non-consumers (Carrquiry, 2003).

The simulations can be performed by making assumptions for the aspects described above and can calculate the intake distributions given those assumptions. A probabilistic approach, as described by Gibney and McCarthy (2004) and Gibney and Van der Voet (2003), in which the probabilities of being a consumer, the frequency of use and the dose per eating occasion are estimated, may be useful (Figure 2.2) (Gibney *et al.*, 2004; 2003). With this methodology, it is possible to combine the various assumptions based on their probability and quantify the uncertainty caused by these assumptions. When several levels of fortification are assumed, probabilistic modeling can help to predict the probability distribution of the concentration of the functional ingredients in foods.

Case study: folic acid fortification

The framework (Figure 2.1) described above is illustrated by the simulation of both mandatory and voluntary folic acid fortification in The Netherlands. Folic acid from supplements was ignored in this illustration. Data used in both simulations are described first. Next, the case-specific steps for mandatory and voluntary fortification are presented and several, case-specific, assumptions are discussed. Finally, in the results section, examples of output of the various fortification scenarios are presented.

Data

The most recent Dutch food consumption data for the total population were used, which is the Dutch National Food Consumption Survey-3 (DNFCS-3) (step 5) (Anonymous, 1998b). Respondents (6250 persons aged 1-97 yr from 2564 households) recorded their food intake over two consecutive days. The data were collected in 1997/1998 and were equally distributed over seasons and the days of the week.

Nutrient intakes were calculated by combining individual consumption data with the Dutch food composition table 2001 (step 4) (NEVO, 2001; Jansen *et al.*, 2002). Since the bioavailability of folic acid is assumed to be higher than that of natural folate, the concentration units were converted into folate-equivalents (Health Council, 2003). Whereas 1 mg folic acid in foods equals 1.7 mg folate-equivalents, 1 mg natural folate is equal to 1 mg folate-equivalents (Bailey, 1998; Sutor *et al.*, 2000). The amounts of functional ingredient added to the products were assumed to be present in the end products.

Because long-term intake was of interest, statistical correction for day-to-day variation was applied using the ISU-method (IML/C-SIDE-software) (ISU, 1996) (step 6) (Gibson, 2005; Hoffmann *et al.*, 2002). Intake distributions were calculated for various age-gender groups. Unless otherwise stated, calculations were performed with Statistical Analysis Software (SAS version 9.1; SAS Institute).

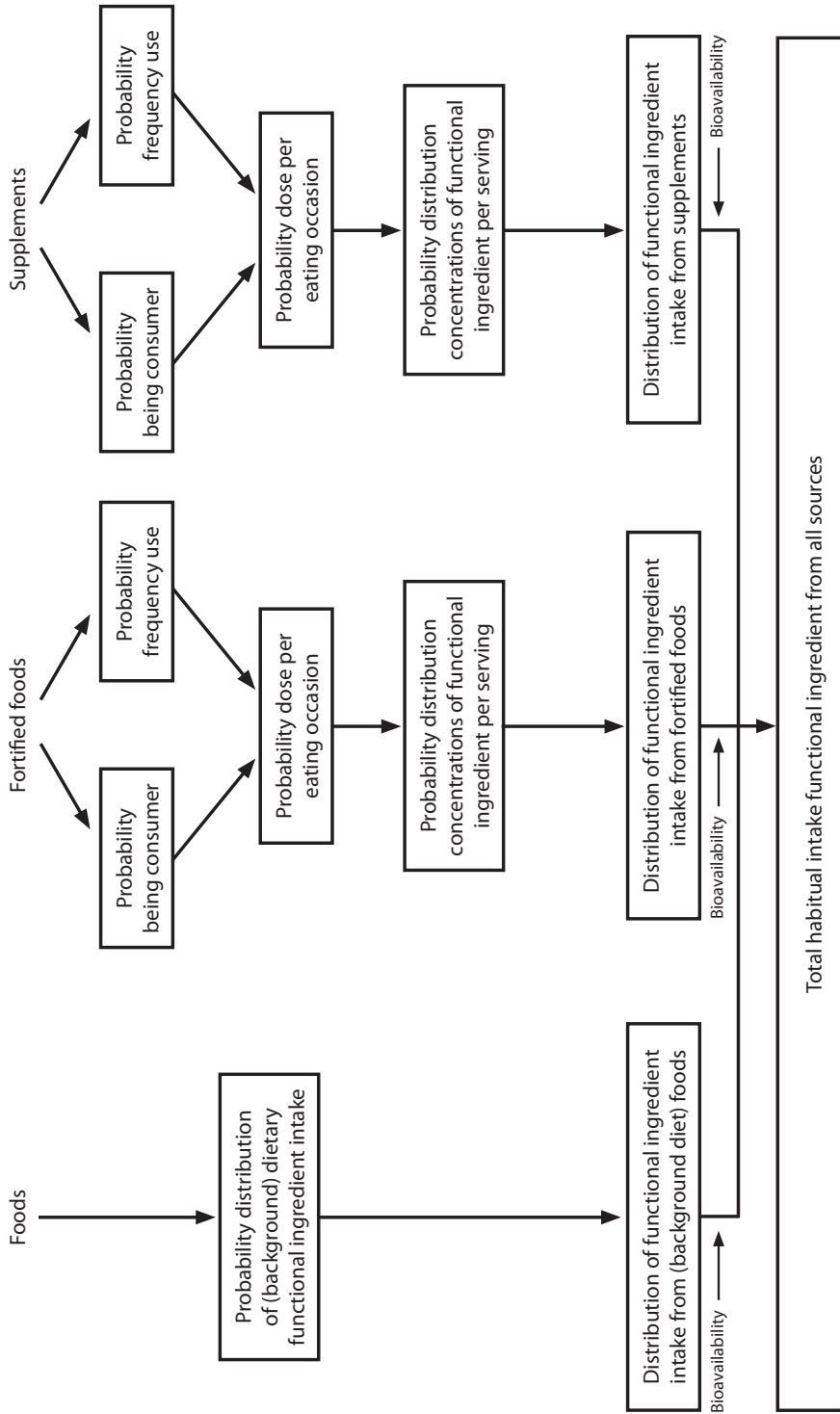


Figure 2.2 Model for probabilistic modeling of a nutrient adapted from Gibney *et al.* (2004) and Gibney *et al.* (2003).

Mandatory folic acid fortification

Simulation of mandatory folic acid fortification (step 1) is illustrated with two staple foods as carrier products (step 2). Bread was selected because of the international experiences with mandatory flour fortification (FDA, 1998a; 1996; Hertrampf *et al.*, 2003). The chosen fixed fortification levels, i.e. 70, 140, 280 and 420 mg per 100 g bread, were based on the level of 140 mg per 100 g flour advised in the USA (step 3) (FDA, 1996). Half and multiples of this level were selected to get an insight on the effect of different fortification levels. To study the effect of mandatory fortification of different products, a second staple food, i.e. (butter) milk, was selected (step 2). Based on experience in scientific studies, four fixed fortification levels were chosen; 20, 40, 80 and 160 mg per 100 ml (step 3) (Verwei, 2004).

In the food composition table, each level of folic acid was added to all (whole) bread or (butter)milk products except for raw milk (step 4). Total dietary folate-equivalent intake was calculated by summation of the total intake of natural folate and folic acid, expressed as folate-equivalents. It was assumed that observed non-consumption on both reported days was true non-consumption.

Voluntary folic acid fortification

Recently several food products (specific brands) got exemption for voluntary folic acid fortification in The Netherlands (www.row.minvws.nl). Of these products, we chose margarine as an example in the simulation of voluntary fortification (steps 1-2). The fortification level of 500 mg per 100 g stated in the application of the manufacturer was used as fixed fortification level in the simulation (step 3).

The proportion of margarine consumers who will use the fortified alternative in the near future is unknown. It was assumed that the market share of the brand in question would be a good indicator, in this case estimated at 30% (GfK Panel Service Benelux). Furthermore, the observed non-consumption on both reported days was assumed to be true non-consumption. Thirty per cent of the margarine consumers on the first observation day were randomly assigned to use folic-acid-fortified margarine. We assumed that all margarine consumers on day 1 had an equal chance to use the fortified margarine and were 100% brand loyal. Because it is unknown which 30% of the margarine consumers will use the fortified margarine, a random assignment was performed 100 times to get an insight on this uncertainty. For each of the 100 assignments, the habitual intake was estimated separately.

Results of case study simulations

Both the results of the simulation of mandatory and voluntary fortification are illustrated only for women aged 19–50 yr ($n = 1,636$, pregnant and lactating women excluded).

Mandatory fortification

The habitual intake distribution of folate-equivalents after simulation of mandatory fortification of bread is presented in Figure 2.3. In comparison to the background diet (i.e. without fortification), the four fortification scenarios show a shift of the total distribution towards higher intake levels (Figure 2.3). This can be explained by the fact that almost all subjects consumed bread. Besides, the intake distributions become wider after fortification. As expected, the higher the fortification level, the wider the distribution of intake levels. The confidence intervals around the curves express only the uncertainty of the estimation of the habitual intake of folate-equivalents using the ISU method, and not any other uncertainty due to, for example, errors in consumption or food composition data. The 95% confidence intervals become wider with an increasing fortification level.

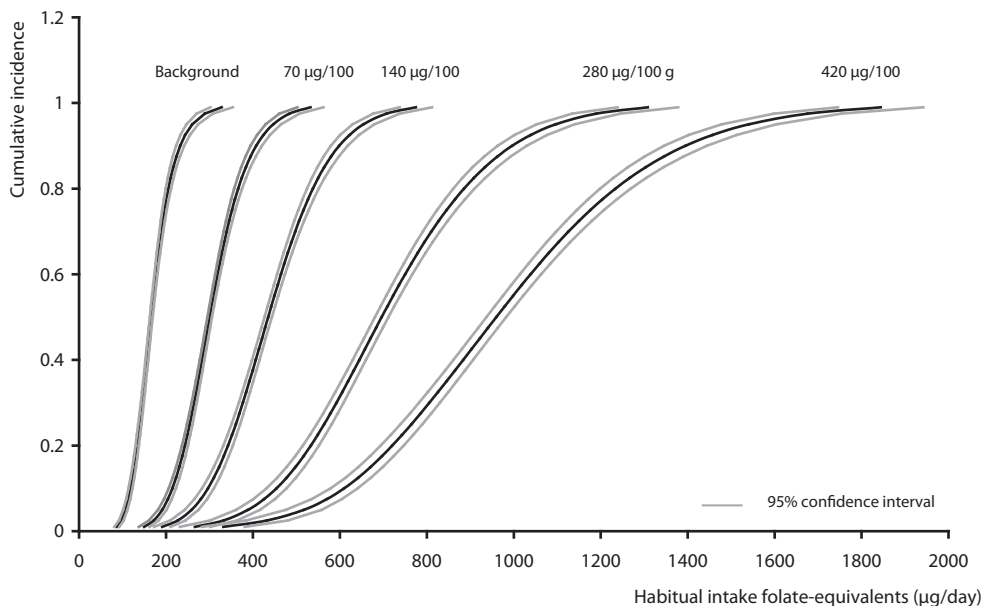


Figure 2.3 Habitual intake of folate-equivalents without (back-ground diet) and with mandatory fortification of bread with folic acid (four different levels) with 95% confidence intervals of habitual intake for women aged 19–50 yr.

The results of the mandatory folic acid fortification of (butter)milk (Figure 2.4) are similar to the results of the mandatory fortification of bread. Again, the distribution becomes wider after fortification. In contrast to the mandatory fortification of bread, the left tail of low folate-equivalent intake remains at an intake level similar to the background diet. This is due to the fact that there are more subjects not consuming (butter)milk compared to bread. For the highest fortification level (i.e. 160 mg per 100 ml), the habitual folate-equivalent intake could not be estimated, probably because of problems with the transformation to a normal distribution. At a fortification level of 80 mg per 100 ml, the intake distribution is not as fluent as the distributions for lower fortification levels. A plot of the probability density of the intake levels shows a distribution curve with two peaks (data not shown).

Voluntary fortification

The 100 simulated habitual folate-equivalent intake distributions after voluntary fortification of margarine are pictured in Figure 2.5a. In comparison with the intake distribution of the background diet, the intake distributions after voluntary fortification are more positively skewed to the right. The left tails of the intake distribution of the background diet and the distribution after voluntary fortification are comparable,

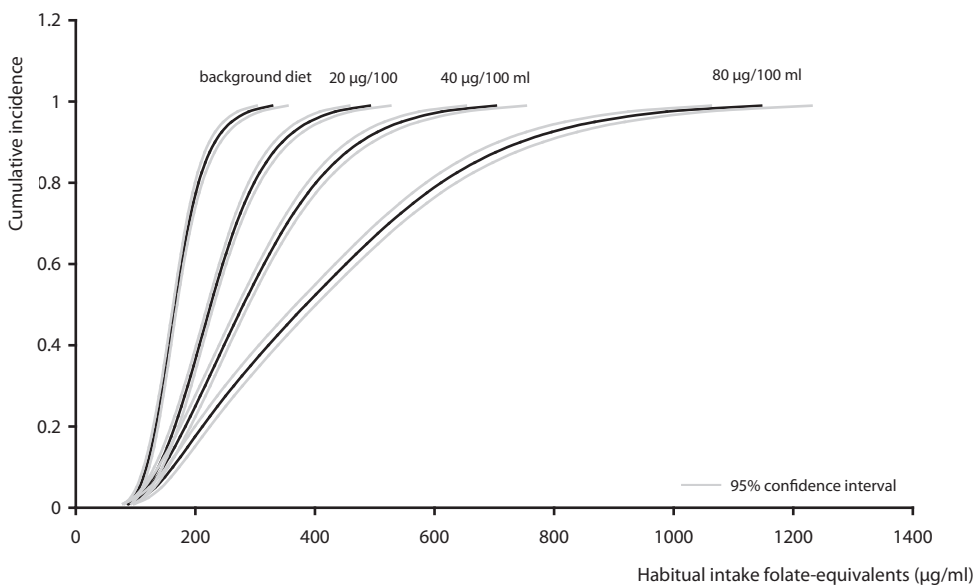
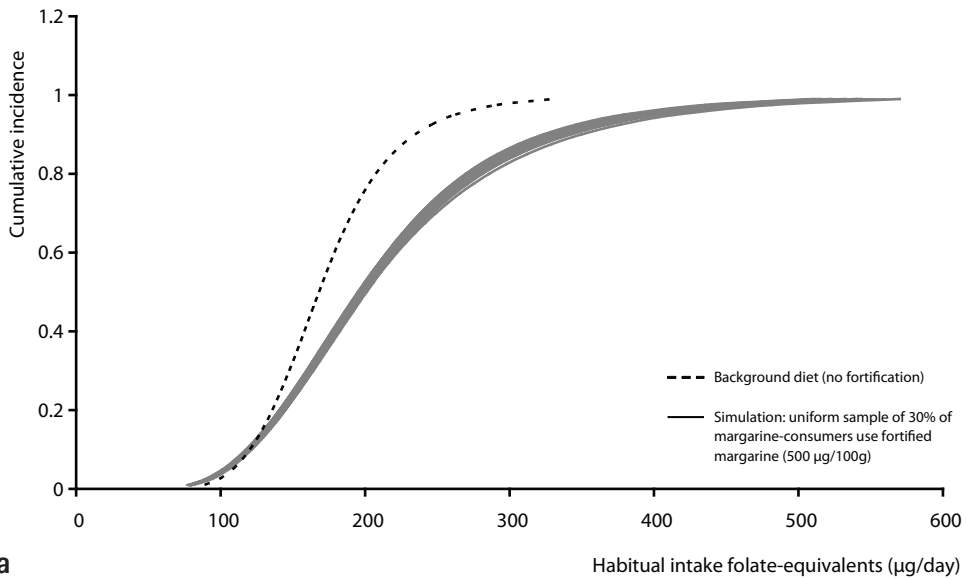
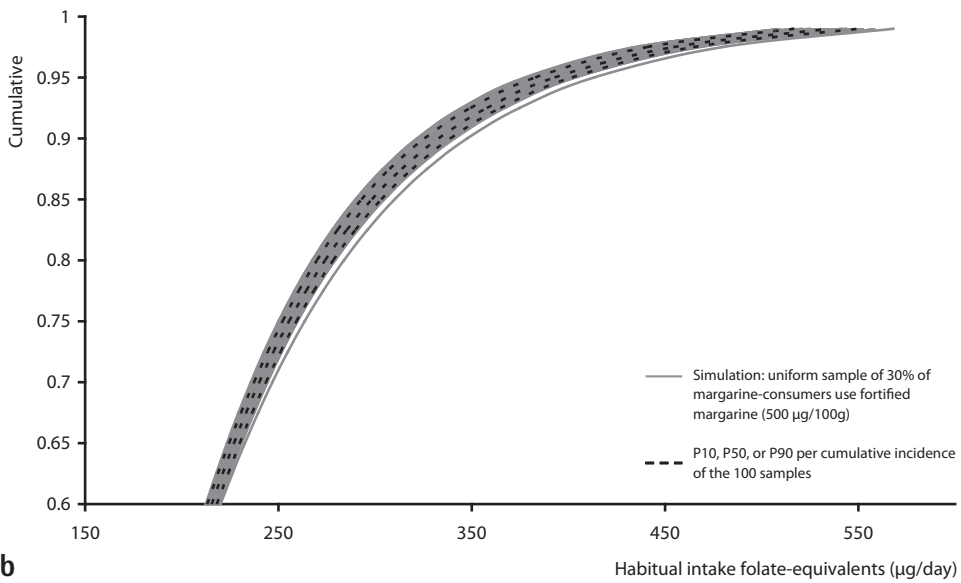


Figure 2.4 Habitual intake of folate-equivalents without (back-ground diet) and with mandatory fortification of (butter)milk with three different levels of folic acid, shown with 95% confidence intervals of habitual intake, for women aged 19-50 yr.



a



b

Figure 2.5 (a) Habitual intake distribution of folate-equivalents of 100 random samples of which a uniform sample of 30% of the margarine-users consume fortified margarine (grey lines) and the habitual intake distribution of folate-equivalents from the background diet (i.e. no fortification) (black dotted line) for women 19-50 yr (100% brand-loyalty). Part of the graph that lies within the oval is pictured enlarged in Figure 2.5b. (b) Upper part of the habitual intake distribution of folate-equivalents of 100 random samples of which a uniform sample of 30% of the margarine-users consume fortified margarine (grey lines) for women aged 19-50 yr; in black dotted lines P10, median and P90 are pictured to quantify the variation between the 100 samples.

representing consumers that do not use fortified products. The folate-equivalent intake range in voluntary fortification becomes wider compared to the background diet and mandatory scenarios.

The differences between the 100 curves reflect the uncertainty of the simulated intake, resulting from the uncertainty which 30% of the margarine consumers will use the fortified margarine. Figure 2.5a shows that the uncertainty is largest in the top part of the curve. This part is shown in more detail in Figure 2.5b, giving the median, 10th and 90th percentiles of these 100 intake distributions.

Discussion

In this Chapter, a general framework for the simulation of the intake of functional ingredients from fortified foods but also from other sources (e.g. other foods and dietary supplements) is described.

Framework

The framework we presented is generally based on a combination of strategies used in already published case studies of simulated mandatory fortification (Bausch-Goldbohm *et al.*, 1995; Brussaard *et al.*, 1995; Burger *et al.*, 2004; Firth *et al.*, 1998; Green *et al.*, 2003; Johnson-Down *et al.*, 2003; Kuhlmann *et al.*, 2005; Raulio *et al.*, 2001; Suojanen *et al.*, 2002). The aim of these case studies was diverse, which likely resulted in the different methods applied. In addition, lack of data and differences in available data may also have had influence on the choice of the method used. In our framework, all steps needed in the simulation of fortification are described in general. Within this framework, it is possible to perform simulations using different types of data and data from various sources, and to give an insight on the resulting uncertainties. Furthermore, the calculation of habitual intake to estimate long-term exposure is a standard procedure in our framework. In addition to the simulation of mandatory fortification, the framework is also applicable for the simulation of voluntary fortification. To our knowledge, at this moment, no (case) studies on the simulation of voluntary fortification have been published.

As shown in our framework, the simulation of mandatory fortification is more straightforward than the simulation of voluntary fortification and requires fewer assumptions. For mandatory fortification, assumptions that are needed concern the type of carrier products, the level of fortification and – when food consumption is assessed with short-term methods – the observed non-consumers vs. true non-consumers. Whereas for the simulation of voluntary fortification, additional assumptions regarding

the market share of the fortified foods, the proportion of and the distribution within the population or subgroups of the population that will consume fortified foods (regular or incidental) are needed. These assumptions will result in uncertainty in the final estimated intake distributions. Moreover, uncertainties in the observed consumption data and available composition data will be of influence in all simulations (WHO, 2006). We plea for an explicit description of the uncertainties, if possible by quantitative estimations of the effects of the uncertainty on the final outcome (for instance, as confidence intervals). When quantification of some uncertainties is not possible, which may often be the case, they should be described thoroughly.

In addition to scenarios mainly based on changes in food supply as described in this Chapter, scenarios based on changes in consumption patterns may also be expected due to, for instance, publicity campaigns. Our framework can easily be extended for this purpose by virtually changing the consumption data, for instance by increasing the number of subjects who will consume a specific food or changing the consumed amount.

Habitual intake

Effects of nutrition are often long term; therefore, habitual exposure is of a greater meaning than acute intake levels. However, long-term intake data are scarce. With food-frequency questionnaires, habitual intake (often over a month or year) can be estimated immediately, though the questionnaires are often qualitative or semi-quantitative, and cover only part of the food supply (i.e. several hundred products). Food consumption surveys usually assess diet by short-term dietary assessment methods that cover only several observation days. With statistical procedures, observed intake can be corrected for within-person variation to estimate habitual intake. Several statistical methods have already been developed to estimate the habitual intake of nutrients or food(group)s (Hoffmann *et al.*, 2002; NRC, 1986; Nusser *et al.*, 1996; Slob, 1993; 2006). These statistical procedures cannot be applied to consumption data with only one observation day per subject. Some of the assumptions made in these statistical methods, like a smooth distribution and homogeneous within-person variation, may be violated due to simulated fortification practices (Dodd, 1996). This may result in data that cannot be transformed to a normal distribution (as is required in some methods) or problems with the estimation of the within-person variation. An adaptation of the current methods is needed to correct the data for within-person variation if the assumptions of current statistical methods are not met. Perhaps, correction for the within-person variation can be done for specific cluster groups which have homogeneous within-person variation (Carriquiry, 2006, personal communication).

Case study

We have illustrated the general framework with case studies for mandatory and voluntary folic acid fortification. At this moment, four case studies of mandatory folic acid fortification are published (Bausch-Goldbohm *et al.*, 1995; Burger *et al.*, 2004; Firth *et al.*, 1998; Green *et al.*, 2003). When these four case studies were compared with our framework, several differences in the simulation method were found. Only one study has estimated the total intake in folate-equivalents, like in our study (Burger *et al.*, 2004). The other three studies have calculated the folic acid intake from fortified foods only (Bausch-Goldbohm *et al.*, 1995), summed the intake of folic acid from fortified foods and supplements, without taking into account differences in bioavailability (Green *et al.*, 2003), or added up intake of dietary folate and folic acid from different sources without correcting for the difference in bioavailability (Firth *et al.*, 1998). Two studies took into account the intake from dietary supplements (Green *et al.*, 2003). Several of the above-described problems with the calculation of the habitual intake were also faced in these case studies.

The assumption that observed non-consumers on the study days are habitual non-consumers will often be incorrect. It is therefore better to estimate the probability of consuming a certain amount on each day. Additional data about the propensity of consumption during a longer timeframe are of use to make valid estimations (Tooze *et al.*, 2006). In the voluntary approach, 30% of the (low-fat) margarine users were uniformly sampled to be a consumer of fortified (low-fat) margarine. It is unlikely that the chance that somebody will be a consumer of fortified products is equal for the whole population (De Jong *et al.*, 2003). An insight on determinants of food consumption may assist in taking valid conditional samples out of the population.

Conclusion

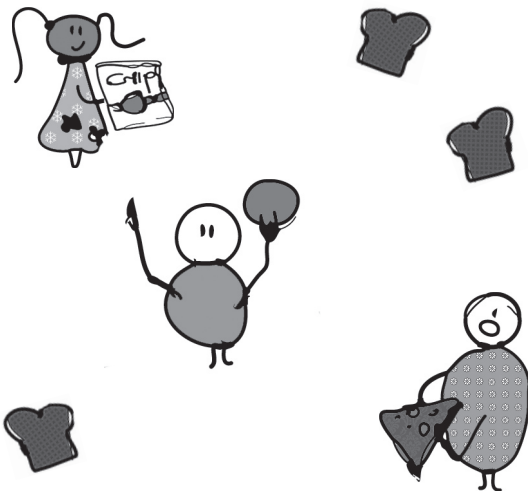
The general framework we presented for the simulation of the intake of functional ingredients from different sources can be applied for a range of aims. Important uses of our framework are getting an insight on changing intake distributions due to changes in, for instance, policies or consumption, finding out the optimal fortification scenario to create an intake of the population between recommendations and the UL, or risk-benefit analyses. A novelty of this framework is that it can be used to estimate intakes not only from mandatory fortification but also from voluntary fortification, as was illustrated by the case study.

The framework describes the different steps required for the simulation of intake and the required data. Even with incomplete data, or data from different sources, the (habitual) intake distributions can be estimated using assumptions, statistical

procedures or probabilistic modeling approaches. The relevant outcome measure is, in most instances, the population distribution of habitual total intake. It is important that the whole procedure of simulation of fortification is described well, so that an insight can be given on the uncertainties and knowledge gaps to be filled in future. Besides, using and describing the same general framework as a basis will help to make outcomes from different studies (and countries) better comparable.

Acknowledgements

We thank A. Carriquiry and G. Camaño-Garcia of the Department of Statistics, Iowa State University, USA for statistical support and invaluable assistance with the SIDE software; D. ter Doest (TNO Quality for Life Institute, Zeist, The Netherlands) for practical assistance with the SIDE software; and A.L.M Dekkers (RIVM) for statistical assistance.



3

Simulation model accurately estimates total dietary iodine intake

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Abstract

One problem with estimating iodine intake is the lack of detailed data about the discretionary use of iodized kitchen salt and iodization of industrially processed foods. To be able to take into account these uncertainties in estimating iodine intake, a simulation model combining deterministic and probabilistic techniques was developed. Data from the Dutch National Food Consumption Survey (1997-1998) and an update of the Food Composition database were used to simulate 3 different scenarios: Dutch iodine legislation until July 2008, Dutch iodine legislation after July 2008, and a potential future situation. Results from studies measuring iodine excretion during the former legislation are comparable with the iodine intakes estimated with our model. For both former and current legislation, iodine intake was adequate for a large part of the Dutch population, but some young children (<5%) were at risk of intakes that were too low. In the scenario of a potential future situation using lower salt iodine levels, the percentage of the Dutch population with intakes that were too low increased (almost 10% of young children). To keep iodine intakes adequate, salt iodine levels should not be decreased, unless many more foods will contain iodized salt. Our model should be useful in predicting the effects of food reformulation or fortification on habitual nutrient intakes.

Introduction

Iodine is required for good functioning of the thyroid and the production of thyroid hormones. Inadequate iodine intake results in iodine deficiency disorders. One of the best known clinical symptoms of iodine deficiency disorders is goiter. In addition, inadequate iodine intake in pregnancy and early childhood results in impaired brain development and, as a consequence, reduced mental function. In many countries, including The Netherlands, the levels of iodine naturally present in foods are not adequate (Andersson *et al.*, 2007). To overcome this, The Netherlands has a long history of using iodized salt, beginning in 1928. Besides iodine deficiency, excessive iodine intakes cause elevated thyroxin and decreased thyroid stimulating hormone concentrations. It remains uncertain whether chronic exposure to these biochemical changes will result in clinical health effects (IOM, 2001; SCF/NDA, 2006).

The best way to gain insight into population iodine status is to measure urinary iodine excretion (WHO *et al.*, 2007). However, such data are scarce. In addition, the potential effects of proposed changes in iodine policy on iodine intake cannot be measured in advance. For this purpose, the estimation of population habitual iodine intake distributions using food consumption and food composition data are required. In The Netherlands, no data have been collected about the discretionary use of (iodized) salt in food consumption surveys, and detailed information about the addition of iodine (iodized salt) in industrially processed foods is lacking in food composition databases. Estimations of market shares of industrially processed foods with added iodine can be used. However, it is uncertain which people will consume those foods. With a probabilistic approach, these uncertainties and other variability can be taken into account. In a probabilistic model, ranges of values for variables in the form of probability distributions are randomly sampled, which is done repeatedly. This is in contrast to a deterministic model in which outcomes are precisely determined through known relationships without any room for random variation.

To estimate habitual total iodine intake, we therefore developed a new simulation model in which the advantages of both the deterministic and probabilistic approaches are combined. In this article, we describe this combined simulation model. The model was applied to estimate habitual total iodine intake in the Dutch population for 3 different scenarios: 1) the former iodine policy (until July 2008); 2) the new iodine policy of 2008; and 3) a potential future change in iodine policy.

Scenarios and methods

Scenarios

A simulation model combining deterministic and probabilistic approaches was developed to estimate habitual iodine intake in the Dutch population for 3 scenarios (Table 3.1). The first scenario represented the iodine policy in The Netherlands until July 2008 (transition period until July 2009). Iodized salt could voluntarily be added to bread and bread-replacing products (70–85 mg I/kg salt), kitchen salt (30–40 mg I/kg salt), and meat products (20–30 mg iodate/kg nitrate grid salt). In the new Dutch iodine policy (scenario 2), the number of foods that may contain iodized salt was extended and the concentration of iodine in salt was decreased. Iodized salt with a maximum level of 65 mg I/kg salt may be applied to bread, bread-replacing products, and other bakery products, and salt with a maximum level of 25 mg I/kg salt may be applied in all other industrially processed foods (excluding drinks containing >1.2 volume% alcohol). In the third scenario, foods to which iodized salt may be added were the same as in the second scenario, but only one single type of iodized salt containing 25 mg I/kg salt was applied. This iodine level is relatively low compared with the historical and current Dutch situation; however, it is comparable to levels used in other European countries (WHO, 2000) and may therefore be considered as an option for future harmonization of iodine levels in salt in Europe.

Simulation model

The model was developed to fit the data of the most recent population-wide National Food Consumption Survey in The Netherlands (1997–1998). Respondents ($N = 6,250$, aged 1–97 yr) were selected from a representative consumer panel of households. For each household member, food intake was recorded on 2 consecutive days (children <13 yr assisted by caretakers) (Hulshof *et al.*, 2003). Quantities of foods were estimated by the subject in household units or natural units. The interviewer measured the volumes of common household measures and weighted regularly consumed foods like slices of bread.

The simulation model is based on the framework for intake simulation of functional ingredients of Kloosterman *et al.* (Chapter 2) and consists of 6 steps (Figure 3.1). Briefly, in steps 1–4, the iodine intake from 4 different potential dietary sources were estimated separately: 1) iodine found naturally in foods; 2) iodine added to industrially processed foods by adding iodized salt; 3) discretionarily added iodized salt; and 4) iodine containing dietary supplements. In the step 5, observed total iodine intake was calculated for each subject on each observation day and each iteration.

Table 3.1 Overview of the different scenarios of use of iodized salt both in industrially processed foods and in discretionary use

Food Group	Scenario 1		Scenario 2a		Scenario 2b		Scenario 3	
	Market share (%)	Iodine (mg/kg salt)	Market share (%)	Iodine (mg/kg salt)	Market share (%)	Iodine (mg/kg salt)	Market share (%)	Iodine (mg/kg salt)
Bread	90	77.5	90	65	90	65	90	25
Bread-replacing products	5	77.5	5	65	50	65	50	25
Brand specific bread-replacing products known to contain iodized salt	100	77.5	100	65	100	65	100	25
Other bakery products	–	–	5	65	50	65	50	25
Meat products	5	25	5	25	50	25	50	25
Other industrially processed foods	–	–	5	25	50	25	50	25
Discretionary used kitchen salt	81	35	81	25	81	25	81	25

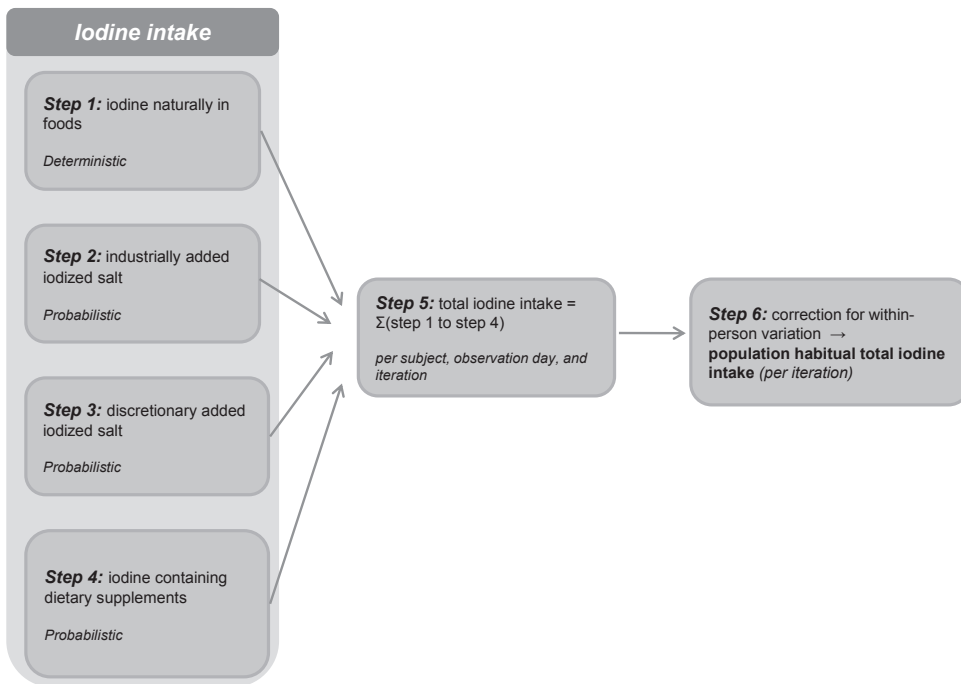


Figure 3.1 Schematic overview of the different steps in the simulation model to estimate population habitual total iodine intake.

Population habitual iodine intake distribution was estimated for each iteration separately in step 6. Unless otherwise stated, we used SAS software (SAS 9.1.3, SAS Institute) for modeling. Population habitual total iodine distributions were compared to the estimated average requirements (EAR) (IOM, 2001) and tolerable upper intake levels (UL) (SCF/NDA, 2006) for iodine to estimate the proportion of the population at risk of inadequate or potentially excessive iodine intakes using a cut-point method (IOM, 2000b). Below, each of the modeling steps is described in more detail.

Step 1: iodine intake from natural sources

Daily iodine intake from natural sources only was calculated in a deterministic way by multiplying the consumed amount of a food by a point estimate of the natural iodine level in that food. The iodine content of foods for special dietary use, such as infant foods and clinical foods, was taken into account in the calculation of natural iodine. Because these foods for special dietary use have separate legislation, we assumed that no additional iodine could be added as iodized salt. Subsequently, the natural iodine intake was summed over all foods per participant per day.

Because the most recent population-wide food consumption data are from 1997–1998, we combined these data with the most recent food composition data to get more accurate estimates of current iodine intake. From 2007 onwards iodine levels were added to the Dutch food composition database (NEVO, 2008). For this study, missing iodine levels were completed and available iodine levels were, if required, updated using the manufacturer's information, scientific literature, foreign food composition tables, or iodine levels from similar food products.

Step 2: iodine intake from industrially added iodized salt

We estimated iodine intake from industrially added iodized salt using a probabilistic approach. Market shares of the use of iodized salt in 35 groups of industrially processed foods were used to estimate iodine intake from industrially added iodized salt.

A random sample proportional to the market share of iodized salt application (Table 3.1) was drawn among consumers of foods from a specific food group. The selected participants were assumed to use the iodized salt-containing variants of all the foods consumed from this food group. Participant selection was independently performed for each observed day. The sampling was repeated for 100 iterations to take into account this uncertainty. For each iteration, the daily intake of iodine from industrially added iodized salt was calculated per subject by multiplying the consumed amount of a food by the amount of added sodium chloride (salt) and a point estimate of the iodine concentration in salt. The total iodine intake from industrially added iodized salt was calculated by summing the iodine intake over all food groups per participant per day per iteration.

Because iodine is only added to industrially processed foods as iodized salt, sodium levels available in the Dutch Food Composition Database were updated using similar procedure as described above for iodine. The proportion of total sodium industrially added as sodium chloride was crudely estimated based on recipe information. For most industrially processed foods, the proportion of added sodium chloride was set at 100%, except for dried and salted shrimp (30%), liquorice (50%), salted fries (70%), all cheese excluding cheese spread (75%), canned vegetables and canned fish (80%), cheese spread, chips, smoked fish (85%), sesame paste, and meat products (90%). The amount of salt in industrially processed foods was estimated as 2.5 times the added sodium concentration, because the molecular weight of sodium chloride (58.5) is 2.5 times the molecular weight of sodium (23).

Because the exact salt iodine levels and market shares of application of iodized salt are unknown, we had to make several assumptions in the 3 different scenarios (Table 3.1). In the first scenario (former iodine policy), the salt iodine concentration was assumed to be the mean of the legal range. The market shares of use of iodized

salt in the different food groups were based on crude information of the Dutch Food and Consumer Product Safety Authority (Erik Konings, Dutch Food and Consumer Product Safety Authority, The Netherlands, personal communication). In scenario 2 (new iodine policy), the 2 defined maximum salt iodine concentrations were applied as point estimates in the model. In scenario 2a, we assumed the same market shares as used in scenario 1. In scenario 2b, the market share was increased from 5 to 50% for foods other than bread. In the scenario of a potential future situation (scenario 3), the same market shares as used in scenario 2b were assumed. To be comparable with salt iodine concentration applied in other European countries, in this scenario a single salt iodine concentration of 25 mg/kg was applied for all industrially processed foods.

Step 3: iodine intake from discretionarily used iodized kitchen salt

A similar probabilistic approach as described for step 2 was performed to estimate daily iodine intake from discretionarily used iodized kitchen salt (step 3). We used an estimation of the proportion of participants using iodized kitchen salt to draw 100 independent samples of participants who were assigned to discretionary use of iodized kitchen salt on both observed days. Foods to which kitchen salt may be discretionarily added were divided into 11 groups. Foods consumed raw were not included, even as foods already containing industrially added salt. For each of these 11 food groups, the amount of salt added per 100 g was estimated based on cookbook recipes and guidelines of the Dutch Food Composition Table. For potato, rice, cereals, and pasta, the amount of salt/100 g food was estimated to be 0.4 g, 0.6 g for vegetables, legumes, and prepared meals, 0.8 g for sauce, and 1.8 g for meat, meat replacers, fish, and egg. We assumed that users of iodized kitchen salt add this salt to all 11 food groups.

For each iteration, we estimated the daily intake of iodine from discretionarily used iodized kitchen salt by multiplying the consumed amount of a food by the amount of salt discretionarily added and the concentration of iodine in kitchen salt. Summation over all food groups resulted in the total daily iodine intake from discretionarily added iodized kitchen salt for each subject on each day for each iteration.

In all 3 scenarios, it was assumed that 95% of the Dutch population discretionarily use kitchen salt and 85% of discretionary salt users use iodized salt (based on information of the Dutch salt industry; Laurens Rupert, Akzo Nobel Salt, The Netherlands, personal communication). The proportion of participants using discretionary iodized kitchen salt was therefore calculated to be 81% (i.e. 95% x 85%). The salt iodine levels varied between the 3 scenarios. In the first scenario (former iodine policy), a salt iodine concentration of 35 mg I/kg salt was assumed, and in scenarios 2 (new iodine policy) and 3, (potential future situation) the concentration was 25 mg I/kg.

Step 4: Iodine intake from dietary supplements

For the estimation of iodine intake from dietary supplements, a probabilistic approach was also used. Within the most recent population-wide Dutch National Food Consumption Survey (1997-1998), no detailed information was available on use of iodine-containing dietary supplements. Based on the results from 2 Dutch food consumption surveys conducted among young adults and young children, it was estimated that 15% of children aged ≤ 12 yr and 15% of adults used iodine-containing dietary supplements (Ocké *et al.*, 2005a; b; 2008). Because most of the iodine-containing dietary supplements were multivitamin/mineral supplements, the percentage of multivitamin users in the 1997-1998 survey was used to estimate that 7% of adolescents (13-17 yr) used iodine-containing dietary supplements (Ocké *et al.*, 2005a). For each age group, a sample as large as the age-specific proportion was drawn to select subjects using iodine-containing dietary supplements. The sampling was repeated 100 times. Among users of iodine-containing dietary supplements, it was assumed that 65% of children (1-12 yr) and 50% of adolescents (13-17 yr) and adults used such a supplement on both observed days (Ocké *et al.*, 2005a; b; 2008). To select these participants using iodine-containing dietary supplements on both observed days, a second sample was drawn from the selection of iodine-containing dietary supplement users proportional to the above assumed percentages. For the participants assigned to use iodine-containing dietary supplements, the amount of iodine was drawn from a uniform distribution of possible amounts. This distribution was based on the 25th to 75th percentile range of observed daily doses in the 2 Dutch food consumption surveys among young adults and young children (Ocké *et al.*, 2005b; 2008). We applied the range of young children (15-50 mg iodine) to children aged 1-12 yr and the range for young adults (50-150 mg iodine) was applied to both adolescents (13-17 yr) and adults. It was assumed that for subjects using iodine-containing dietary supplements on both observed days, the amount of iodine was equal on each day.

Step 5 and 6: total observed iodine intake and habitual iodine intake

In step 5, the observed total iodine intake was calculated by adding the iodine intake from the 4 different sources for each subject, on each observation day, for each iteration separately. This resulted in 100 total iodine intakes per participant per day.

In the food consumption survey database, data on 2 days of dietary intake were available. This was a poor estimator of habitual intake (i.e. average intake over a longer period of time) because of the within-person variability in dietary intake. In step 6, we used statistical modeling to estimate the within- and between-person variability. For each iteration, the distribution of habitual intake (the long-run average) was estimated

based on only the between-person variability using the ISU-method (developed at Iowa State University) (SIDE/IML version 1.11, 2001) (Nusser *et al.*, 1996). This was done at the level of population subgroups, so no individuals could be identified that had an extremely high or low intake, but the proportion of the subgroup with a habitual intake below a specific cut-off level can be estimated.

Results

In general, habitual iodine intake increased with age and was higher among men than women (Table 3.2). In scenario 1, representing the iodine policy until July 2008 in The Netherlands, the mean habitual iodine intake ranged from 121 mg/d for young children (1-3 yr) to 305 mg/d for adult men. The habitual iodine intake in scenario 2a (new Dutch iodine legislation; similar market shares to scenario 1, but extended number of foods containing iodized salt and lower salt iodine concentration) was similar to the habitual intake distribution of scenario 1. The mean habitual iodine intake ranged from 118 mg/d for young children (1-3 yr) to 300 mg/d for adolescent boys (15-17 yr). When market shares of industrially processed foods containing iodized salt increased from 5 to 50% in combination with the new iodine legislation (scenario 2b), the mean habitual iodine intake increased ~15%, ranging from 137 mg/d for young children (1-3 yr) to 348 mg/d for adult men. If only one type of iodized salt is allowed, with a relatively low iodine concentration (25 mg I/kg salt), as in scenario 3, then the mean habitual iodine intake decreased 10-15% to a range of 103 mg/d for young children (1-3 yr) to 260 mg/d for adult men.

The differences in habitual iodine intake distributions among scenarios 1, 2b, and 3 are illustrated for children aged 1-3 yr (Figure 3.2). Using scenario 1 as a reference, the increased market share of foods containing iodized salt, although with smaller salt iodine concentrations (scenario 2b), resulted in a shift toward higher intakes. In scenario 3 (one single low salt iodine concentration), the distribution not only shifted toward lower iodine intake levels, but the distribution was also steeper compared with the other 2 scenarios.

The percentage of subjects with a habitual iodine intake below the EAR was in general highest for young children and slightly higher in women than in men (data not shown). In the scenarios of the former legislation (scenario 1) and the new legislation with low market shares (scenario 2a), the percentage of young children (1-3 yr) with iodine intakes that were too low (below EAR) was comparable, 4.7 and 5.8%, respectively (Figure 3.3). Increasing the market share in scenario 2b resulted in a decrease to 1.8% of young children with inadequate intakes.

Table 3.2 Mean and distribution (5th, 50th, and 95th percentile) of habitual total dietary iodine intake (µg/day) of the Dutch population for 3 different scenarios¹

Age category (year)	n	Scenario 1					Scenario 2b					Scenario 3				
		Mean	P5	P50	P95		Mean	P5	P50	P95		Mean	P5	P50	P95	
Children 1-3	254	121 (117-123)	65 (64-69)	118 (115-119)	188 (181-192)	137 (134-142)	79 (75-81)	135 (132-137)	205 (196-216)	103 (100-106)	59 (55-62)	100 (99-102)	156 (151-159)			
Children 4-6	276	154 (151-158)	92 (85-100)	150 (145-155)	230 (223-236)	174 (170-178)	113 (109-118)	172 (168-174)	243 (238-251)	125 (122-127)	81 (75-87)	122 (119-125)	177 (167-187)			
Boys 7-10	141	216 (208-223)	148 (137-166)	215 (206-221)	289 (272-308)	243 (235-251)	172 (144-199)	242 (229-250)	324 (296-339)	173 (168-178)	120 (101-135)	170 (163-176)	233 (215-257)			
Girls 7-10	171	180 (174-186)	107 (93-115)	178 (173-181)	264 (250-281)	209 (204-214)	138 (130-147)	206 (200-209)	280 (274-295)	151 (147-155)	98 (89-106)	150 (146-153)	215 (205-228)			
Boys 11-14	174	257 (249-263)	153 (144-169)	255 (245-259)	376 (355-398)	297 (289-305)	197 (165-208)	295 (288-306)	425 (401-455)	214 (209-221)	136 (129-144)	209 (204-214)	301 (289-325)			
Girls 11-14	162	215 (207-223)	144 (134-162)	217 (205-222)	297 (286-305)	248 (240-256)	170 (161-188)	244 (236-254)	327 (315-343)	181 (175-185)	123 (115-132)	177 (174-183)	246 (232-261)			
Boys 15-17	142	303 (294-313)	182 (142-198)	300 (289-308)	438 (397-472)	346 (336-356)	233 (220-246)	344 (333-356)	476 (445-500)	243 (233-250)	161 (146-188)	239 (230-248)	339 (320-355)			
Girls 15-17	138	228 (221-235)	140 (121-154)	226 (218-238)	329 (297-349)	265 (256-273)	171 (158-184)	266 (254-276)	368 (358-386)	193 (185-198)	124 (113-132)	192 (185-196)	273 (249-299)			
Men 18+	2,155	305 (303-308)	181 (175-186)	300 (296-302)	448 (441-451)	348 (346-350)	219 (212-223)	344 (340-346)	494 (489-499)	260 (258-262)	162 (160-165)	255 (252-256)	375 (370-378)			
Women 18+	2,637	239 (238-241)	146 (142-148)	236 (235-238)	347 (343-352)	271 (270-273)	176 (172-178)	267 (266-269)	378 (374-383)	210 (208-211)	134 (133-136)	206 (204-208)	300 (297-304)			

¹ Results presented as P50 (P5-P95) of the 100 iterations in each simulation.

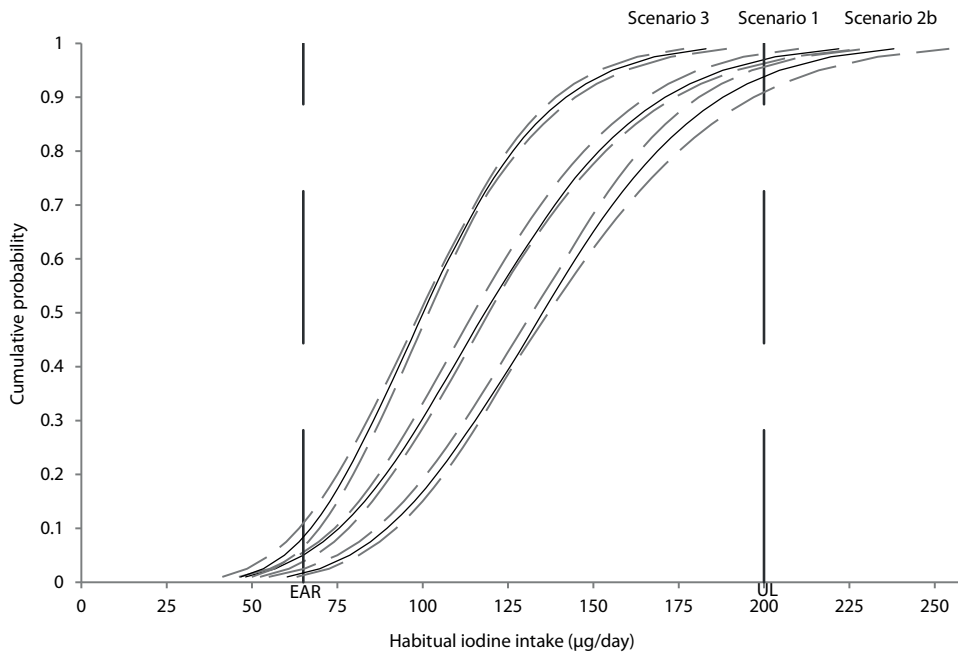


Figure 3.2 Habitual total iodine intake ($\mu\text{g}/\text{day}$) distribution* for Dutch children aged 1-3 years for 3 different scenarios. Scenario 1, Dutch iodine legislation until July 2008; Scenario 2b, Dutch iodine legislation after July 2008 with high market share of iodized salt-containing foods; Scenario 3, potential future scenario. * Results presented P50 (black line) and P5 & P95 (dotted lines) of 100 iterations per simulation

Reduction of the salt iodine concentration in scenario 3 resulted in an increase to 9.3% in the percentage of young children with inadequate iodine intakes. In all scenarios, the percentage of the remaining age categories (≥ 4 yr) with an iodine intake that was too low was $< 1\%$ (data not shown).

In general, the percentage of participants with a habitual iodine intake above the UL was little higher for men than women and was highest for children (1-10 yr). In scenario 1, the percentage of children (1-10 yr) with excessive intakes ranged from 1.5-3.6% (Figure 3.4, children aged 1-3 yr). In all other age categories, the percentage of participants with a habitual iodine intake above the UL was $< 1\%$; somewhat lower percentages of 0.8-2.5% of the children (1-10 yr) were found for scenario 2a. Increasing the market share in scenario 2b resulted in an increase in the percentage of participants with potentially excessive iodine intakes; 2.0-10.8% of the children aged 1-10 yr and the boys aged 11-17 yr had a habitual iodine intake above the UL. In the other age categories, this percentage was $< 1\%$. Reducing the salt iodine concentration to

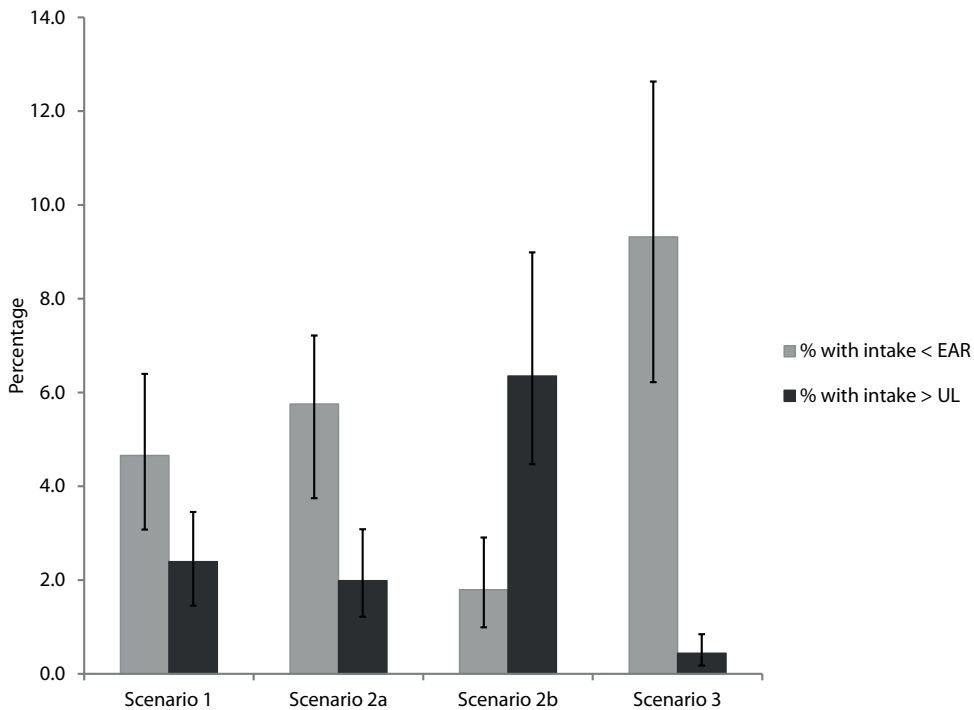


Figure 3.3 Percentage of children (1-3 yr) with habitual iodine intakes below the EAR and percentage of children with habitual iodine intakes above UL for 4 different scenarios. Percentages presented as P50 of 100 iterations, error bar represents P5-P95 range of 100 iterations, $n = 254$. Scenario 1, Dutch iodine legislation until July 2008; Scenario 2a, Dutch iodine legislation after July 2008 with low market share of iodized salt-containing foods; Scenario 2b, Dutch iodine legislation after July 2008 with high market share of iodized salt-containing foods; Scenario 3, potential future scenario.

25 mg I/kg salt (scenario 3) resulted in a decrease in the percentage of participants with excessive intakes. In all age categories, the percentage with a habitual iodine intake above UL was <1%.

Discussion

We presented a simulation model to estimate habitual total dietary iodine intake in The Netherlands. A novelty of this model is that it makes use of a combination of deterministic and probabilistic techniques to take into account observed individual dietary patterns and several uncertainties in data. From our simulation study, it can

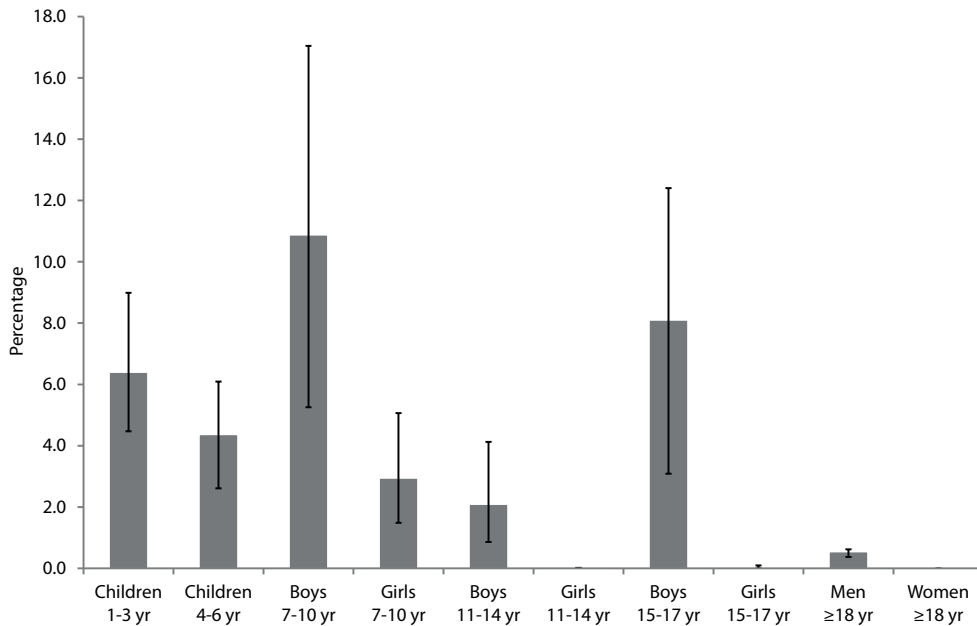


Figure 3.4 Percentage of Dutch population with habitual iodine intakes above UL for scenario 2b. Percentages presented as P50 of 100 iterations, error bar represents P5-P95 range of 100 iterations, $N = 6,250$.

be concluded that, as also stated by WHO (Andersson *et al.*, 2007), iodine deficiency was under control during the former iodine legislation in The Netherlands (until July 2008). Young children aged 1–3 yr old had the largest proportion of inadequate intake (<5% had intakes below EAR). Under the current Dutch iodine legislation, compared with the former, the number of foods that may contain added iodized salt increased and the iodine level in salt decreased. When the market shares of iodized salt-containing industrially processed foods will not increase to the desired higher percentages as assumed scenario 2b, iodine deficiency is expected to be still under control. The percentage of young children with iodine intakes below EAR increased slightly to 5.8%. An increase of the market share by stimulation of the use of iodized salt in industrially processed foods from 5 to 50% logically decreases the percentage of participants with intakes below the EAR (<2%). Reducing the salt iodine level to 25 mg/kg and a market share of 50% for iodized salt-containing industrially processed foods resulted in an increased percentage of the Dutch population with intakes below EAR, especially young children (almost 10%). With the current practice, in which only ~5% of foods contain iodized salt, the percentage of the Dutch population with inadequate iodine intakes could even be higher. The observation that young children

are at the highest risk of inadequate iodine intake may be caused by the fact that some of these children consume specific infant foods instead of bread. These specific infant foods generally contain less iodine than bread.

The intake estimates in this article are based on simulations using individual level data from food consumption surveys, population level estimates of market shares, and various assumptions. Some of the assumptions are inherent to predicting potential future scenarios, as others are required because of inadequate data. Our estimations of iodine intake under the former legislation (until July 2008) were comparable with the results of a recently conducted Dutch study measuring iodine excretion in 24-h urine samples. In this study, mean iodine excretion was 297 mg/d for men and 244 mg/d for women (Wilson-Van den Hooven *et al.*, 2007), which corresponds to an intake of 323 and 265 mg/d, respectively (IOM, 2001) (our estimation was 305 and 239 mg/d, respectively). The small differences may not be explained by only the assumptions made in our simulation model but also by differences in study population (such as age distribution), inaccuracy in iodine values in the food composition tables, and underestimation of dietary intake in the food consumption surveys. In a duplicate diet study performed in The Netherlands among young children aged 2–6 yr, the mean iodine intake was 142 mg/d (E. Jansen, M. Ocké, unpublished data). This amount lies between the mean iodine intakes we estimated for children 1–3 yr (121 mg/d) and 4–6 yr (154 mg/d). The comparable results indicate that our estimates of iodine intake under the former legislation are valid.

Our study also has limitations. We used data from the last population-wide food consumption survey, which is 10 yr old (1997–1998). Therefore, we combined these data with most recent food composition data (from 2007 and updated for this study) to obtain an updated picture of iodine intakes from current foods. Apart from alterations in food composition, alterations in food habits over time also occur. In the period from 1987 to 1997, bread consumption tended to have a non-significant decrease (Health Council, 2002). In The Netherlands, bread is an important source of iodine because of the large-scale use of iodized bread salt; continuation of this trend after 1997 might have influenced our results. In addition, in dietary assessment and monitoring studies, energy intake is underestimated. This was also the case in some age categories in the food consumption survey (an average of 5% for men, 10% for women, no underestimation for young children), which might have resulted in a similar underestimation of total iodine intake (Health Council, 2002).

In nutrition science, a deterministic approach is usually applied to estimate (habitual) nutrient intakes. A disadvantage of this approach is that uncertainties or variability in concentration or consumption data cannot be taken into account. A mean value or worst-case approach is often applied and the latter results in an overestimation of

both tails of the intake distribution. To take into account uncertainty or variability, a probabilistic approach can be used. However, in probabilistic approaches, samples are usually drawn from intake distributions of separate food groups, assuming independence between intakes of the food groups. As a consequence, the complex interrelationships in individual dietary patterns is not taken into account as such, which then will result in an overestimation of both tails of the intake. Alternatively, a correlation between intakes of different foods is sometimes taken into account when using parametric modeling (Paulo *et al.*, 2005). Parametric modeling of whole diets can be very complex; therefore, we kept intact the individual dietary pattern as observed in the food consumption survey to take into account the correlation between the intake of foods. A simple version of the model presented in this Chapter was described previously by us (Chapter 2); however, to our knowledge, this is the first model in nutrition science that combines both techniques for several uncertainties at the same time while keeping the observed individual dietary pattern intact and estimating habitual intake. The model is deterministic where possible and probabilistic where needed.

In these simulations, we used point estimates of salt iodine concentrations rather than distributions of possible concentrations, because data about the distribution of salt iodine concentrations are currently lacking. When such data become available, the variation in iodine concentration can easily be taken into account in our model. However, the necessity of making the model more complex by taking into account the variation in iodine concentration should be considered. In the estimation of the habitual intake, random selection of a distribution of possible concentrations results in the mean concentration of that distribution. In these cases, a point estimate of the mean concentration is probably accurate enough.

All sampling was performed with 100 iterations to take into account the uncertainty and variability. To study the precision of the model, we performed a duplicate simulation for 1 scenario. The duplicate simulation differed only in which participants were drawn in the samples of iodized salt users or consumers of food groups that contain iodized salt. Results from these duplicate simulations were comparable; e.g. the mean iodine intake for men was estimated to be 348 mg/d in both simulations, but the CI differed slightly: 346–350 compared with 345–351 mg/d. As expected, for age–gender categories with a small number of participants, we observed a larger variation in estimated mean (or percentiles in distribution) between the 100 different iterations, indicating greater uncertainty in the estimated iodine intake. Consequently, there was also a larger discrepancy between the estimations of percentage of participants with intakes above UL or below EAR in these age–gender categories between the duplicate scenarios. The difference, however, was small; e.g. the percentage of boys aged 7–10 yr exceeding the UL was estimated to be 10.8% (5.3–17.0) or 11.9% (4.8–15.9).

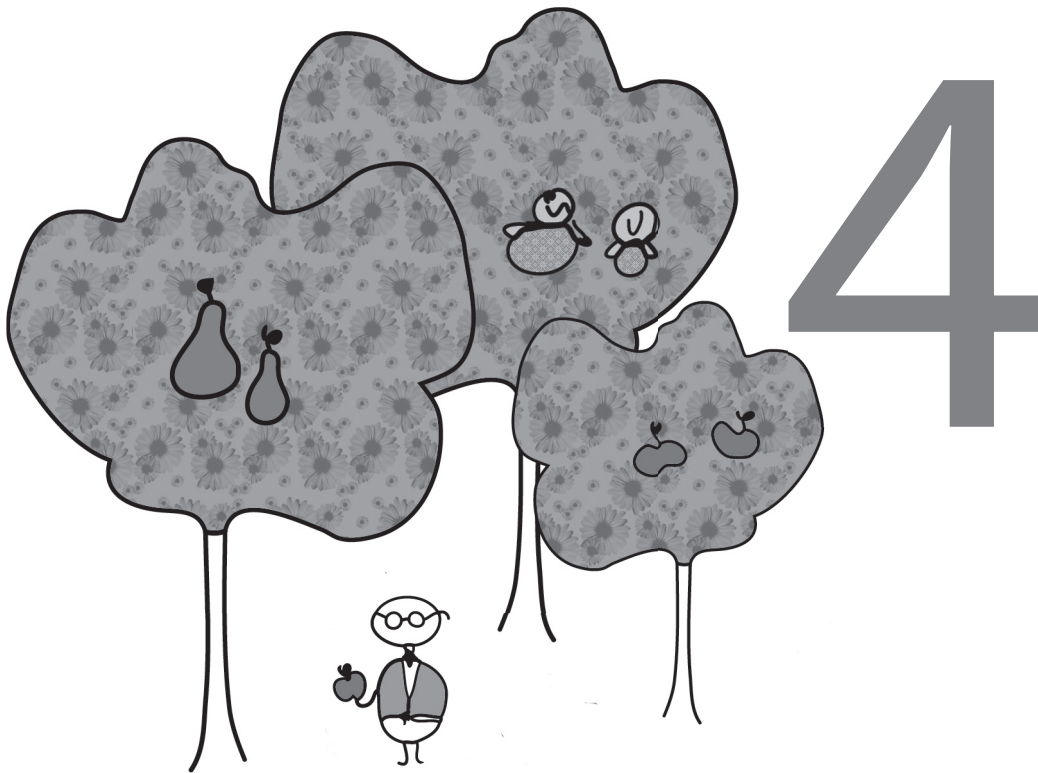
The estimated iodine intake distributions for The Netherlands were compared with the UL for iodine set by the European Scientific Committee on Food (SCF) (SCF/NDA, 2006). The long-term clinical health effects associated with intakes above the UL remain unclear. The Institute of Medicine (IOM) in the US also set a UL for iodine (IOM, 2001) based on the same health effects as SCF did (i.e. biochemical changes). However, due to the application of a lower uncertainty factor, the UL set by IOM is higher than that set by SCF; the age-specific UL set by IOM range from 200–1100 mg/d, whereas those from SCF range from 200–600 mg/d. The choice of the UL will therefore have a considerable impact on the estimation of the percentage of the population having potentially excessive iodine intakes. More research is required to determine the long-term clinical health effect of the observed biochemical changes at high iodine intakes.

We applied our model to examples of former, current, and potential future habitual iodine intake in The Netherlands. If data become available, our model can also be used to estimate habitual iodine intakes for other countries, using country-specific assumptions. Differences among countries should also be considered in the European discussion regarding minimum and maximum levels of vitamins and minerals (including iodine) in foods (Directorate E, 2006). Currently, iodine deficiency is not under control in many European countries (Andersson *et al.*, 2007). Our simulation study showed that under the new Dutch iodine legislation, iodine intake is expected to remain adequate. To avoid the potential future risk of iodine deficiency disorders in the Dutch population, it is not advisable to reduce the salt iodine concentration to levels more common in other European countries (10–25 mg I/kg salt).

The general concept of our model may be used for nutrients other than iodine, especially for questions regarding the effects of potential future policies or expected changes in food composition, in which parts of the input data are missing or uncertain. To be able to estimate the change in habitual intake of nutrients, and to estimate the proportion of the population with inadequate or potentially excessive intakes, the approach described in our article seems promising for further development.

Acknowledgements

We thank H. A. M. Brants and M. Jansen-van der Vliet for updating the food composition data for most recent information on iodine and sodium concentrations.



Reduction of salt: will iodine intake remain adequate in The Netherlands?

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Abstract

Salt is the main vehicle for iodine fortification in The Netherlands. A reduction in salt intake may reduce the supply of iodine. Our aim was to quantify the effect of salt reduction on the habitual iodine intake of the Dutch population and the risk of inadequate iodine intake. We used data of the Dutch National Food Consumption Survey (1997–1998) and an update of the food composition database to estimate habitual salt and iodine intake. To take into account uncertainty about the use of iodized salt (industrial and discretionary) and food supplements, a simulation model was used. Habitual iodine and salt intakes were simulated for scenarios of salt reduction and compared with no salt reduction. With 12, 25 and 50% salt reduction in industrially processed foods, the iodine intake remained adequate for a large part of the Dutch population. For the extreme scenario of a 50% reduction in both industrially and discretionary added salt, iodine intake might become inadequate for part of the Dutch population (up to 10%). An increment of the proportion of industrially processed foods using iodized salt or a small increase in iodine salt content will solve this. Nevertheless, 8–35% of 1 to 3 yr old children might have iodine intakes below the corresponding estimated average requirement (EAR), depending on the salt intake scenario. This points out the need to review the EAR value for this age group or to suggest the addition of iodine to industrially manufactured complementary foods.

Introduction

Too high salt (sodium) intakes are associated with the risk of elevated blood pressure and, as a consequence, increased risk of cardiovascular diseases (CVD). Even a modest reduction of salt intake at the population level will result in a decrease in blood pressure and thus a prevention of CVD (He *et al.*, 2002; 2007). A maximum salt intake level of 5–6 g/d is recommended for adults (Health Council, 2006; IOM, 2004; SACN, 2003; WHO, 2003). This recommendation should not be seen as an optimum or tolerable upper intake level, but rather as a feasible target. For the long term a maximum salt intake level of 3 g/d is proposed (He *et al.*, 2003). In The Netherlands, similar to other countries, the current salt intake is too high. For adults the mean salt intake is estimated at about 8–10 g/d (Health Council, 2000b; Intersalt, 1988; Van den Hooven *et al.*, 2007; Van Kreijl *et al.*, 2004) and for children (aged 5–10 yr) the mean salt intake is estimated at about 6 g/d (Schreuder *et al.*, 2007). Authorities and food industries in several European countries, and also in The Netherlands, have started initiatives to reduce the population salt intake (FNLI, 2008; FSA, 2006).

In many countries, including The Netherlands, iodine levels naturally present in the diet are not adequate (Andersson *et al.*, 2007; Van Rees-Wortelboer *et al.*, 1987). To prevent iodine-deficiency disorders, iodized salt is used. Reduction of salt will therefore not only result in the desired reduced salt intakes but also in unwanted reduced iodine intakes. Currently, the iodine status of the Dutch population is adequate (Andersson *et al.*, 2007; Health Council, 2008c; Wilson-Van den Hooven *et al.*, 2007), but this may become inadequate with reductions of salt intake. Regular monitoring of the iodine status in the population is a good measure to identify an existing potential problem. In contrast, modeling the iodine intake for a population presuming changes in salt intake can give quantitative insight into the potential problems beforehand and may help policy makers at an early stage to adapt their iodine policy. To our knowledge no studies have been published quantifying the effect of salt reduction strategies on the population iodine intake. We recently developed a simulation model which accurately estimates the total iodine intake of the Dutch population using data from the Dutch National Food Consumption Survey (Chapter 3). In the present study we applied this model to estimate the habitual total iodine and salt intake of the Dutch population for several scenarios of salt reduction strategies and we compared the salt intake distributions with the recommended maximum level to get quantitative insight into the changes in population salt intake. The iodine intake distributions were compared with the estimated average requirement (EAR) and tolerable upper intake level of iodine to predict whether iodine intake will remain adequate and safe for different age groups within the population.

Methods

Data of the Dutch National Food Consumption Survey-3 (DNFCS-3) were used to estimate habitual total iodine and salt intake. This survey is the most-recent population-wide food consumption survey in The Netherlands and has been described in detail elsewhere (Hulshof *et al.*, 2003). Briefly, data were collected in 1997-1998 and respondents (N 6250; aged 1-97 yr and selected from a representative consumer panel of households) recorded their food intake with a food record on 2 consecutive days.

From 2007 onwards, iodine levels were added to the Dutch food composition database (NEVO) (NEVO, 2008) For the present study, missing iodine levels were completed and available iodine levels were, if required, updated using manufacturers' information, scientific literature (Haldimann *et al.*, 2005; Rasmussen *et al.*, 2000), foreign food composition tables (Danish (2005), Finnish (2006), German (1994, 2006), UK (1991, 1993, 1995, 1996, 2002)), or iodine levels from similar food products. All recipes were recalculated using the updated iodine levels. Sodium levels available in NEVO (NEVO, 2008) were updated as well, using a similar procedure as for iodine. As iodine is added to industrially processed foods as iodized sodium chloride, the proportion of total sodium industrially added as sodium chloride was roughly estimated based on recipe information. When the proportion of natural sodium was estimated to be 10% or less of total sodium content, industrially added salt was set at 100%. For most industrially processed foods the proportion of added sodium chloride was set at 100%, except for salted fries (70%), canned vegetables (80%), sesame paste (90%), all cheese excluding cheese spread (75%), cheese spread (85%), chips (crisps) (85%), liquorices (50%), smoked fish (85%), canned fish (80%), dried and salted shrimps (30%) and meat products (90%).

Simulation model

Due to the lack of data about the discretionary use of (iodized) kitchen salt and market shares of industrially processed foods containing iodized salt, a simulation model combining deterministic approaches with probabilistic approaches was used to estimate both habitual iodine and salt intake. We have described this model in detail elsewhere (Chapter 3). Briefly, we defined different potential dietary sources for both salt intake ((a) sodium present in industrially processed foods, and (b) discretionary sodium added during cooking or consumption) and iodine intake ((a) naturally present in foods, (b) added to industrially processed foods, (c) discretionary iodine added via kitchen salt, and (d) iodine-containing dietary supplements). For all these sources, iodine and salt intakes were estimated separately for each subject on each observation

day. The intakes of iodine from natural sources and salt (calculated from total sodium $\times 2.5$) present in industrially processed foods were calculated using a deterministic approach. The consumed amount of a food was multiplied with the concentration of iodine or salt in that food. For all other potential sources of iodine or salt intake (i.e. industrially added, discretionary use of kitchen salt, dietary supplements (iodine only)) we applied a probabilistic approach to be able to take into account uncertainty and variability. For each potential source we estimated the proportion of foods that will contain iodized salt or the proportion of consumers that will use (iodized) salt or iodine-containing dietary supplements. A sample of the study population (discretionary salt and dietary supplements) or of the consumers (industrially added iodized salt) as large as these proportions was drawn and selected to consume the iodized or iodine-containing variants. To take into account the uncertainty of who will actually use these products, each sample was drawn for 100 iterations. To be able to take into account that subjects will not be aware of purchasing foods containing iodized salt we subdivided the group of industrially processed foods into thirty-five food groups that may contain iodized salt (Chapter 3). For each food group the probabilistic approach was applied separately and independently for each observation day. It was assumed that subjects assigned to discretionary use of (iodized) salt would do that for all selected eleven food groups and on both observed days. For each of these eleven food groups a point estimate of discretionary use of (iodized) salt was estimated (Chapter 3).

From the subjects selected to use iodine-containing dietary supplements, a second sample was drawn to select subjects using iodine-containing dietary supplements on both observed days. The amount of iodine consumed from dietary supplements was drawn from an age group-specific (children, adolescents, adults) uniform distribution (Chapter 3). The consumed dose was assumed to be equal on both days. In The Netherlands, sodium-containing dietary supplements are not used frequently (Van den Hooven *et al.*, 2007); therefore sodium intake from this source was not taken into account.

Total iodine and salt intake was calculated by summation of the intake of iodine or salt from all potential sources per subject, per observation day per iteration, resulting in 100 possible total intakes. Habitual total iodine and salt intake was calculated by correcting the data for within-individual variation using the Iowa State University (ISU) method (SIDE/IML version 1.11, 2001; Iowa State University, Ames, IA, USA) (Nusser *et al.*, 1996). Unless stated otherwise, SAS software (SAS 9.1.3; SAS Institute Inc., Cary, NC, USA) was used for modeling.

Population habitual total iodine intake distributions were compared with the EAR set by the Institute of Medicine (IOM, 2001) and tolerable upper intake levels set by

the European Union Scientific Committee on Food (SCF/NDA, 2006) to estimate the proportion of the population at risk of too low or too high iodine intakes using the cut-point method (taking EAR or upper intake level as the cut-point) (IOM, 2000b). The habitual total salt intake distribution (calculated as total sodium x 2.5) was compared with the recommended maximum salt intake level set by the Health Council of The Netherlands (adults) (Health Council, 2006) and the Scientific Advisory Committee on Nutrition (children) (SACN, 2003).

Salt reduction scenarios

Habitual iodine and salt intake was estimated for different scenarios of salt reduction strategies and for a reference situation without salt reduction (Table 4.1). In The Netherlands, salt with a maximum of 65 mg iodine/kg salt (high iodized salt) may be used in bread, bread-replacing products and other bakery products, and salt with a maximum level of 25 mg iodine/kg salt (low iodized salt) may be used in all other industrially processed foods (excluding drinks containing >1.2% alcohol by volume). This policy does not only account for Dutch food producers but also for food imported from other countries. From the Dutch salt industry we know that their salt contains on average 58 mg iodine/kg salt (high iodized salt) or 20 mg iodine/kg salt (low iodized salt) (based on information of the Dutch salt industry; L Rupert, Akzo Nobel Salt, The Netherlands, personal communication). These levels were applied as point estimates in the salt reduction scenarios under current iodine policy. In the current market situation, at maximum 5% of all industrially processed foods (excluding bread) contain iodized salt.

As it is unclear in which industrially processed foods iodized salt is added, this percentage was used as the market share. In bread, the use of iodized salt is more common due to a covenant between the authorities and bakeries; therefore for bread a market share of 90% was applied (Chapter 3).

The scenarios of salt reduction strategies were based on international experiences, mainly from UK and Ireland (FSAI, 2007; FSA, 2006) and initiatives of the Federation of the Dutch Food and Grocery Industry (FNLI) in the Taskforce Salt. In the first scenario, industrially added sodium chloride was reduced by 12% in all foods; this percentage was based on the current commitment of Dutch bakeries (Table 4.1). In the second scenario, a salt reduction of 25% was chosen and in the third scenario an even higher salt reduction of 50% was presumed. For the fourth scenario the median salt intake (from all sources) of adults was reduced to the level of the recommended maximum intake of salt (i.e. 6 g/d) (Health Council, 2006).

Table 4.1 Different scenarios of use of iodized salt and salt reduction strategies

Food group	Market share (%)	Iodine (mg iodine/kg salt)	Percentage salt reduction in different food groups (%)				
			Reference	Scenario 1	Scenario 2	Scenario 3	Scenario 4*
Bread	90	58	0	12	25	50	50
Bread-replacing products	5	58	0	12	25	50	50
Brand-specific bread-replacing products known to contain iodized salt	100	58	0	12	25	50	50
Other bakery products	5	58	0	12	25	50	50
Meat products	5	20	0	12	25	50	50
Other industrially processed foods	5 [†]	20	0	12	25	50	50
Discretionary used iodized kitchen salt (total kitchen salt)	81 (95)	20	0	0	0	0	50 [†]

* To achieve a mean habitual salt intake of adults equal to recommended maximum salt intake of 6 g/d.

[†] Not only iodized kitchen salt, but total kitchen salt.

Results

Habitual salt intake

In general, habitual salt intake increased with age, and was higher for men than for women. For the current situation (i.e. reference) the median habitual salt intake ranged from 4.2 g/d for young children (aged 1-3 yr) to 10.8 g/d for adult men (Table 4.2). The percentages of the population with intakes above the recommended maximum level for salt intake are high and ranged in this scenario from 88% to almost 100% (Figure 4.1). About 25% of total salt intake originated from discretionary added kitchen salt; this percentage showed a small increase with age (data not shown).

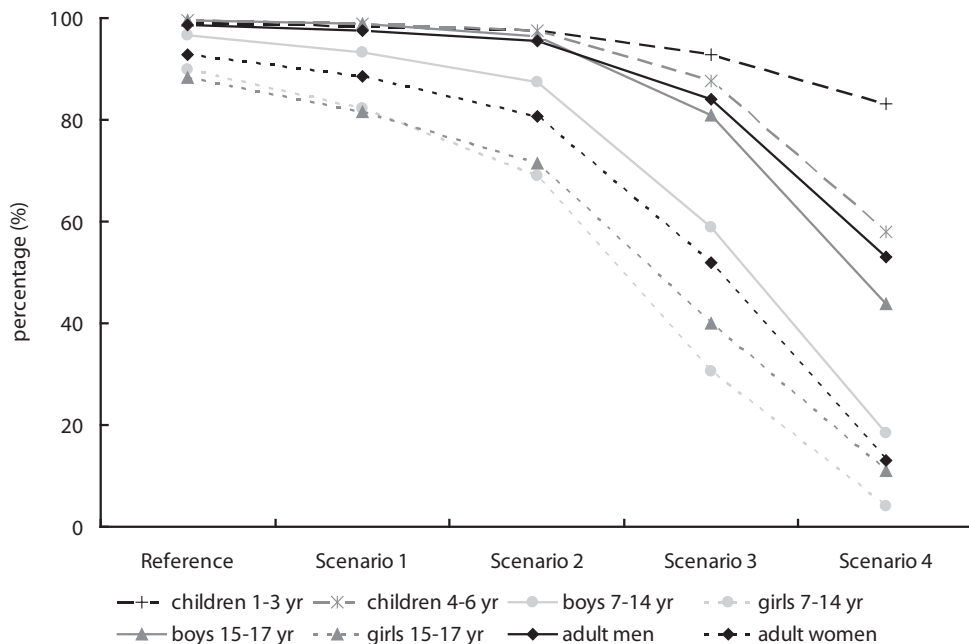


Figure 4.1 Percentage of the Dutch population with habitual total salt intakes (based on total sodium intake) above the recommended maximum level, for different scenarios of salt reduction strategies: reference, no salt reduction; scenario 1, 12% salt reduction in industrially added salt; scenario 2, 25% salt reduction in industrially added salt; scenario 3, 50% salt reduction in industrially added salt; scenario 4, 50% salt reduction in industrially and discretionary added salt. The percentages are based on 100 iterations for estimating the intake profile; values are presented as median of 100 iterations. The recommended maximum levels for the different age groups are: 1-3 yr, 2g/d; 4-6 yr, 3 g/d; 7-10 yr, 4 g/d; 11-14 yr, 5 g/d; ≥ 15 yr, 6 g/d (Health Council, 2006; SACN, 2003).

Table 4.2 Habitual salt* intake (g/day) in the Dutch population for different salt reduction strategies (median and 95th percentile[†])

Age category	Max. recommended intake (g/d) ^{‡c}	Reference		Scenario 1		Scenario 2		Scenario 3		Scenario 4	
		No salt reduction		12% salt reduction [§]		25% salt reduction [§]		50% salt reduction [§]		50% salt reduction	
		P50	P95	P50	P95	P50	P95	P50	P95	P50	P95
Children	2	4.2	6.4	3.9	6.0	3.6	5.5	3.1	4.7	2.6	3.8
Children	3	5.2	7.1	4.9	6.6	4.5	6.1	3.8	5.1	3.1	4.1
Boys	5	7.2	9.5	6.7	8.9	6.2	8.1	5.2	6.7	4.2	5.5
Girls	5	6.4	8.7	6.0	8.2	5.5	7.5	4.6	6.4	3.8	5.0
Boys	6	9.0	12.8	8.3	11.9	7.6	10.9	6.3	9.0	5.1	7.3
Girls	6	7.7	10.1	7.2	9.4	6.6	8.6	5.5	7.1	4.4	5.8
Boys	6	10.3	13.9	9.5	12.8	8.7	11.8	7.2	9.6	5.8	7.8
Girls	6	8.0	11.4	7.5	10.6	6.9	9.7	5.7	8.0	4.6	6.5
Men	6	10.8	15.4	10.0	14.3	9.2	13.1	7.6	10.8	6.1	8.6
Women	6	8.4	11.8	7.8	10.9	7.2	10.0	6.1	8.3	4.8	6.6

* Based on total sodium intake.

[†] Median and 95th percentile presented as P50 of the results of 100 iterations; variation between the 100 iterations was on average \pm 2% for median and \pm 3% for 95th percentile.[‡] For adults from the Health Council of The Netherlands (Health Council, 2006), for children and adolescents from the UK Scientific Advisory Committee on Nutrition (SACN, 2003).[§] Only salt reduction in industrially processed foods.

As a logical consequence of salt reduction, salt intake decreased in the four scenarios compared with the current situation (i.e. reference). Salt reductions of 12, 25 or 50% in industrially processed foods decreased the habitual total salt intake on average by 7, 15 and 30% compared with the current intake (Table 4.2). With these salt reductions in all age-sex groups the percentages with salt intakes above the recommended maximum level remained high; 80–99, 68–97 and 28–93%, respectively (Figure 4.1). In general, the highest percentages were observed among young children (aged 1–8 yr) and men. To reach a median habitual salt intake for adult men of about 6 g/d a 50% salt reduction in both industrially processed foods and discretionary used kitchen salt was needed (scenario 4). In this scenario, salt intake reduced on average by 40% (Table 4.2) and the percentages with intakes above the maximum recommended intake level in the different age-sex groups decreased to 3–83% (Figure 4.1). Young children (aged 1–3 yr) still had a median salt intake above the maximum recommended level (2.6 g/d); for children aged 4–6 yr the median salt intake was close to the maximum intake level (3.1 g/d). To get the median habitual total salt intake for young children (aged 1–3 yr) close to the recommended maximum intake level (i.e. 2.1 g/d), a salt reduction of 50% in industrially added salt in combination with no discretionary use of kitchen salt was required.

Habitual iodine intake

In general, iodine intake was higher for men than for women and increased with age. In the reference situation (no salt reduction), the median habitual iodine intake ranged from 105 mg/d for young children aged 1–3 yr to 268 mg/d for boys aged 15–17 yr (Table 4.3). A total of 8% of young children had a habitual iodine intake below the current EAR (Figure 4.2); however, for the other age-sex groups, habitual iodine intakes below the EAR were small (<5%). The percentage of the population with habitual iodine intakes above the upper intake level was small in all cases (<5%).

As iodized salt (industrial and discretionary) is an important source of iodine intake, reduction of salt also reduced habitual iodine intake. Salt reduction of 12, 25 or 50% in industrially processed foods resulted on average in a 6, 12 or 25% reduction in habitual iodine intake, but the 5th percentile of iodine intake remained near or above the corresponding EAR values for most age groups (Table 4.3; Figure 4.2). The percentage of the population with habitual iodine intakes below the EAR slightly increased (1–11%) for age groups older than 3 yr in the fourth scenario, which included reduction of both industrially and discretionary added salt (Figure 4.2). Percentages below the EAR of iodine among young children (aged 1–3 yr) were 10% to 35% for scenarios 1 to 4 of salt intake, respectively (Figure 4.2).

Table 4.3 Habitual iodine intake ($\mu\text{g}/\text{d}$) in the Dutch population for different salt reduction strategies (median and 5th percentile*)

Age category	EAR ($\mu\text{g}/\text{day}$) [†]	Reference		Scenario 1		Scenario 2		Scenario 3		Scenario 4	
		No salt reduction		12% salt reduction [‡]		25% salt reduction [‡]		50% salt reduction [‡]		50% salt reduction	
		P50	P5	P50	P5	P50	P5	P50	P5	P50	P5
Children 1-3 yr	65	105	60	99	54	94	53	82	46	73	42
Children 4-6 yr	65	135	87	128	80	118	74	101	64	90	59
Boys 7-10 yr	73	194	138	181	133	166	118	142	100	125	90
Girls 7-10 yr	73	159	99	151	98	140	91	121	77	107	72
Boys 11-14 yr	95	227	147	211	135	196	125	168	105	148	97
Girls 11-14 yr	95	189	126	179	123	166	114	142	97	125	89
Boys 15-17 yr	95	268	177	249	163	231	151	195	127	172	117
Girls 15-17 yr	95	200	134	188	120	176	113	151	94	133	87
Men 18+ yr	95	264	162	249	155	232	144	201	125	175	113
Women 18+ yr	95	204	130	194	124	183	117	162	103	141	92

EAR, estimated average requirement.

* Median and 5th percentile presented as P50 (P5-P95) of the results of 100 iterations; variation between the 100 iterations

was on average \pm 5% for median and \pm 10% for 95th percentile.

[†] set by Institute of Medicine (USA) (IOM, 2001).

[‡] only salt reduction in industrially processed foods.

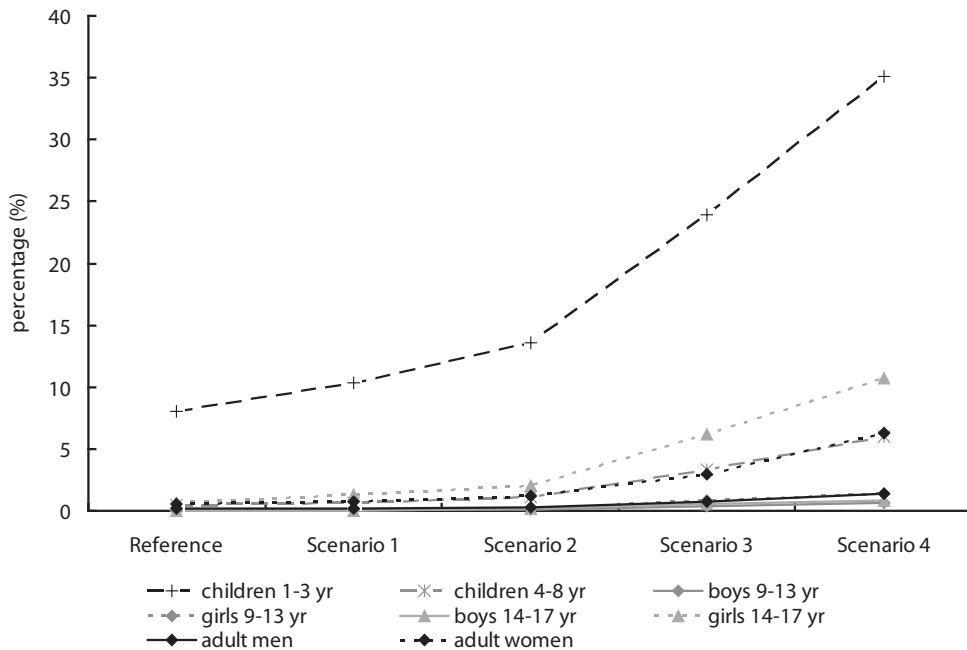


Figure 4.2 Percentage of the Dutch population with habitual iodine intakes below the current estimated average requirement (EAR), for different scenarios of salt reduction strategies: reference, no salt reduction; scenario 1, 12% salt reduction in industrially added salt; scenario 2, 25% salt reduction in industrially added salt; scenario 3, 50% salt reduction in industrially added salt; scenario 4, 50% salt reduction in industrially and discretionary added salt. The percentages are based on 100 iterations for estimating the intake profile; values are presented as the median of 100 iterations. The current EAR for the different age groups are: 1-6 yr, 65 μ g/d; 7-10 yr, 73 μ g/d; 11 yr and older, 95 μ g/d (IOM, 2001).

Discussion

In discussions about salt reduction concerns about the parallel decrease in iodine intake are often mentioned, since salt is the main vehicle for iodine fortification in many countries. In the present study, we quantified the effects of potential scenarios of salt reduction on habitual total iodine intake in the Dutch population. In the current situation, without salt reduction, the habitual iodine intake seems adequate for a large part of the Dutch population. With salt reductions of 12, 25 and 50% in industrially processed foods this remained the case. For the extreme scenario of 50% reduction in both industrially and discretionary added salt, iodine intake might become inadequate for part of the Dutch population.

Only for infants did we observe high percentages with intakes below the EAR, i.e. about one-third of this age group in the case of 50% salt reduction. However, the EAR for these children (aged 1-3 yr) was based on one single balance study in which malnourished children were nutritionally rehabilitated (IOM, 2001). It can be questioned whether the level of iodine that is needed for well-nourished children to maintain their iodine balance is as high as the iodine level that is needed to achieve nutritional rehabilitation. When the EAR of adults was extrapolated down based on metabolic weight (i.e. $\text{weight}^{0.75}$) the EAR of young children would be 36 mg/d, which is considerably lower than 65 mg/d (the current EAR) (IOM, 2001). Taking the lower cut-off value of 36 mg/d, less than 5% of these children had intakes below this value (data not shown). We recommend doing more research to assess the iodine requirements of well-nourished young children before conclusive statements on a potential public health risk for young children are drawn.

Dutch iodine policy changed in 2008 (Health Council, 2008c). In this new policy, more foods are allowed to include iodized salt. The salt iodine levels in this new policy are based on the assumption that 50% of industrially processed foods will use iodized salt. Currently this proportion is about 5%, and an increment of the proportion of industrially processed foods using iodized salt from 5% to 50% will result in adequate iodine intakes for virtually the whole population, including young children (Chapter 3). With large salt reductions, also an increase in the proportion of industrially processed foods using iodized salt from 5% to 50% is enough to reduce the percentage of the population, excluding young children, with iodine intakes below the current EAR to less than 5% (data not shown). Even mandatory iodization will not result in adequate iodine intakes for young children (data not shown). To increase the habitual iodine intake of children aged 1-3 yr to intake levels above the EAR (i.e. 65 mg/d) under major salt reduction strategies, salt iodine levels should be increased (for instance, a salt iodine level of 80 mg iodine/kg salt) in combination with a 50% market share of industrially processed foods using iodized salt (data not shown). An alternative is to recommend and stimulate the addition of iodine to industrially manufactured complementary foods.

The present study shows that the long-term goal of the Federation of the Dutch Food and Grocery Industry (FNLI) of a mean salt reduction of 20-30% (FNLI, 2008), which is similar to salt reduction goals in other countries (FSAI, 2007; FSA, 2006), is not sufficient to reduce total salt intake to or below the level of the maximum recommended salt intake. A larger salt reduction of 50% (both industrially and discretionary) is required to reach a median habitual total salt intake for adults of about 6 g/d. An even larger salt reduction of 50% in industrially processed foods in combination with no discretionary use of salt is needed for young children (aged 1-6 yr) to reach a median habitual salt intake at their age-specific recommended maximum salt intake (data not shown) (SACN,

2003). This underlines the additional importance of changing consumer behaviour in the use of discretionary added salt. In order to prevent compensation behaviour of industrial salt reduction, this should be a gradual process supported by the whole food industry. In Finland, salt reduction initiatives already started several decades ago. Also the discretionary use of salt reduced (Laatikainen *et al.*, 2006); this may indicate that compensation behaviour was minor.

A limitation of the present study is that Dutch national food consumption data from 1997–1998 were used; these are the most recent monitoring data covering all ages. To get more up-to-date results, these consumption data were combined with the most up-to-date food composition data taking into account changes in food composition since 1997–1998. In 2005–2006 a food consumption survey was conducted among young children (aged 2–6 yr). Application of our model to these data resulted in median habitual total salt intakes that were slightly lower (4.0 g/d for children aged 2–3 yr; 4.7 g/d for children 4–6 yr). Also the median estimated habitual iodine intakes were lower (89 mg/d for children aged 2–3 yr; 113 mg/d for children aged 4–6 yr). The observed differences are small and results are in same order of magnitude as the results presented in the present Chapter. These calculations imply that the indications of habitual salt and iodine intake in the different scenarios of salt reduction seem still valid for the current Dutch situation.

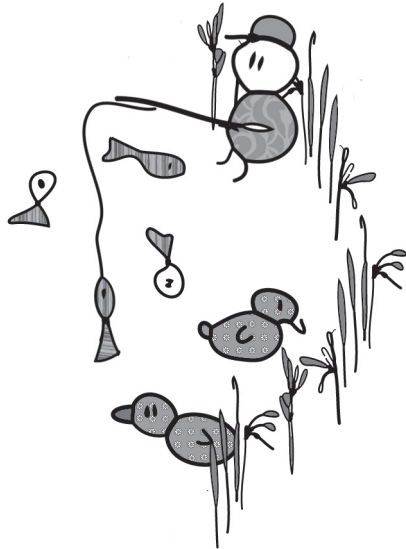
A strength of the study is that the model we used to estimate habitual iodine and salt intake was earlier shown to accurately estimate habitual iodine intakes in The Netherlands (Chapter 3). The habitual total salt (sodium) intakes that we estimated with this model for adults were somewhat higher but in same order of magnitude as the results from other Dutch studies (Health Council, 2000b; Intersalt, 1988; Schreuder *et al.*, 2007; Van den Hooven *et al.*, 2007; Van Kreijl *et al.*, 2004). The small differences between our model and these three studies may not only be due to the model assumptions, but might also be caused by differences in the study populations (for example, age distribution). The comparability in results indicates that our model is a useful tool to estimate both habitual salt and iodine intake accurately in the Dutch population. The salt reduction scenarios applied in the present study were generic reductions in all industrially processed foods. Differences in technological feasibility of salt reductions between food groups were not considered; however, with our model these can be taken into account in future studies. The present study, nevertheless, does show what large salt reductions are needed in the Dutch population and gives first indications on the effect on iodine intake.

In conclusion, the present study showed that with small salt reductions, iodine intakes remain adequate in a large part of the Dutch population. These small reductions in the total habitual salt intake will not come close to the maximum recommended salt

intake levels. A more pronounced salt reduction is therefore needed, for instance, 50% reduction of both industrially and discretionary added salt. A small part of the Dutch population (up to 10%) might then have inadequate habitual iodine intakes. An increment in the number of industrially processed foods using iodized salt or a small increase in iodine salt content will solve this.

Acknowledgements

We would like to thank H. A. M. Brants and M. Jansen-van der Vliet for updating the food composition data for most recent information on iodine and sodium concentrations and C. Wilson-van der Hooven for assistance in defining the salt reduction scenarios.



5

Statistical method for estimating the distribution of habitual total micronutrient intake from foods and dietary supplements; illustrated for vitamin D intake in young children

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Abstract

In the estimation of habitual micronutrient intake from both food and dietary supplements from short-term measurements challenges with heterogeneous variances and multimodality are observed. With a simple 'first add then shrink' approach, the estimation of habitual total micronutrient intake is biased. This may be observed by lower estimates for habitual total intake as compared to habitual intake from food only, which is not consistent. A three-part model is proposed according to the 'first shrink then add' approach. In this model, the habitual micronutrient intake from (a) food among non-supplement users, (b) food among supplement users, and (c) supplements is estimated separately. The new model is an extension of a model developed by the US National Cancer Institute. The habitual total micronutrient intake for the population is estimated by the convolution of these three habitual intake distributions and accounting for their interdependence. Using data of the Dutch food consumption survey among young children, habitual total vitamin D intake was estimated using the proposed model. The results show that the modeling solves the problem of biased estimates: habitual total intakes are always similar or higher than habitual intakes from food sources only. Further, the multimodal shape of the total vitamin D intake distribution is retained. This proposed method provides more precise estimates of the habitual total intake distribution and results in better estimates of the proportion of the population with intakes below/above cut-point values. The proposed methodology could be useful for other complex situations, like episodically consumed foods with high micronutrient levels.

Introduction

Estimations of habitual intake are needed to get insight in the adequacy of population nutrient intake. Habitual intake is defined as the long-term average intake. In many national food consumption surveys, food consumption is measured on the short-term; e.g. (repeated) 24-hr recall. From repeated measurements, habitual population intake distributions can be estimated by statistical correction for within-person variation. Several statistical software programs are currently available to estimate habitual intakes for regularly consumed nutrients or foods (one-part model) (Dekkers *et al.*, in preparation; Hoffmann *et al.*, 2002; Nusser *et al.*, 1996; Slob, 1993; Tooze *et al.*, 2010; Waijers *et al.*, 2006) or for episodically consumed nutrients or foods (two-part model) (De Boer *et al.*, 2009; Dekkers *et al.*, in preparation; Slob, 2006; Tooze *et al.*, 2006).

Next to food consumption, for at least part of the population, dietary supplements are also a source of micronutrients. Estimated habitual total micronutrient intake must include intake from both sources. A straightforward approach to estimate the habitual total micronutrient intake distribution seems to first sum the observed micronutrient intakes from both foods and dietary supplements per subject per day and subsequently adjust for within-person variation; 'first add then shrink' approach. This 'first add then shrink' approach does not consider potential differences in within- and between-person variance in the micronutrient intake from foods or dietary supplements (i.e. heterogeneous variance), differences in intake from foods between users and non-users of dietary supplements, and multimodality in the distribution caused by the two different sources of intake. Therefore, the results of the 'first add then shrink' approach may not be valid estimates of the habitual total micronutrient intake distribution. Applying this approach to data from a Dutch food consumption survey among children aged 2–6 yr (DNFCS-young children) created interpretation problems. For some micronutrients at low percentiles of the intake distribution the estimated habitual intake from food sources and dietary supplements together was lower than the estimated habitual intake from food sources only. For example, the 5th percentile of habitual total vitamin D intake was 1.0 µg/d, whereas the habitual intake from food sources alone was 1.1 µg/d (Ocké *et al.*, 2008). Related interpretation problems have been reported by Garriguet (2010b).

Recently, two alternative approaches were proposed to address challenges in combining intake data from food and dietary supplements. In the first approach it was proposed to first estimate the habitual intake for each different source separately and combine these distributions of habitual intake to get the habitual total intake distribution (Bailey *et al.*, 2010; Dodd *et al.*, 2009; Slob *et al.*, 2010); the so-called, 'first shrink then add' approach. Secondly, it was proposed to estimate habitual total intake separately for

users and non-users of dietary supplements (Garriguet, 2010a; b). In line with both earlier proposed ideas we have developed a new statistical method to estimate the habitual total micronutrient intake distribution taking the method developed by the USA National Cancer Institute (NCI-method) as a starting point (Tooze *et al.*, 2010; 2006).

The objective of this chapter is to present the method and illustrate it by estimating the habitual total vitamin D intake using data from the DNFCs-young children. Vitamin D-containing dietary supplements are commonly taken by Dutch young children, because additional vitamin D intake from dietary supplements or fortified foods is advised up to 4 yr of age (Weggemans *et al.*, 2009b).

Subjects and methods

The Dutch National Food Consumption Survey-young children (DNFCs-young children) is a representative, cross-sectional survey conducted in 2005-2006 among children aged 2-6 years old ($N=1,279$) (Ocké *et al.*, 2008). Data on food and dietary supplement consumption were recorded by the caretaker of each child in pre-structured diaries on two nonconsecutive days (8-13 days in between). Trained dieticians entered the data from the diaries into the EPIC-soft computer program. Vitamin D intakes from food were calculated using an extended version of the 2006 Dutch food composition database (NEVO, 2006). Vitamin D intake from dietary supplements was calculated using the Dutch supplement database (NES) (Buurma-Rethans *et al.*, 2008), which was up-dated for DNFCs-young children. In addition to the diaries, information on, amongst others, background, general characteristics of child's diet, and use of dietary supplements in the previous month, was collected with an additional questionnaire. Caretakers were asked if their child had taken dietary supplements during the last month (yes/no). If they said yes, caretakers were asked to fill in whether their child had used (yes/no) specific types of dietary supplements during the last month, including vitamin D, multivitamin, vitamin A-D, and multivitamin/mineral supplements. Bodyweight and height were measured by trained interviewers.

The statistical method presented in this chapter needs a subdivision of the study population in users and non-users of vitamin D-containing dietary supplements. *Non-users* were defined as subjects who did not record vitamin D-containing dietary supplement use on any of the 2 survey days and who did not report the use of vitamin D, vitamin A-D, multivitamin, or multivitamin/mineral supplements in the additional questionnaire. All other children were considered as potential *users* of dietary supplements.

Improved method for estimation habitual total intake from food and dietary supplements

The proposed statistical method for estimating the distribution of the habitual total micronutrient intake (i.e. from both food and dietary supplements) is an extension of the NCI-method (Tooze *et al.*, 2010; 2006). Our method is based on a three-part statistical model and allows for covariates and correlation between some of the parts. The three parts correspond to the estimation of the habitual micronutrient intake distribution for each of the main sources and subgroups separately:

1. habitual micronutrient intake distribution from food for *non-users* of dietary supplements
2. habitual micronutrient intake distribution from food for *users* of dietary supplements
3. habitual micronutrient intake distribution from dietary supplements for dietary supplement users.

In a final step, the three habitual micronutrient intake distributions are combined to estimate the habitual total micronutrient intake distribution for the whole population, a so-called 'first shrink then add' approach. This method is schematically presented in Figure 5.1.

Model components

The first part of our model applies to *non-users* of dietary supplements:

$$\text{Transformed Record Amount} = \text{Mean}_0 + \text{Person-specific Effect}_0 + \text{Within-person Variability}_0 \quad (1)$$

where the observed vitamin D intake amounts from food are transformed by a Box-Cox transformation with transformation parameter λ_0 , Mean_0 indicates the group mean of the transformed intakes, possibly as a function of covariates, $\text{Person-specific Effect}_0$ indicates an individual-level deviation from the group mean, and $\text{Within-person Variability}_0$ is an error term that reflects day-to-day variation in intake as well as other random errors of the estimation. The *Person-specific Effect* is normally distributed with mean equal to zero and the between-person variance (σ_{bo}^2). The *Within-person Variability* is normally distributed with mean equal to zero and within-person variance (σ_{wo}^2).

The second and third part of our model apply to users of dietary supplements, and jointly model the probability to consume vitamin D-containing dietary supplements on a given day and the amount of vitamin D intake from food sources (2).

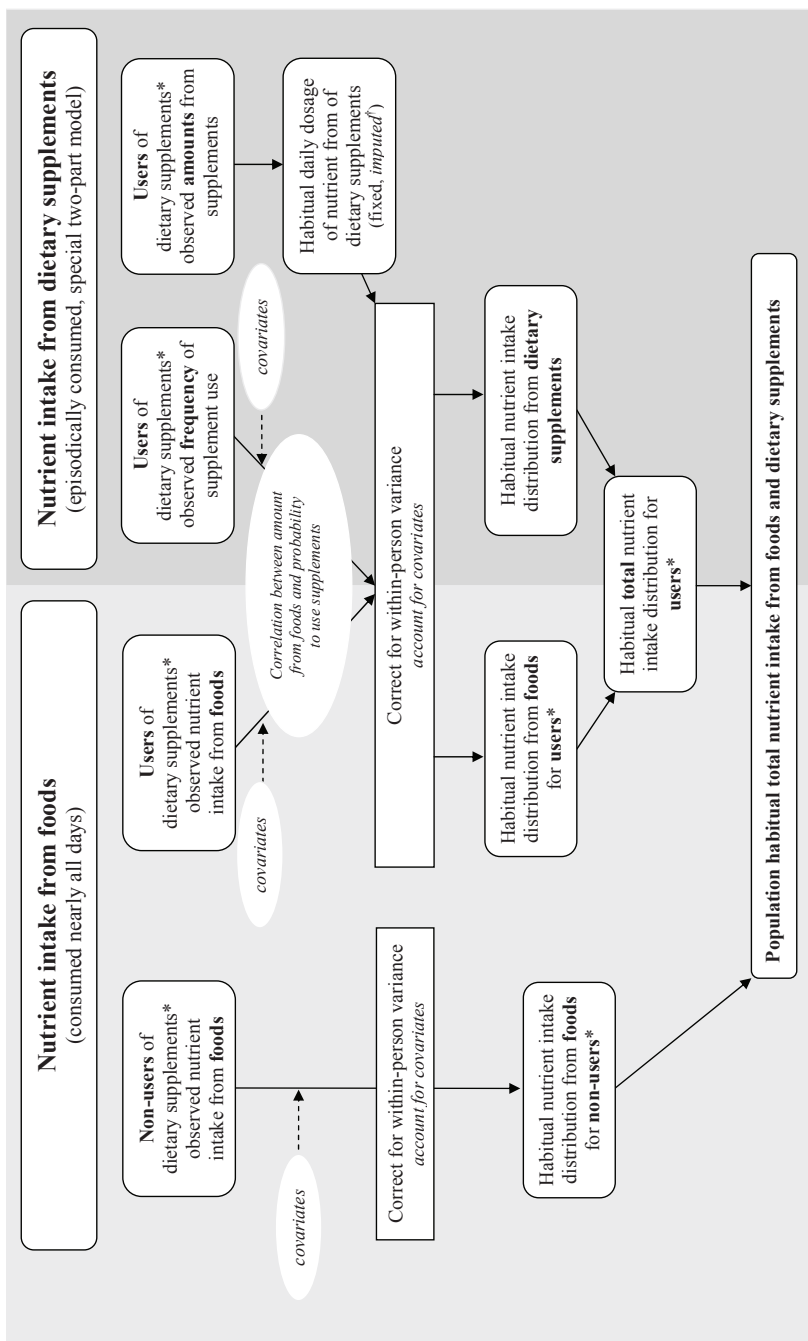


Figure 5.1 Schematic overview of three-part model to estimate habitual total micronutrient intake distributions from foods and dietary supplements; nutrient can stand for any nutrient present in foods and dietary supplements. Dashed arrows and italic fonts represent voluntary model options.

* Users are defined as possible users of dietary supplements containing the nutrient of interest; non-users do not use such dietary supplements.

† In the example presented in this chapter habitual daily dosage is considered to be known from 2 food records (or imputed), but in other cases it might need to be estimated as well.

$$\text{Transformed Record Amount} = \text{Mean}_1 + \text{Person-specific Effect}_1 + \text{Within-person Variability}_1 \quad (2)$$

$$\text{Logit(Probability of Supplement Use)} = \text{Mean}_2 + \text{Person-specific Effect}_2$$

where the *Person-specific Effect*₂ has mean zero and between-person variance σ_{b2}^2 , the outcome variable in the logistic regression is the use/non-use of supplements on the sampled days. The second part models the vitamin D intake from food for dietary supplement users and is the same as (1) but now with transformation parameter λ_1 , *Mean*₁, *Person-specific effect*₁ (with between-person variance σ_{b1}^2); and *Within-person Variability*₁ (with within-person variance σ_{w1}^2).

All three parts of the model allow different sets of covariates.

For children with vitamin D intakes from dietary supplements recorded on both survey days, the amounts of vitamin D taken from dietary supplements did not vary much between the days. About 85% recorded the same vitamin D dosage on both survey days. The person-specific habitual daily vitamin D dosage was therefore assumed to be the mean recorded amount on user-days only. For the remaining 15% with unequal positive vitamin D dosages on the 2 survey days, the difference was on average 3.4 μg (range 0.5-12.5 μg).

About 20% of the possible users of vitamin D-containing dietary supplements did not record a vitamin D-containing dietary supplement in the food diaries. For these possible users, no person-specific dosage information was available and therefore a dosage was imputed based on the dosage distribution of the users with information. To account for the uncertainty of imputation, the imputation was repeated 5 times and standard errors of estimates were computed using the method of Rubin (1987).

Combination of the three model components into total intake for the whole population

The habitual intake distribution is first estimated separately for users and non-users of vitamin D-containing dietary supplements. For *non-users*, as in the NCI-method (Tooze *et al.*, 2010; 2006), the individual covariate values (slopes) are used to obtain a fixed effect estimate of the group mean transformed intake on a typical day. To properly reflect between-person variation, the contribution of the person-specific random effects must be incorporated, however, these effects are unobservable. Therefore, a value is chosen at random from the estimated distribution of person-specific random effects. In order to improve the precision, for each individual in the sample, 100 pseudo-persons were generated (Monte Carlo) with the same fixed effect estimate,

but with different simulated person-specific effects. This results in 100 observations of the intake on the transformed scale that has no within-person variance component for each single individual in the original sample. This data is back-transformed to the original scale using a 9-point quadrature formula that adjusts for the within-person variance component that was omitted. From these back-transformed data (I) the percentiles of the habitual micronutrient intake distribution from food sources for *non-users* of dietary supplements are estimated.

For *users* of vitamin D-containing dietary supplements, a fixed effect estimate of the probability to take a supplement on a typical day and a fixed effect estimate of the vitamin D intake amount from foods are obtained from the models (2). Again, for each individual in the sample, 100 pseudo-persons were generated (Monte Carlo) to which the person-specific random effects of both parts of the model (two-dimensional random effect vectors) together with the specified estimated correlation are added. These 100 observations of each model component on the transformed scale have no within-person variance component. Both parts of the model are back-transformed to the original probability or amount scales, using the inverse of the logit transformation and the 9-point quadrature formula respectively, to get i) the habitual probability to take vitamin D-containing dietary supplements and ii) the habitual vitamin D intake from food sources. The habitual vitamin D intake from dietary supplements (iii) is obtained by multiplication of the person-specific dosage with the probability to use dietary supplements (i). Combination of ii) and iii) gives the habitual total vitamin D intake from food and dietary supplements for *users* (II), from this data the percentiles of the habitual total intake distribution can be estimated (from ii) and iii) the percentiles of the habitual intake distribution from respectively food and dietary supplements can be estimated for *users*).

From the combination of the simulated back-transformed data for non-users (I) and users (II) the percentiles of the habitual total vitamin D intake distribution for users and non-users of dietary supplements together can be obtained. In the combination of these datasets, the proportions of users and non-users of dietary supplements are preserved.

Modeling options

The three-part model has two types of modeling options: the incorporation of covariates and the incorporation of modeling correlation. These two modeling options will be presented below, including how we did incorporate these options in our analyses to estimate habitual total vitamin D intake.

Covariates

In the three-part model covariates can be added separately to each part of the model; 1) amount from food for non-users of dietary supplements, 2) probability to use dietary supplements, 3) amount from food for users of dietary supplements. Including covariates serves four main purposes:

1. Modeling group means as functions of individual-level covariates allows efficient estimation of intake distributions for subpopulations where complete stratification is not feasible due to limited sample size, if other model parameters such as variance components are similar across the subpopulations
2. The group-level effect of individual- and time-dependent characteristics on mean usual intake can be assessed directly by testing model parameters for statistical significance
3. Nuisance effects due to sample selection procedures can be adjusted for explicitly; for example, the sample mean reported intake on the first 24-hour recall may be systematically higher than the sample mean of subsequent recalls due to respondent fatigue. By adding a dummy variable for recall day to the model, it is possible to estimate distributions based on the predicted group mean on the first recall day
4. The effects of time dependent covariates such as day-of-week and season on habitual intake can be explicitly modeled by averaging predicted weekday- or season-specific estimates of habitual intake in proportion to theoretical balance, even if the sample data are collected in unequal proportions across days of the week or season

For the estimation of habitual total vitamin D intake several potential covariates were considered based on proposed association with vitamin D intake from foods or use of dietary supplements. In the first part of the model, regarding intake amount from foods for *non-users* of dietary supplements, sex, season (spring-summer-autumn-winter), survey day, week-weekend-day (i.e. Monday to Friday – Saturday to Sunday), body weight, and education of the mother were considered. For the estimation of the probability to use vitamin D-containing dietary supplements the proposed covariates were; sex, season (May to August – September to April), week-weekend-day, education of the mother, type of supplement recorded in the additional questionnaire (i.e. none; vitamin D-specific; multivitamin; multivitamin/mineral), dose of vitamin D from supplements. In the estimation of the amount of habitual vitamin D intake from foods for *users* of dietary supplements the same covariates were used as for non-users with the addition of type of supplement recorded in the additional questionnaire, and dose

of vitamin D from supplements. Continuous variables were included “as-is”, whereas dummy variables (multi-category covariates) were made for variables containing more than 2 groups.

An overall F-test was performed separately for each part of the model. Further, F-tests were performed for all multi-category covariates and t-tests for the single-category covariates. Covariates were included if the overall F-test was ≤ 0.15 and for a multi-category covariate the F-test was ≤ 0.15 or for a single-category covariate the t-test was ≤ 0.15 . Because only one round of model selection was performed, we used a p -value of 0.15 to help guard against inadvertent removal of an important covariate due to multi-co-linearity with other covariates in the model. The covariates selected with this procedure for the amount model-part of users or non-users only were also included in the amount model of the other group, even if these p -values were > 0.15 . Once the candidate set of important covariates was determined using the above procedure, two additional multivariable F-tests were performed. First, the entire set of “kept” covariates was tested for significance. Then, the entire set of “dropped” covariates was tested. In all cases, the p -value for the set of kept covariates was < 0.09 , while the p -value for the dropped set was > 0.30 .

Correlation

It is not inconceivable that a subject having low nutrient intake from foods would compensate for that by frequently using dietary supplements. On the other hand, some studies suggest that, compared to non-users, users of dietary supplements tend to have higher nutrient intake amounts from foods (Li *et al.*, 2010; Mullie *et al.*, 2010; Murphy *et al.*, 2007; Rock, 2007). To be able to take into account such potential relationship between the intake from foods and probability to use dietary supplements, a correlation between these two factors may be included in the model by allowing the person-specific effects in model (2) to be correlated. A t-test can be used to assess the statistical significance of this correlation.

Statistical analyses

The habitual vitamin D intake distribution from foods, dietary supplements, and both foods and dietary supplements was estimated for the whole population as well as separately for users and non-users of vitamin D-containing dietary supplements. With a cut-point method (IOM, 2000b) the proportions of the population with intakes below cut-off values for the adequate intake (AI) (Health Council, 2000a), estimated average requirement (EAR) (IOM, 2000b) and above the tolerable upper intake level (UL) (SCF/NDA, 2006) were estimated. Even though supplement dose was not found to be an important covariate, the results of this chapter refer to the multiple imputation analysis, unless

otherwise stated. The impact of incorporation of covariates and correlation was studied by running the model with and without covariates or correlation.

As a sensitivity analysis, the habitual vitamin D intake from foods and both food and dietary supplements was also estimated with the original NCI-method (Tooze *et al.*, 2010; 2006) using a 'first add then shrink' approach. The results are compared with the results of the model proposed in this chapter. To compare both habitual intake distributions, the proportions of the population with intakes below arbitrarily chosen cut-off values were also estimated with both methods. For the sensitivity analyses, we chose not to use the multiple imputation procedure, and instead ran all models on the original non-imputed data. Potential dietary supplement users with no habitual dose information were assigned at zero supplement intakes for both of their recall days, and in the 'first add then shrink' method, recall-specific reported amounts from dietary supplements were added to the corresponding reported amounts from food sources.

All analyses were performed separately for the age groups 2-3 yr and 4-6 yr. The analyses were weighted for socio-demographic variables (i.e. age, gender, educational level of head of the household, region, and urbanization level) and season to make the results representative for the Dutch population of 2-6 yr, unless otherwise stated. All statistical analyses were performed using SAS software (version 9.2, SAS Institute Inc, Cary, NC). Standard errors for estimates were computed using the bootstrap method (separately within each imputation, if required) with 200 bootstrap samples. Previous analysis indicates that more than 200 bootstrap samples would dramatically increase the computation time without meaningful improvement in the stability of the estimated standard errors (Tooze *et al.*, 2010).

Results

In Table 5.1 selective characteristics of the study population are presented. Among 2-3 yr old children, 68% were possible users of vitamin D-containing dietary supplements, among 4-6 yr old children this was 38%. A vitamin D-specific dietary supplement was most frequently reported among children 2-3 yr old, whereas among 4-6 yr old children multivitamin/mineral supplements were most frequently reported. The mean observed vitamin D intake from food was higher for 4-6 yr old children compared to 2-3 yr old children ($p=0.002$), and similar between users and non-users of dietary supplements. The observed mean vitamin D intake from dietary supplements, as well as from foods and dietary supplements together was highest for children 2-3 yr compared to 4-6 yr ($p<0.001$).

Table 5.1 Characteristics (proportion (%) or mean (SD)) of the study population: total population and separately for users and non-users of dietary supplements containing vitamin D, by age group, DNFCs-young children 2005-2006, weighted for socio-demographic factors and season

	2-3 yr			4-6 yr			p-value**
	Total	Users dietary supplements*	Non-users dietary supplements*	Total	Users dietary supplements*	Non-users dietary supplements*	
n (%)	640	438 (68%)	202 (32%)	639	242 (38%)	397 (62%)	<0.0001
% girls	49%	50%	47%	49%	47%	50%	0.45
Age (yr)	2.5 (0.5)	2.5 (0.5)	2.6 (0.5)	5.0 (0.8)	4.9 (0.8)	5.0 (0.8)	0.03
Bodyweight (kg)	15.4 (2.5)	15.2 (2.5)	15.7 (2.5)	21.2 (3.8)	20.7 (3.5)	21.5 (4.0)	0.006
% autumn/winter	50%	51%	46%	50%	56%	46%	<0.0001
% weekend days (Sa-Sun)	27%	27%	28%	30%	28%	32%	0.10
% recorded vitamin D supplement use ^e	-	87%	-	-	70%	-	-
% recorded vitamin D supplement use on 1 day ^f	-	20%	-	-	19%	-	-
% reported use any supplement ^g	66% [†]	93%	9%	40% [†]	96%	7%	<0.0001
% reported use vitamin D-specific supplement ^g	36%	53%	-	3%	8%	-	-
% reported multivitamin	7%	10%	-	9%	24%	-	-
% reported multivitamin/mineral ^h	20%	29%	-	23%	62%	-	-
Vitamin D intake from food (µg/d) [†]	1.85 (1.11)	1.83 (1.07)	1.89 (1.20)	2.04 (1.10)	1.99 (0.88)	2.08 (1.20)	0.33
Vitamin D intake from supplements (µg/d) [†]	2.65 (3.04)	3.88 (2.95)	0	0.66 (1.67)	1.78 (2.36)	0	<0.0001
Vitamin D intake from food & supplements (µg/d) [†]	4.50 (3.23)	5.71 (3.15)	1.89 (1.20)	2.70 (2.03)	3.77 (2.62)	2.08 (1.20)	<0.0001

* defined as subjects who did either or both recorded vitamin D supplement use on at least one observed day and/or reported vitamin D, multivitamin, or multivitamin/mineral supplement use during last month in the additional questionnaire

** difference between users and non-users of vitamin D-containing dietary supplements

[†] 2-3 yr 12 missing values, 4-6 yr 2 missing values

[†] based on food diary on two independent days; dietary intake average of observed intakes

^g based on additional questionnaire

The observed vitamin D intake from dietary supplements showed spikes at specific amounts, especially for children 2–3 yr old. Spikes were observed at 1.25, 2.5, 5, 7.5, and 10 μg , the largest spike was observed at 5 μg . It is likely that this is caused by the recommendation for children up to 4 yr to take vitamin D-containing supplements with a specific dosage; in 2005–2006 when the data was collected the recommended amount was 5 $\mu\text{g}/\text{d}$. In addition, the dosage of vitamin D allowed in dietary supplements for the general population is restricted to a maximum of 5 μg (for specific subpopulations, including young children, a maximum of 15 μg is allowed) (Anonymous, 1994).

Model parameters

The model parameters to estimate habitual *total* vitamin D intake with the proposed model are presented in Table 5.2. Correlation between vitamin D intake from foods and probability to use vitamin D-containing supplements was taken into account in the model. Only for children aged 4–6 yr this correlation was statistically significant ($r=0.36$, $p=0.047$). Few potential covariates were kept in the reduced model. In the parts modeling amount from food these were, bodyweight in both age groups, and gender in 4–6 yr olds. In the part modeling probability to use dietary supplements no covariates were included in the reduced model.

Lambda (λ) represents the Box-Cox transformation parameter in the two parts of the model estimating vitamin D intake from food. When λ is 0 a log-transformation is applied, if λ equals 1 no transformation is applied. It could be generally stated that the higher λ , the less skewed is the original distribution. For the youngest age group the estimated λ_0 and λ_1 (for non-users and non-users of vitamin D-containing dietary supplements respectively) were similar ($\lambda_0=0.28$ and $\lambda_1=0.30$). For the older children (4–6 yr) λ was higher for non-users ($\lambda_0=0.40$) compared to users of vitamin D-containing dietary supplements ($\lambda_1=0.26$). This indicates that the shapes of the population distributions of habitual vitamin D intake from food sources are dissimilar between users and nonusers of dietary supplements for this age group.

Unlike the children 2–3 yr, the within-person variances was higher for non-users of vitamin D-containing dietary supplements ($\sigma_{wo}^2=0.47$) compared to users ($\sigma_{w1}^2=0.33$) aged 4–6 yr. The between-person variance for intake amount from food sources (σ_{bo}^2) was higher for non-users compared to users of vitamin D-containing dietary supplements (σ_{b1}^2) in both age groups. The estimated between-person variance for probability to use vitamin D-containing dietary supplements was higher among 4–6 yr old children ($\sigma_{b2}^2=13.2$) compared to 2–3 yr old children ($\sigma_{b2}^2=6.2$). The modeled probability distributions to use dietary supplements containing vitamin D on a given day are graphically presented in Figure 5.2. Children aged 2–3 yr were more likely to use dietary supplements compared to 4–6 yr olds, the mean probability was 0.52 and 0.22 respectively.

Table 5.2 Model parameters (SE) for vitamin D by age group, for intercept, covariates, and correlation also p-value is presented (user = user of vitamin D containing dietary supplements)

Model parameters	Subgroup or covariate		p-value	
	2-3 yr	4-6 yr		
Box-Cox transformation parameter (λ_0)	non-users users	0.30 0.28	0.40 0.26	
Box-Cox transformation parameter (λ_1)	Intercept (Mean ₀)	0.23 (0.31)	0.21 (0.22)	0.34
Non-users amount from food	bodyweight	0.017 (0.019)	0.021 (0.010)	0.04
	gender	-	0.040 (0.077)	0.60
Users probability use supplements	Intercept (Mean ₂)	2.23 (0.27)	1.01 (0.32)	0.002
Users amount from food	Intercept (Mean ₁)	0.032 (0.184)	-0.017 (0.189)	0.93
	bodyweight	0.030 (0.012)	0.027 (0.009)	0.002
	gender	-	0.13 (0.06)	0.048
Within-person variance from food (σ_{w0}^2)	non-users	0.40 (0.04)	0.47 (0.04)	
Within-person variance from food (σ_{w1}^2)	users	0.41 (0.04)	0.33 (0.03)	
Between-person variance amount from food (σ_{b0}^2)	non-users	0.30 (0.06)	0.28 (0.05)	
Between-person variance amount from food (σ_{b1}^2)	users	0.16 (0.04)	0.10 (0.03)	
Between-person variance probability use supplements (σ_{bc}^2)	users	6.21 (1.70)	13.20 (4.06)	
Correlation probability use supplements & amount from food		-0.04 (0.11)	0.36 (0.17)	0.047

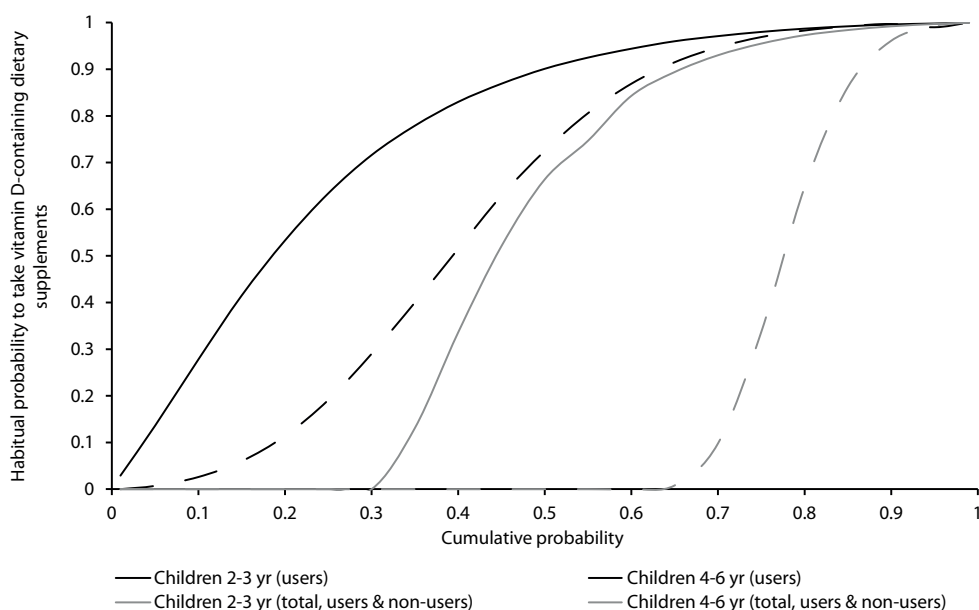


Figure 5.2 Habitual probability to use vitamin D-containing dietary supplements for users of vitamin D-containing supplements (black) and for the total sample including users and non-users, separately for children 2-3 yr old (solid curve) and children 4-6 yr old (dotted curve).

Habitual vitamin D intake

With the proposed model, the median habitual *total*/vitamin D intake was 3.8 $\mu\text{g}/\text{d}$ for children 2-3 yr and 2.3 $\mu\text{g}/\text{d}$ for children 4-6 yr (Table 5.3). The median habitual *total* vitamin D intake was higher for users of vitamin D-containing dietary supplements compared to non-users; among 2-3 yr old children 5.5 $\mu\text{g}/\text{day}$ vs. 1.7 $\mu\text{g}/\text{day}$ and among 4-6 yr old children 3.3 $\mu\text{g}/\text{day}$ vs. 2.0 $\mu\text{g}/\text{day}$. The habitual vitamin D intake from food sources only was comparable between users and non-users of vitamin D-containing dietary supplements and was somewhat higher for children aged 4-6 yr compared to 2-3 yr olds. The habitual vitamin D intake from dietary supplements (users only) was higher among 2-3 yr old children compared to 4-6 yr olds.

Comparing the habitual *total*/vitamin D intake distributions with the habitual vitamin D intake distribution from food sources only showed that with the proposed model, the estimated values for habitual *total* intake were always higher than or at least equal to the estimated values for habitual intake from food sources only.

In both age groups the habitual *total* vitamin D intake was in large part of the population below the EAR of 10 $\mu\text{g}/\text{d}$ (IOM, 2010). Only among users of dietary

Table 5.3 Habitual intake distributions of vitamin D estimated with the three-part method using the 'first shrink then add' approach proposed in this chapter for intake from food sources, dietary supplements and total intake from both sources for the total population and separately for users* and non-users* of dietary supplements, by age category

Age	Method	Population	Vitamin D ($\mu\text{g}/\text{day}$)					
			Mean	P5	P25	P50	P75	P95
2-3 yr	Total intake	total	4.4	1.1	2.1	3.8	6.3	9.8
		non-users*	1.9	0.8	1.3	1.7	2.3	3.4
		users*	5.6	2.1	3.6	5.5	6.7	11.0
	Intake from foods	total	1.8	0.9	1.4	1.8	2.2	3.1
		non-users*	1.9	0.8	1.3	1.7	2.3	3.4
		users*	1.8	1.0	1.4	1.8	2.2	2.9
	Intake from supplements	total	2.6	0	0	1.9	4.6	7.9
		users*	3.8	0.5	1.8	3.7	4.9	9.1
	4-6 yr	Total intake	total	2.7	1.1	1.7	2.3	3.2
non-users*			2.1	1.0	1.5	2.0	2.5	3.5
users*			3.7	1.5	2.3	3.3	4.4	7.4
Intake from foods		total	2.0	1.0	1.5	2.0	2.4	3.3
		non-users*	2.1	1.0	1.5	2.0	2.5	3.5
		users*	2.0	1.2	1.6	1.9	2.3	3.0
Intake from supplements		total	0.6	0	0	0	0.7	3.0
		users*	1.7	0.0	0.4	1.2	2.4	5.0

* defined as subjects who did either or both record vitamin D supplement use on at least one observed day and/or report vitamin D, multivitamin, or multivitamin/mineral use during last month in the additional questionnaire

supplements 7% of the children aged 2-3 yr and 3% of those aged 4-6 yr had a habitual vitamin D intake above the EAR. The Dutch Health Council set an AI for vitamin D, which is 5.0 $\mu\text{g}/\text{d}$ for children 2-3 yr and 2.5 $\mu\text{g}/\text{d}$ for children 4-6 yr (Health Council, 2000a). For 61% of the 2-3 yr old and 77% of the 4-6 yr old children the habitual *total* vitamin D intake was below the AI. Habitual intakes above the UL (i.e. 25 $\mu\text{g}/\text{d}$ (SCF/NDA, 2006)) were not observed.

The impact of imputation and incorporation of correlation or covariates

There were some differences between the distributions estimated with and without imputation. For the estimations of habitual intake from food sources only at the percentiles, these differences were negligible (less than 0.2% deviation). The estimated habitual *total* vitamin D intake at the percentiles differed more between the imputed

and the original dataset (-2.2-15.3% deviation). This was expected as for about 20% of the users the vitamin D dosage from supplements was imputed. The largest differences were observed around the median.

The impact of incorporating correlation between the amount of vitamin D from food and the probability to use vitamin D-containing dietary supplements on the estimated habitual vitamin D intake was minor. For the percentiles the differences in estimated habitual *total* vitamin D intake were small, less than 0.5% for children 2-3 yr and up to 2.4% for children 4-6 yr old.

The impact of incorporation of covariates was studied using the original data set (without imputation). Inclusion of bodyweight, and among 4-6 yr olds also gender as covariates had minor effects ($\leq 0.5\%$) on the finale estimates of habitual vitamin D intake.

Comparison of 'first add then shrink' with 'first shrink then add'

In Figure 5.3 the habitual intake distributions for *total* vitamin D and vitamin D from foods sources only estimated with a 'first add then shrink' approach using the original NCI-method (Tooze *et al.*, 2010; 2006) are compared to those obtained with the proposed model (without imputation and covariates). Comparing the estimated habitual *total* vitamin D intake at the percentiles of the distribution between both approached resulted in differences that ranged from -29.3%-33.1% for children 2-3 yr and from -18.6%-29.0% for children 4-6 yr (Figure 5.3). From Figure 5.3 it is clearly observed that with the 'first add then shrink' approach, the habitual *total* vitamin D intake (grey solid curve) at the lower intake percentiles was estimated lower than the habitual vitamin D intake from food sources only (grey dotted curve), since the grey solid curve lies above the grey dotted curve. This incompatible finding in estimation of habitual *total* vitamin D intake was not observed with the proposed model using the 'first shrink then add' approach (black curves). In addition, the multi-modal shape in the observed *total* vitamin D intake distribution (mean over 2 days) of children aged 2-3 yr old was preserved with the 'first shrink then add' approach, but disappeared in the results of the 'first add then shrink' approach. These differences are also reflected in the estimation of the proportion of the population with intakes below specific cut-off values (Table 5.4). The proportions with habitual *total* vitamin D intakes below the EAR or UL were high (>95%) and estimated in the same order of magnitude with both approaches. However, using lower cut-off values differences in the estimated proportion with lower habitual *total* vitamin D intakes up to 12 percent points were observed. Such a high difference is for instance observed for children aged 4-6 yr old at a cut off value of 2.5 $\mu\text{g}/\text{d}$ (i.e. AI as set by the Dutch Health Council). In addition, for the 'first add then shrink' approach the proportion with habitual vitamin D intakes below a cut-off value of 1 $\mu\text{g}/\text{d}$ is lower for intake from food sources only (4.3%)

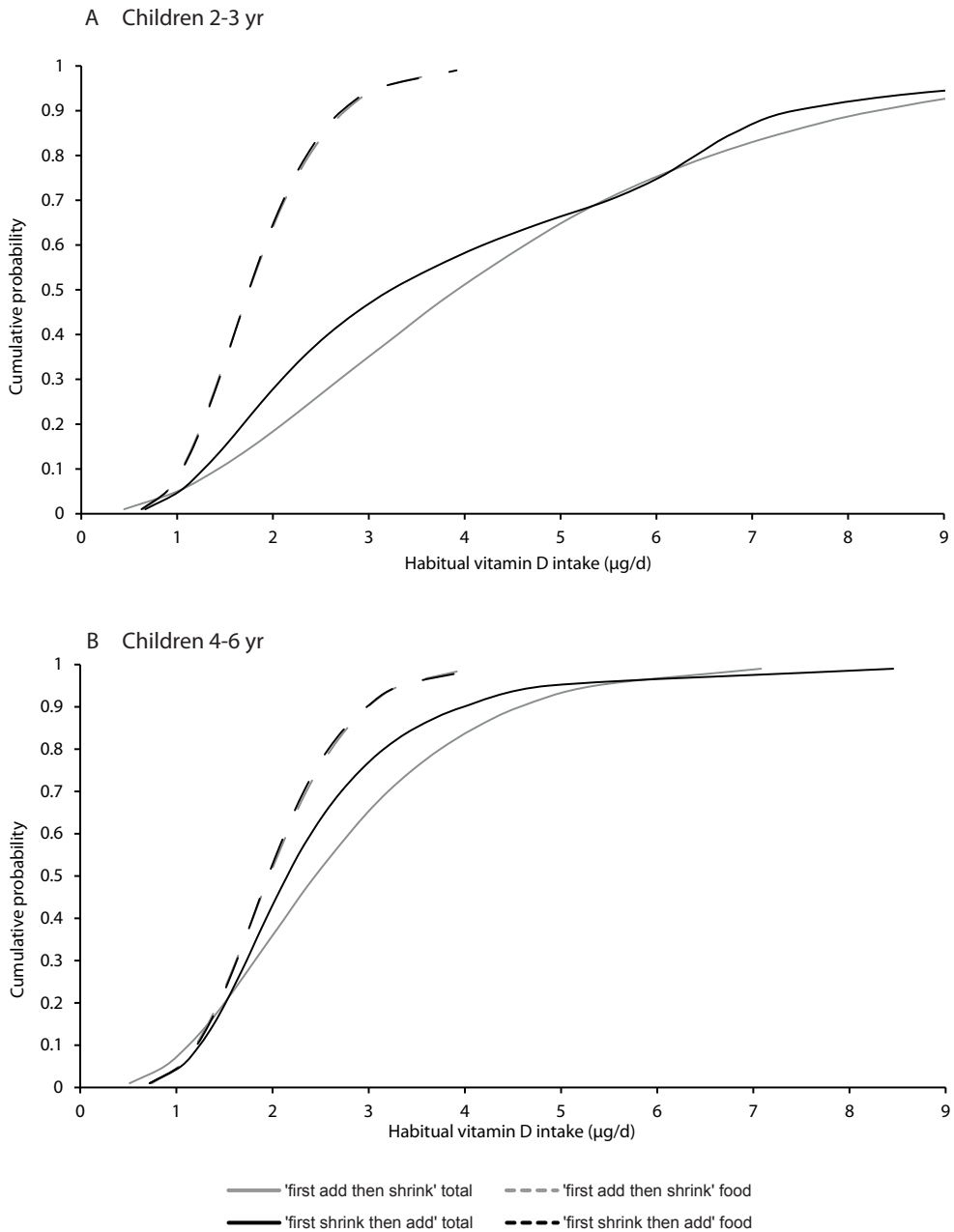


Figure 5.3 Habitual total vitamin D intake distribution (solid curves) and habitual vitamin D intake distribution from food sources only (dotted curves) estimated with a 'first add then shrink' approach (grey curves) and a 'first shrink then add' approach (black curves), separate for A) 2-3 yr old children and B) 4-6 yr old children.

Table 5.4 Proportion of the population with habitual vitamin D intakes below specific cut-off values by age group as estimated with a 'first add then shrink' approach and a 'first shrink then add' approach (without imputation and without covariates)

Age	Method	Vitamin D source	Within-person variance	Between-person variance	Proportion (%) below cut-off value									
					1.0	1.5	2.5*	3.5	5.0*	10*	15	25*		
2-3 yr	First shrink then add	total	‡	‡	4.6	15.1	38.7	53.0	66.4	95.9	99.5	100		
	First add then shrink	total	0.21	1.26	5.0	11.0	26.7	43.4	64.9	95.1	99.5	100		
	First shrink then add	food	‡	‡	8.1	33.8	84.7	97.8	99.9	100	100	100		
	First add then shrink	food	0.41	0.62	8.3	34.3	83.8	97.9	99.9	100	100	100		
4-6 yr	First shrink then add	total	‡	‡	4.1	19.5	63.5	85.2	95.4	99.3	99.8	100		
	First add then shrink	total	0.22	0.52	7.2†	20.0	51.7	75.9	93.1	100	100	100		
	First shrink then add	food	‡	‡	4.3	22.7	77.2	96.3	99.9	100	100	100		
	First add then shrink	food	0.44	0.44	4.3†	23.3	76.0	96.5	99.9	100	100	100		

* Health Council of The Netherlands set an AI at 5 µg/d or 2.5 µg/d for respectively 2-3 yr and 4-6 yr (Health Council, 2000a); Institute of Medicine set an EAR at 10 µg/d (IOM, 2010); the EFSA set an UL at 25 µg/d (SCF/NDA, 2006)

‡ Proportion with intakes below this cut-off value is higher for total intake than for intake from food sources only

† The 'first shrink then add' approach gives 5 estimates of within- and between-person variances, see Table 5.2 for within- and between-person variances in the proposed model with imputation and with covariates. These values were very similar to those of the proposed model without imputation and without covariates.

than for *total* intake (7.2%), for children 4–6 yr old. For the proposed model these proportions are 4.3% and 4.1% respectively.

In the 'first add then shrink' approach, especially the between-person variance is very different comparing the models for *total* vitamin D intake and vitamin D intake from food sources only (Table 5.4). For children aged 2–3 yr the between-person variance is 6 times higher in the 'first add then shrink' approach for *total* vitamin D intake compared to intake from food sources only. For children 4–6 yr old this difference is 2.5 times. These differences were expected, as the between-person variance in the model for *total* vitamin D intake, reflects the between-person variances of both food and dietary supplements.

Discussion & conclusion

In this chapter we proposed a three-part model to estimate habitual *total* micronutrient intake from food and dietary supplements for the whole population using a 'first shrink then add' approach. The model was illustrated for *total* vitamin D intake in children. In the three-part model, habitual micronutrient intake is first estimated separately for non-users and users of dietary supplements; and within users separately for intake from foods and dietary supplements. The three habitual intake distributions are combined to result in the distribution of habitual *total* intake for the whole population. Our study showed that the proposed model did solve the inconsistency that occurred in the 'first add then shrink' approach in which at the lower percentiles of the habitual intake distribution the *total* intake was estimated to be lower than the intake from food sources only. In our model the estimates of habitual *total* intake were always higher or at least equal compared to the estimates of habitual intake from food sources only. In addition, the face validity of the proposed model seems better than that of the 'first add then shrink' approach, because the multimodality of the vitamin D intake distribution among children 2–3 yr is preserved after correction for within-person variation. The 'first add then shrink' approach was also applied using the method of the Iowa State University (ISU) (Nusser *et al.*, 1996). As with the NCI-method, at the lower percentiles of the intake distribution the estimated habitual *total* vitamin D intake was lower than the estimated habitual vitamin D intake from food sources only. However, unlike the NCI-method, with the ISU-method the multi-modal shape was preserved (data not shown). This suggests that the transformation used in the ISU-method (2-part transformation, 1) power transformation followed by 2) non-parametric transformation based on grafted polynomial model) is more flexible regarding non-normal distributions compared to the Box-Cox transformation used in the NCI-method. In addition, with the ISU-method a t-test for heterogeneous measurement error variance is performed.

As expected, the outcome was more significant for *total* vitamin D intake compared to vitamin D intake from food sources only.

As far as we know this is the first time this three-part model is proposed to estimate habitual *total* micronutrient intake. Recently others have suggested to perform separate analyses for intake from food and dietary supplements ('first shrink then add') (Bailey *et al.*, 2010; Dodd *et al.*, 2009) or to estimate habitual *total* nutrient intake separately for non-users and users of dietary supplements (Garriguet, 2010a; b). In our model we combined the advantages of both ideas into one model.

The advantage of the 'first shrink then add' approach is that potential differences in the within- and between-person variances in the micronutrient intake from food or dietary supplements are not tarred with the same brush to get estimates of one within- and one between-person variance as in the 'first add then shrink' approach. In the 'first shrink then add' approach, in each model part the data is corrected for its specific within-person variation, keeping its specific between-person variation.

There are several potential advantages of performing separate analyses for users and non-users of dietary supplements. First, potential differences in micronutrient intake pattern can be taken into account. For example in our illustration of the model, in the youngest age group the between-person variance of the vitamin D intake from foods was higher for non-users of dietary supplements than for users. This is reflected in the estimation of habitual vitamin D intake from foods which is somewhat wider for non-users compared to users. Second, separate analyses make it possible to incorporate correlation between the use of dietary supplements and the micronutrient intake from foods. And third, these separate analyses make it possible to estimate in one run the habitual intake distribution from each source separately.

The proposed model can incorporate both correlation and covariates. The effects of these incorporations on the estimation of habitual *total* vitamin D intake were small in our study population. The correlation was statistically significant for the age group 4-6 yr, but it was relatively small ($r=0.36$) and therefore the impact was minor. Although the effects of correlation and covariates for the estimation of the habitual vitamin D intake distribution in this study population were small, it might be possible that for other micronutrients or in other study populations the effects are more pronounced.

The development of our model was case-driven, this means that data as available in DNFCS-young children was a starting point. There are some limitations regarding this data to address. In the DNFCS-young children food consumption data is collected with a food diary on two independent days. For the estimation of habitual intake, it is assumed that the data collected on the short-term is an unbiased estimator of the

true intake (Dodd *et al.*, 2006; Nusser *et al.*, 1996; Tooze *et al.*, 2006). From several studies it is known that this is not the case (Crispim *et al.*, 2011; Lissner *et al.*, 2007; Ocké *et al.*, 1997). As a consequence the estimation of habitual intake may still contain some bias.

Data on the use of dietary supplements was available from the dietary records as well as from an additional questionnaire. From the additional questionnaire only information on whether or not a specific type of dietary supplements was used during the last month was available. Unfortunately, no details on e.g. frequency of use, amounts, duration of use, or type were requested in the additional questionnaire. As a consequence, it was difficult to identify the non-users of vitamin D-containing dietary supplements. Some subjects could be misclassified as not all multivitamin(/mineral) supplements contain vitamin D. Of the multivitamin(/mineral) supplements present in the Dutch supplement composition database, about 65% contained vitamin D (data not shown). Further, the use of dietary supplements was reported over a relatively short time-frame; 8-13 days in the dietary record and 1 month in the additional questionnaire. As a result no information is available of the episodically use of dietary supplements over longer time-frame e.g. 1 yr, including e.g. within-person differences over seasons. Our study suggests that the use of dietary supplements is more common in winter compared to summer, as the frequency of the season winter was higher among users of dietary supplements and the summer lower. This could have affected the estimations of probability to use dietary supplements, as some subjects may be misclassified as non-user and as potential differences in use of dietary supplements within a longer time frame (e.g. one year) are not included. In the NHANES study detailed information on the use of dietary supplements (including, type, frequency of use, duration, and dosage) was collected, however over a relatively short time frame of 30 days (Bailey *et al.*, 2010). In the new DNFCS (2007-2010), the use of dietary supplements is reported separately for winter-time and the remaining of the year, in addition the frequency of use of predefined supplement types is reported for both periods. Both examples of recent more detailed data collection on use of dietary supplements will improve the estimates of habitual *total* intake. But for better estimates of habitual *total* micronutrient intake, more detailed information on the use of dietary supplements over a longer time frame (at least covering all seasons) is required.

The supplement composition data was obtained from label information rather than from analytical values, there are however studies suggesting overages (Consumentenbond, 2011; Dwyer *et al.*, 2007; Roseland *et al.*, 2008). An underestimation of the vitamin D intake could therefore be possible. In our model, the vitamin D dosage from dietary supplements was a fixed value. For the subjects identified as users, but without dosage information from the food records, a value was imputed. As a result the habitual *total* vitamin D intake in the population increased compared to a model without imputation.

However, in our view, the results with the imputed data more accurately reflect the true distribution of habitual intake. For most of the study population with positive vitamin D intake from dietary supplements on both survey days, the dosages were equal on the two days, suggesting little within-person variation in dosage. However, the relative short timeframe of data collection could have caused some bias. There was no information on, e.g., brand loyalty or possible dosage fluctuations in time.

The habitual *total* vitamin D intake estimated with the proposed model remains below the UL in both age groups. So risks accompanying too high vitamin D intakes are unlikely. In both age groups the habitual vitamin D intake from both sources is below the EAR as set by the IOM in large part of the population. Only a small proportion of the subjects using dietary supplements had intakes above this EAR. The EAR was set under conditions of minimal exposure to sunlight (IOM, 2010). As vitamin D can be produced by the skin under influence of UV-radiation, the EAR may be an overestimation for subjects exposed to sun light. The Dutch Health Council set an AI for vitamin D considering exposure to sun light (Health Council, 2000a). Comparison of the habitual *total* vitamin D intake shows that in both age groups the median habitual *total* intake is below the AI. This means that no statement can be made about the adequacy of the vitamin D intake. Among users of dietary supplements aged 4-6 yr old, the median habitual *total* vitamin D intake (i.e. 2.3 µg/d) is close to the AI (i.e. 2.5 µg/d). These results indicate that many children 2-3 yr old do not get a daily vitamin D-containing dietary supplement with the advised vitamin D dosage. Recently there were changes in the advice for young children to take vitamin D-containing dietary supplements. The dosage was elevated from 5 µg/d to 10 µg/d (Health Council, 2008b). The DNFCs-young children was however conducted in 2005-2006. Potential changes in vitamin D dosages due to the new advice are therefore not reflected.

We proposed a model to estimate habitual *total* intake from food and dietary supplements. The main problems in this estimation are the heterogeneous variances between intake from food and dietary supplements and the multimodal shape of the *total* intake distribution. The ideas of our model are however generic. Also for other examples showing heterogeneous variances (e.g. intake from fortified foods or foods with (extreme) high levels of a specific nutrient, like liver (vitamin A), fish (n-3 fatty acids)) or multimodality (e.g. in food safety the intake from few different foods (Slob *et al.*, 2010)), the ideas presented in this chapter could be useful tools. The proposed model was developed in SAS as an extension of the original NCI-method (Tooze *et al.*, 2010; 2006). However, the idea of the three-part model could also be incorporated in other existing methods estimating the habitual intake distributions and improve the estimates for *total* nutrient intake. The development of our model was case-driven. As a consequence, some adaptations have to be made when the survey data is different.

In conclusion, our model is an improvement on the currently existing models and approaches for estimating habitual *total* micronutrient intake. Although the development of the model was data driven, the ideas are generic and could be applied on other types of data as well. In addition, these ideas could be useful to model habitual intake for other complex issues. It is recommended to improve the data collection on use of dietary supplements, by reporting details on e.g. frequency of use, amount, dosage, type, but also by including a larger time frame of data collection to incorporate differences over time, e.g. over seasons.



6

Safe addition of vitamins and minerals to foods: setting maximum levels for fortification in The Netherlands

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Abstract

Background: In 2004, the European Court of Justice decided that the prohibition of fortification with vitamin A, vitamin D, folic acid, selenium, copper, and zinc in The Netherlands conflicts with the principle of free movement of goods in the European Union. This decision led to a change in the Dutch policy, resulting in a more flexible handling of requests for exemption from this prohibition to fortify. Therefore, an investigation was proposed in which it would be determined whether a general exemption could be granted for food fortification with a certain maximum safe amount per micronutrient.

Aim of the study: To develop a risk assessment model to estimate maximum safe fortification levels (MSFLs) of vitamins and minerals to foods on the Dutch market, and to evaluate these levels to derive allowed fortification levels (AFLs), which can be used for a general exemption.

Methods: We developed a risk assessment model to estimate MSFLs of vitamins and minerals to foods on the basis of existing models. We used European tolerable upper intake levels in combination with national food consumption data to estimate MSFLs for fortification of foods for several age groups. Upon extensive stakeholder dialogue, the risk manager considered these estimated MSFLs and the final AFLs for a general exemption were set.

Results: For folic acid, vitamin A, and vitamin D, the MSFLs were calculated in the risk-assessment model. Children up to 6 yr old were the group most sensitive to folic acid fortification, and they had an MSFL of 0 $\mu\text{g}/100$ kcal, but following a risk management evaluation, this was upgraded to an AFL of 100 $\mu\text{g}/100$ kcal. The MSFL for vitamin D was 3.0 $\mu\text{g}/100$ kcal (children 4–10 yr old), and the risk manager increased this to an AFL of 4.5 $\mu\text{g}/100$ kcal. Children up to 10 yr old, men, and postmenopausal women were the groups most sensitive to vitamin A fortification (MSFL = 0 $\mu\text{g}/100$ kcal). Because these groups represent a large part of the population and because of the seriously harmful effects of excessive vitamin A, the risk manager did not allow a general exemption.

Conclusions: The combination of a risk assessment model and risk manager evaluation led to the setting of AFLs for general exemption of fortification with folic acid and vitamin D. This model is also applicable for other micronutrients, for which an UL is derived, and in other countries.

Introduction

Foods are fortified with micronutrients and other bioactive compounds to prevent deficiencies or to provide additional health effects. Furthermore, the use of health claims on products after fortification is thought to result in better marketing. As fortification with micronutrients should be safe for the whole population, unacceptably large intakes of micronutrients from all sources should be prevented. For this purpose, tolerable upper intake levels (ULs) are established (SCF/NDA, 2006).

Because of the small range between recommended daily intakes and ULs and the lack of proof of a nutritional need, fortification with vitamin A, vitamin D, folic acid, selenium, copper, and zinc is prohibited in The Netherlands (Anonymous, 1996). Addition of these six micronutrients was only allowed in the case of substitution (e.g., vitamins A and D in margarine as a substitute for butter) or restoration (for instance, because of losses during processing) (Anonymous, 1996). In December 2004, the Court of Justice of the European Communities decided that the prohibition of fortification with these six micronutrients contradicted the free movement of goods, a fundamental principle in the Treaty Establishing the European Community (Anonymous, 2005a). This decision means that market introduction of fortified foods can only be prohibited if it can be proved that the degree of fortification (e.g., level of fortification or quantity of foods fortified) may harm public health. This decision led to a change of Dutch policy, resulting in a more flexible handling of requests for exemption from the Dutch Commodity Act that prohibits fortification with these six micronutrients (Anonymous, 2005b). Exemption will only be granted if there is no harm to public health, based on the results of the most recent international scientific research.

Because of this court decision, each request for individual exemption had to be evaluated for the risk of exceeding the UL. At first, requests for individual exemption were evaluated in order of receiving. To evaluate the risk of exceeding the UL, consumption of the new fortified product by the Dutch population was simulated by replacing the unfortified food products with the new fortified product within the Dutch National Food Consumption Survey (DNFCS) (e.g., the consumption of all kinds of breakfast cereals as monitored within the DNFCS was replaced by the new fortified breakfast cereals). The resulting habitual daily intake (P95) of the micronutrient was compared with the UL. If the UL was not exceeded, the exemption was granted. This approach resulted in the exemption of very few products and turned out to be an unrealistic worst-case approach. Furthermore, the procedure resulted in an administrative overload and long waiting periods for the industry. Therefore, and in anticipation of upcoming European legislation (Directorate E, 2006), an investigation was proposed in which it would be determined whether a general exemption could be granted for food fortification with a certain maximum safe amount per

micronutrient. A model was needed to calculate the national maximum level of a specific micronutrient that can safely be added to foods. Several such models have recently been developed (Directorate E, 2006; Domke *et al.*, 2004a; b; Flynn *et al.*, 2003; Rasmussen *et al.*, 2005). First, an International Life Science Institute (ILSI) Europe model (2002) (Flynn *et al.*, 2003), which was followed by models by Domke *et al.* (Domke *et al.*, 2004a; b) and Rasmussen *et al.* (Rasmussen *et al.*, 2005). The latter is an adapted version of the ILSI Europe model (Flynn *et al.*, 2003). These models were developed for the purpose of calculating the maximum amount of micronutrients that can be added to each 100 kcal of a given food (Flynn *et al.*, 2003; Rasmussen *et al.*, 2005) or each food portion (Domke *et al.*, 2004b). The intake of micronutrients from non-fortified foods and dietary supplements must be taken into account for this calculation. Domke *et al.* also estimate the maximum amount of micronutrients in dietary supplements by dividing the space between the UL and the level of intake from non-fortified foods. Most models are theoretical approaches, and data regarding their practical use in decision- or policy-making have not yet been published, although the published acceptable levels of addition per 100 kcal by Rasmussen *et al.* have been implemented as the Danish maximum levels for fortification (Rasmussen, personal communication, 2006). Besides these models that calculate a maximum fortification level, models that calculate the optimal intake for the population (taking into account both too low and too high intakes) are also being developed (Hirvonen *et al.*, 2006; Renwick *et al.*, 2004). In view of the present application, the derivation of maximum safe fortification levels (MSFLs), these models on optimal intake were not taken into account. The question how to create an optimal micronutrient intake is outside the scope of this Chapter.

On the basis of the existing models to calculate a maximum fortification level, a model adapted to the Dutch practical situation was developed for the Dutch authorities to derive for the fortification with micronutrients. This article first describes the model for the derivation of maximum amounts of micronutrient fortification in The Netherlands, and then it illustrates the use of the micronutrient specific data and assumptions in the calculation of the MSFLs for folic acid, vitamin A, and vitamin D. The article concludes with the considerations and the final allowed fortification level (AFL) of the risk management.

Methods

Models to calculate safe maximum levels of addition of micronutrients are published, among others, by ILSI, Rasmussen and Domke (Domke *et al.*, 2004a; b; Flynn *et al.*, 2003; Rasmussen *et al.*, 2005). We developed a model for the Dutch situation, based

on (elements of) the models of ILSI, Rasmussen and Domke. Below, we will amplify on the main differences between the models and our filling-in for the Dutch model.

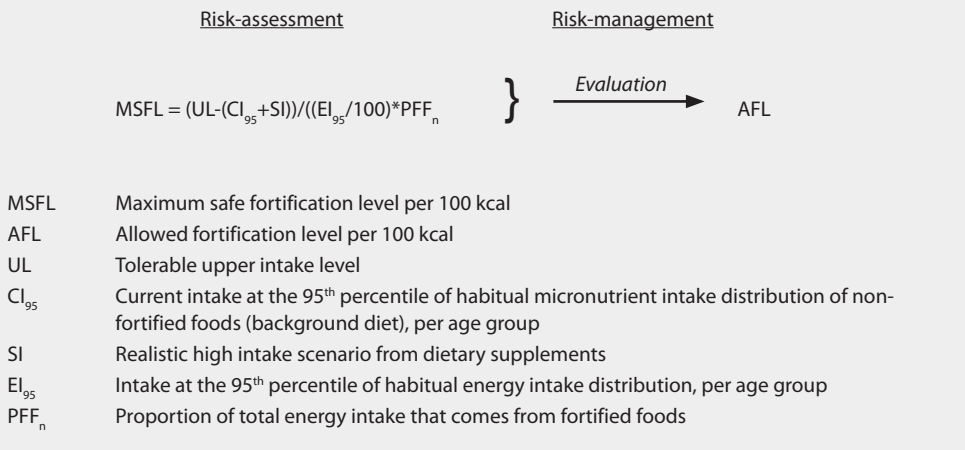
The ILSI Europe and Rasmussen *et al.* models differ in several aspects from Domke *et al.*'s model. Instead of the calculation per portion size as applied by Domke *et al.*, both ILSI Europe and Rasmussen *et al.* calculate the maximum fortification level per 100 kcal. For our Dutch model, we also calculate with 100 kcal portions because the variation in mean daily energy intake is low compared to for instance the variation in micronutrient or carbohydrate intake (Van Staveren *et al.*, 2006). Moreover, there is no univocal definition of portion size in The Netherlands. Another important difference is that Domke *et al.* not only establish maximum fortification levels, but they also establish maximum levels for dietary supplements. Because maximum safe addition levels of vitamins and minerals in dietary supplements will be regulated via European Union legislation, we did not determine them in our model (Directorate E, 2006). Similarly to ILSI Europe and Rasmussen *et al.*, we estimated the current intake of micronutrients from dietary supplements and took them into account. Our Dutch model is principally based on the ILSI Europe model (Flynn *et al.*, 2003) and Rasmussen *et al.*'s extended model (Rasmussen *et al.*, 2005), with adaptations to the Dutch practical situation. The formula is equal to the one used by Rasmussen *et al.*, however some of the factors are differently derived (see below).

Our model calculates the maximum safe level for fortification with a micronutrient per 100 kcal of the food (MSFL) for various age groups with the mathematical formula presented in Box 6.1. The lowest MSFL, i.e., the MSFL for the most sensitive group, is then advised to be the overall maximum acceptable fortification, as is common practice in toxicological risk assessment.

Tolerable upper intake level (UL)

The UL is the maximum level of total chronic daily intake of a nutrient that is unlikely to pose a risk of adverse health effects to humans. In general, the UL is related to total daily intake from all sources including non-fortified foods as well as fortified foods and dietary supplements. In Europe, the Scientific Committee on Food (SCF) and the Scientific Panel on Dietetic Products, Nutrition and Allergies (NDA) set age-specific ULs (SCF/NDA, 2006). Due to lack of data, the ULs for children are usually extrapolated from the ULs for adults based on bodyweight. In anticipation of future European policy (Directorate E, 2006), these age-specific European ULs were used as model input rather than the national ULs, which is similar to the model of Rasmussen *et al.* (Rasmussen *et al.*, 2005). ILSI Europe has also used European ULs, although only the values for men (Flynn *et al.*, 2003).

Box 6.1 Formula for the calculation of the maximum safe fortification level with micronutrients per 100 kcal food (MSFL) (Rasmussen *et al.*, 2005)



Current intake of energy and micronutrients from non-fortified foods (EI_{95} & CI_{95})

Micronutrients are naturally present in the diet (further referred to as 'background diet'). Because it is important to consider the intake from all possible sources to assess the risk, the intake from the background diet has to be included in the calculations. To estimate the intake of energy and micronutrients from the background diet, it is important to use the most up-to-date country- and age-specific data available. In view of the precautionary principle (Anonymous, 2000; Coppens *et al.*, 2006), we calculated the age-specific habitual intake (also referred to as usual intake) at the 95th percentile of the distribution of energy and the specific micronutrients from the background diet on the basis of data from the most recent Dutch National Food Consumption Surveys (DNFCS): DNFCS-3 and DNFCS-2003. The DNFCS-3 was carried out in 1997-1998 for the whole population (1-97 yr) and the DNFCS-2003 was carried out in 2003 for young adults (19-30 yr) (Hulshof *et al.*, 2003; Ocké *et al.*, 2005b). In the DNFCS-3, a 2-day dietary record method was used to collect data on two consecutive days. In the DNFCS-2003, data were collected with a 2-day, 24-hour recall method using EPIC-SOFT, a computer-assisted interview method. We estimated the habitual intake of both micronutrients and energy with statistical correction for the within-person variation using the Iowa State University method (C-SIDE software) (ISU, 1996; Nusser *et al.*, 1996).

Rasmussen *et al.*'s model uses results from the Danish dietary survey in which a 7-day prospective food recall method was used to calculate the daily intake of micronutrients

from non-fortified foods (95th percentile) and energy intake (95th percentile) (Rasmussen *et al.*, 2005). ILSI Europe used pan-European estimates of the 95th percentile of intake of micronutrients based on seven national surveys. Some of these surveys already include voluntary fortification of foods with micronutrients and the intake of dietary supplements (Flynn *et al.*, 2003). Furthermore, the pan-European 95th percentile of energy intake was estimated from five national surveys.

Current intake of micronutrients from dietary supplements (SI)

In addition to the intake from the background diet, the micronutrient intake from dietary supplements (SI) has to be taken into account in order to get a good estimate of the total intake from all sources. In The Netherlands, similar to other Western countries, the use of dietary supplements has increased and takes a more important place in the total micronutrient intake (Ocké *et al.*, 2005a). Preferably, the habitual micronutrient intakes of non-fortified foods and dietary supplements are calculated together. This method takes into account the facts that not everybody uses dietary supplements, not all supplement users use the supplements daily, and supplement users and non-users may have different eating habits (De Jong *et al.*, 2003). However, due to lack of information about supplement use, a calculation of combined habitual intake is not possible at this time. Therefore, we used two realistic high-intake scenarios of dietary supplements based on the limited Dutch dietary supplement data available: one for adults (≥ 18 yr old) and one for children (1–17 yr old). The scenario for adults was based on the P90–P95 of both the intake of micronutrients from dietary supplements in young adults (19–30 yr) reported by the DNFCs-2003 (Ocké *et al.*, 2005a) and the levels of micronutrients present in dietary supplements (for adults) available in The Netherlands (Anonymous, 2002b). The scenario for children was based on P90–P95 of the infants' intake of dietary supplements (Breedveld *et al.*, 2002) and the levels of micronutrients present in dietary supplements for children, that are available in The Netherlands (Anonymous, 2002b).

We determined the SI differently than Rasmussen *et al.* and ILSI Europe did. Rasmussen *et al.* chose to set the SI at 100% of the reference values for the recommended daily intake of vitamins and minerals because this is the content of the most used multi-vitamin-mineral supplement in Denmark (Rasmussen *et al.*, 2005). The ILSI Europe model does not include the intake from dietary supplements because only a minority of the population is expected to use them (Directorate E, 2006; Flynn *et al.*, 2003).

Fraction of energy intake that can and will be fortified (PFF_n)

Not all foods on the market can or will be fortified. The fraction of total energy intake that will finally be fortified consists of two parts: (1) the proportion of total energy

intake that can be fortified; for example, it is unlikely that fresh products such as vegetables, fruits and meat will be fortified; and (2) the proportion of the energy intake of foods available for fortification that actually will be fortified. Due to practical constraints such as costs and processing, not all foods available for fortification will be fortified with a particular micronutrient.

The first part of the fraction was set at 30%, which is lower than the 50% set by both ILSI Europe and Rasmussen *et al.* Main argument for the lower percentage was that the large part of the energy intake in the Dutch population is delivered by the traditional dinner, which consists in general of fresh products like meat, vegetables, and potatoes. The second part of the fraction was equal to the one ILSI Europe and Rasmussen *et al.* set at 50% (worst case). This resulted in a fraction of the energy intake available for fortification ($PF_{n,n}$) of 15% (i.e., 30% * 50%).

Results

Risk assessment: deriving MSFLs

We illustrate the applicability of the Dutch model by deriving MSFLs of folic acid, vitamin A, and vitamin D. Tables 6.1, 6.2, and 6.3 present the factors used for the calculation of the MSFLs for folic acid, vitamin A, and vitamin D. The classification into age groups is based on the age categories used by NDA/SCF to define the ULs (SCF/NDA, 2006) and is different for folic acid, vitamin A, and vitamin D. We calculated the 95th percentile of habitual energy intake for each age group. The habitual energy intake of children increases with age (Tables 6.1–6.3). The 95th percentile of the habitual energy intake for men is greater than that for women; there is a small decline of habitual energy intake with age for both genders.

Folic acid

Folic acid is the synthetic form of folate, a natural component in the diet. An UL has been established only for folic acid and not for folate. For this reason, the calculation does not consider the intake of folate from the background diet. At the time the food consumption surveys were conducted, fortification with folic acid was not permitted in The Netherlands, which results in an intake from the background diet (CI_{95}) of 0 µg/day. The SI of folic acid was estimated to be 300 µg/day for children and adolescents and 600 µg/day for adults. Filling in these factors in the formula of Box 6.1 resulted in a maximum fortification level for folic acid of 0 µg/100 kcal for children 1–6 yr old to 110 µg/100 kcal for women older than 65 yr (Table 6.1). For children and adolescents, the MSFL for folic acid fortification increased with age because of an increase in UL

Table 6.1 Maximum safe fortification levels and allowed fortification level of folic acid based on Dutch consumption data and European tolerable upper levels of intake for specific age groups

Age group	n	UL (µg/day)	CI ₉₅ [*] (µg/day)	SI (µg/day)	E ₉₅ (SE) (kcal/day)	Max. safe fortification level (MSFL)		Allowed fortification level (AFL) (µg/100 kcal)
						(µg/100 Kcal)	PFF _n = 0.10 ^s	
Children								
1-3[†]	254	200	0	300	1,890 (67)	0		
4-6[†]	276	300	0	300	1,995 (56)	0		
Children	312	400	0	300	2,456 (63)	27		
Children	336	600	0	300	3,154 (117)	63		
Adolescents	280	800	0	300	3,518 (150)	95		
Men								
18-30[†]	525	1,000	0	600	4,010 (112)	67	100	100
Women	579	1,000	0	600	2,867 (62)	93	140	
Men	352	1,000	0	600	3,751 (130)	71	106	100
Women	398	1,000	0	600	2,581 (76)	103	155	
Men	950	1,000	0	600	3,529 (64)	76	113	
Women	1,100	1,000	0	600	2,721 (48)	98	147	
Men	420	1,000	0	600	3,427 (109)	78	117	
Women	479	1,000	0	600	2,647 (74)	101	151	
Men	260	1,000	0	600	3,106 (119)	86	129	
Women	410	1,000	0	600	2,432 (65)	110	164	

The most sensitive age groups are bolded; CI₉₅[†] percentile of habitual dietary folic acid intake; E₉₅[†] percentile of habitual energy intake; SI, supplement intake; PFF_n[†] proportion of energy intake that *can* and *will* be fortified; UL, tolerable upper intake level.

^{*} Dietary intake of folic acid only, folate is not taken into account because the UL is based on folic acid only.

[†] Based on consumption data from the DNFCS-3 (1997-1998) (Huisshof *et al.*, 2003).

[‡] Based on consumption data from the DNFCS 2003 (Huisshof *et al.*, 2004; Ocké *et al.*, 2004; Ocké *et al.*, 2005b).

[§] Additional calculation with exactly the same results as for PFF_n = 0.15 in combination with a scenario of low dietary supplement intake (i.e. 400 µg), only calculated for adults.

Table 6.2 Maximum safe fortification levels of vitamin A* based on Dutch consumption data and the European upper levels of intake for specific age groups

Age group	n	UL (µg/day)	CI ₉₅ (SE) (µg/day)	SI (µg/day)	EL ₉₅ (SE) (kcal/day)	Max. safe fortification level (MSFL) (µg / 100 Kcal) PFF _n = 0.15
Children						0
1-3[†]	254	800	1,269 (216)	800	1,890 (67)	0
4-6[†]	276	1,100	1,553 (262)	800	1,995 (56)	0
7-10[†]	312	1,500	1,055 (116)	800	2,456 (63)	0
Children	336	2,000	1,153 (131)	800	3,154 (117)	10
Adolescents	280	2,600	1,429 (205)	800	3,518 (150)	70
Men	352	3,000	1,886 (261)	1,200	3,751 (130)	0
Women	398	3,000	1,203 (162)	1,200	2,581 (76)	154
Men	2,155	3,000	2,363 (132)	1,200	3,642 (50)	0
Women	1,679	3,000	1,350 (83)	1,200	2,785 (39)	108
Women	889	1,500	1,441 (108)	1,200	2,555 (53)	0

The most sensitive age groups are bolded; CI₉₅[†], 95th percentile of habitual dietary vitamin A intake; EL₉₅[†], 95th percentile of habitual energy intake; SI, supplement intake; SE, standard error; PFF_n, proportion of energy intake that *can* and *will* be fortified; UL_n, tolerable upper intake level.

* Not including provitamin A.

[†] Based on consumption data from the DNFCs-3 (1997-1998) (Hulshof et al., 2003).

[‡] Based on consumption data the DNFCs 2003 (Hulshof et al., 2004; Ocké et al., 2004; Ocké et al., 2005b).

Table 6.3 Maximum fortification levels and allowed fortification level of vitamin D based on Dutch consumption data and European tolerable upper levels of intake for specific age groups

Age group	n	UL (µg/day)	Cl ₉₅ (SE) (µg/day)	SI (µg/day)	El ₉₅ (SE) (kcal/day)	Max. safe fortification level (MSFL) (µg/100 Kcal)		Allowed fortification level (AFL) (µg/100 kcal)
						PFF _n = 0.15	PFF _n = 0.10*	
Children	254	25	4.8 (0.6)	10	1,890 (67)	3.6	5.4	
Children	588	25	4.4 (0.2)	10	2,334 (50)	3.0	4.5	4.5
Children	252	50	6.5 (0.6)	10	2,935 (100)	7.6	11.4	
Adolescents	445	50	7.6 (0.5)	10	3,509 (116)	6.2	9.2	
Men	352	50	6.5 (0.4)	10	3,751 (130)	6.0	8.9	
Women	398	50	5.2 (0.4)	10	2,581 (76)	9.0	13.5	
Men	950	50	8.9 (0.4)	10	3,529 (64)	5.9	8.8	
Women	1,100	50	6.4 (0.3)	10	2,721 (48)	8.2	12.3	
Men	314	50	11.3 (1.2)	10	3,410 (128)	5.6	8.4	
Women	332	50	6.7 (0.6)	10	2,623 (90)	8.5	12.7	
Men	197	50	9.8 (1.0)	10	3,315 (124)	6.1	9.1	
Women	270	50	6.6 (0.6)	10	2,528 (87)	8.8	13.2	
Men	169	50	12.2 (1.8)	10	3,067 (141)	6.0	9.1	
Women	287	50	8.6 (0.8)	10	2,487 (86)	8.4	12.6	

The most sensitive age groups are bolded; Cl₉₅th percentile of habitual dietary vitamin D intake; El₉₅th percentile of habitual energy intake; SI, supplement intake; SE, standard error; PFF_n[†] proportion of energy intake that can and will be fortified; UL, tolerable upper intake level.

[†] Based on consumption data from the DNFC-3 (1997-1998) (Hulshof *et al.*, 2003).

[†] Based on consumption data from the DNFC-3 (1997-1998) (Hulshof *et al.*, 2004; Ocké *et al.*, 2004); using DNFC-3, men 18-30 yr had an MSFL of 5.4 µg/100kcal and women 18-30 yr had an MSFL of 8.1 µg/100kcal.

* Additional calculation with exactly the same results as for PFF_n = 0.15 in combination with low scenario of dietary supplement intake (i.e. 5 µg).

over the age groups. For adults, men generally had lower MSFLs than women due to a higher energy intake. Based on the most sensitive age group (i.e., children 1–6 yr) the MSFL is 0 $\mu\text{g}/100$ kcal. For the most sensitive adult group (i.e., men 18–30 yr) the MSFL is 67–71 $\mu\text{g}/100$ kcal. Our calculated MSFL for the most sensitive group is lower for folic acid than the acceptable level of addition of Rasmussen *et al.*, 23 $\mu\text{g}/100$ kcal for the most sensitive group (1–3 yr), while we calculated 0 $\mu\text{g}/100$ kcal for children 1–6 yr old. This difference is mainly caused by a lower estimation of the SI by Rasmussen *et al.*, which was based on Danish legislation. In our calculations, the current intakes from dietary supplements were estimated based on the amount of folic acid available in dietary supplements on the Dutch market.

Vitamin A

Part of the vitamin A is consumed as provitamin A (for instance, carotenoids). However, the UL is defined for the intake of vitamin A as pure retinol and retinyl esters only because it is thought that the intake of provitamin A will not significantly contribute to the toxicity of high intakes of vitamin A (SCF/NDA, 2006). When we use the term 'vitamin A', we refer to pure retinol and retinyl esters. Due to the risk of osteoporosis, the UL for postmenopausal women is much lower than that for other women (SCF/NDA, 2006). In our study population, the distinction between premenopausal and postmenopausal women could not be made exactly; therefore, it was assumed that women older than 50 yr are representative for the group of postmenopausal women.

When the food consumption surveys were carried out, vitamin A addition was only allowed for margarine and low-fat margarine as a substitute for butter. This substitution will continue in The Netherlands, and therefore the fortification of (low-fat) margarine with vitamin A was included in the calculation of the CI_{95} . The SI was estimated to be 800 μg vitamin A/day for children and adolescents and 1,200 μg vitamin A/day for adults. The habitual dietary vitamin A intake varied from 1,055 $\mu\text{g}/\text{day}$ to 2,363 $\mu\text{g}/\text{day}$. For children, the age group 4–6 yr had the greatest vitamin A intake (1,553 $\mu\text{g}/\text{day}$). Men had a larger intake than women. The vitamin A intake of premenopausal and postmenopausal women (i.e., older than 50 yr) was comparable (Table 6.2). Filling in these factors in the formula (Box 6.1) resulted in a MSFL for vitamin A of 0 μg vitamin A/100 kcal for children 1–10 yr old, men and post-menopausal women, 154 μg vitamin A/100 kcal for women 19–30 yr old and for older children and adolescents, the MSFL is 10–70 μg vitamin A/day. In conclusion, the MSFL for vitamin A will be 0 μg vitamin A/100 kcal on the basis of the most sensitive groups (i.e., children 1–10 yr, men 18 yr old or more, and postmenopausal women). Our results for vitamin A were the same as Rasmussen *et al.*'s, i.e., 0 μg vitamin A/100 kcal.

Vitamin D

At the time when the DNFCs-3 and the DNFCs-2003 were carried out, addition of vitamin D was only allowed for margarine and low-fat margarine as a substitute for butter. Because this substitution is expected to continue in The Netherlands, this fortification practice was included in the calculation of the CI_{95} . The 95th percentile of habitual dietary vitamin D intake varied from 4.4 $\mu\text{g}/\text{day}$ to 12.2 $\mu\text{g}/\text{day}$ (CI_{95}). Vitamin D intake increased with age for children, although children 1-3 yr old had a slightly greater intake than children 4-10 yr old. For men, the 95th percentile of habitual vitamin D intake lies between 6.5 $\mu\text{g}/\text{day}$ and 12.2 $\mu\text{g}/\text{day}$ and for women, between 5.2 $\mu\text{g}/\text{day}$ and 8.6 $\mu\text{g}/\text{day}$ (Table 6.3). The SI was estimated to be 10 μg vitamin D/day for children, adolescents, and adults.

Entering these factors into the formula (Box 6.1) resulted in a MSFL for vitamin D of 3.0 $\mu\text{g}/100$ kcal for children 4-10 yr old to 9.0 $\mu\text{g}/100$ kcal for women 19-30 yr old. The MSFL increased with age for children, although children 4-10 yr old had a slightly lower MSFL than children 1-3 yr old. Due to a smaller habitual energy and vitamin D intake, the MSFL for women is greater than that for men. In conclusion, the MSFL of vitamin D is 3.0 $\mu\text{g}/100$ kcal based on the most sensitive group (i.e., children 4-10 yr). For the most sensitive adult group (men 51-60 yr), the MSFL is 5.6 $\mu\text{g}/100$ kcal. Our MSFL for vitamin D (3.0 $\mu\text{g}/100$ kcal for children 4-10 yr old) is greater than Rasmussen *et al.*'s acceptable level of addition: 1 $\mu\text{g}/100$ kcal for children 7-10 yr old. This is mainly due to the difference in PFF_n . Rasmussen *et al.* used a more strict PFF_n of 25% whereas we used a PFF_n of 15%.

Risk-management: setting AFLs for general exemption

After the risk was assessed, a risk manager considered all the important issues and decided what maximum level of fortification will be allowed and included in a general exemption. In The Netherlands, proposed changes and additions to the Dutch Commodity Act are discussed with stakeholders (e.g., organizations of trade and industry, consumers organizations, authorities) in a Regular Consultation on the Commodity Act. Representatives of individual companies cannot participate in the Regular Consultation on the Commodity Act.

Several consultations regarding the results (Tables 6.1-6.3) of the risk assessment for fortification with folic acid, vitamin A, and vitamin D resulted in a general exemption for folic acid of 100 $\mu\text{g}/100$ kcal and for vitamin D of 4.5 $\mu\text{g}/100$ kcal. No general exemption was given for vitamin A. A main general consideration is that this national policy will be temporary, as European legislation is expected to come into effect within a few years (Directorate E, 2006).

Folic acid

The UL of folic acid for adults is based on the risk of masking vitamin B₁₂ deficiency, for children an UL is extrapolated from this adult value based on bodyweight. Because of an ongoing discussion about the value of the UL for children extrapolated from the UL for adults, the risk manager decided to focus on the results of the risk assessment for adults only. It was thought that such an extrapolation would be conservative because the risk of vitamin B₁₂ deficiency for children was thought to be low. Furthermore, at that time, exemptions had been requested for only a few product types and some specific brands. Therefore, the risk manager expected that the chance of children consuming all available folic-acid-fortified products was small. In discussions with the stakeholders, which considered the temporary character of this national policy and the number of requests for exemption, the PFF_n of 15% was judged to be rather conservative. Using the dietary intake at the 95th percentile of the distribution (CI₉₅) and the 90-95th percentile of intake from dietary supplements (SI) was also judged to be quite conservative. Therefore, two additional calculations were done, one with a PFF_n of 10% and the other with a low intake scenario of dietary supplements (i.e., 400 µg for adults). Both scenarios resulted in a maximum level for fortification in the most sensitive adult group (men aged 18-30 yr) of 100-106 µg/100 kcal (Table 6.1). For practical reasons, the risk manager rounded this value off to an AFL of 100 µg folic acid/100 kcal. Because of this relatively liberal AFL and the fact that the value was based on the MLF of adults, it was decided to monitor the intake of folic acid from fortified foods. If the results of the monitoring show that the long-term intake exceeds the UL in specific population groups, appropriate measures can be taken.

Vitamin D

For vitamin D the derivation of the UL for children is based on critical effects observed in children, whereas for folic acid UL-values for children were established by extrapolation only (SCF/NDA, 2006). Therefore, the maximum fortification levels for children from the risk assessment were considered. As for folic acid, this will be a temporary policy for only a couple of years and it was thought that the PFF_n of 15% and the high-intake scenario from dietary supplements are rather conservative estimates. In addition, only one request for exemption was received at that time for vitamin D fortification, and the risk manager did not expect more exemption requests. Thus, similar additional calculations with a PFF_n of 10% or a scenario of smaller intakes from dietary supplements (i.e., 5 µg) were done for vitamin D. The calculations resulted in a MSFL of 4.5 µg vitamin D/100 kcal for the most sensitive group (children aged 4-10 yr) (Table 6.3). The risk manager adopted this MSFL and set the AFL at 4.5 µg/100 kcal. Again, the risk manager desires monitoring of vitamin D and energy intake for insight into current intakes and proportions of energy intake fortified. If long-term intakes exceed the ULs, appropriate measures can be taken.

Vitamin A

In contrast to the liberalization for folic acid and vitamin D, the risk manager did not liberalize the results from the risk assessments for vitamin A. To the opinion of the risk manager, exceeding the UL of vitamin A has more serious consequences for public health than exceeding the ULs for folic acid and vitamin D. In addition, the 95th percentile of habitual dietary vitamin A intake of several age groups already exceeded the UL, even without considering the vitamin A intake from dietary supplements. Furthermore, at this time no request for exemption has been received, although one product for which an exemption for folic acid was requested also contained vitamin A. So the AFL was set at 0 µg/100 kcal. The stakeholders in the consultation agreed with this decision.

Exception for low-energy products

An exception was made for light variants of products (low-energy products). According to the model, products low in energy may be fortified with smaller amounts of the micronutrient than the more energy-dense counterparts. In view of the obesity trend and the healthy image of light products, this was considered undesirable. Therefore, light products may be fortified with amounts similar to the amounts approved for their more energy-dense counterparts.

Discussion

We presented a model for the derivation of maximum amounts of micronutrient fortification in The Netherlands. A novelty of this publication is that besides the theoretical model, the practical applicability for The Netherlands is shown including both the risk-assessment and risk-management aspects. The model has already contributed to new Dutch policy-making, as the allowed level for fortification for folic acid and vitamin D are applied as a general exemption in 2007 (Anonymous, 2007).

Applicability of the model

Although the model can already be applied with the available data in The Netherlands, it is recommended to improve the monitoring of consumption of fortified foods and dietary supplements within The Netherlands. Such data are very useful to check the model parameters and to keep them up-to date. If necessary, AFLs can be adjusted. It is recommended to monitor the intake of fortified foods and dietary supplements as part of the national food consumption survey (Rompelberg *et al.*, 2006; WHO, 2006). Food frequency questionnaires specifically for fortified functional foods and dietary supplements in a representative sample of the population would be a useful tool.

In addition composition databases of fortified foods and dietary supplements are recommended (Rompelberg *et al.*, 2006).

Risk management

The discussions about the risk-assessment results with the different stakeholders worked well for the risk manager. This resulted in broad insight into the various points of view of the stakeholders. Ultimately the risk manager took the final decision, and in all these cases the stakeholders agreed with the final outcome. The risk assessment was based on the precautionary principle. However, with a view to the fact that this will be a temporary policy, the outcome of the risk assessment was judged to be rather conservative for folic acid and vitamin D. In contrast, the market may change, the date the European legislation will come into effect can be later than expected, and people may consume more fortified foods than estimated. Therefore, monitoring the intake of micronutrients from fortified foods is a very important tool for warranting the safety of the population. If monitoring shows that some groups within the population have habitual intakes that exceed the ULs, adaptations should be made. Especially children may be vulnerable. A food consumption survey is currently being conducted among children in The Netherlands. These data will provide insight into the micronutrient intake from natural foods, fortified foods and dietary supplements during 2005/2006.

Additional considerations

Some factors that were not taken into account in MSFL risk assessment are worth considering, and they can be implemented in the model or taken into account in the risk management if necessary. First, we made an exception for the fortification level of 'light' products in our risk management. This exception was not considered in the calculation and can therefore theoretically lead to micronutrient intakes that are too large even if the energy intakes are not exceptionally high. Monitoring the use of fortified 'light' products will be necessary to avoid frequent users exceeding the UL. Second, some products are intended for a specific population or target group only. If there is little risk that the product will be used by non-target groups, the risk manager can make an exception to the model. Instead of using the calculated MSFL for the most vulnerable group, the MSFL for the specific target group can be used as a maximum for this specific product. Again, monitoring of the use of these products is important, and mentioning the target groups, as well as non-target groups, on the product package might be considered.

The vitamin levels in products may decrease over time. Therefore, it is possible that the amount of vitamin added by manufacturers is greater than the amount declared

on the packages (Quinlivan *et al.*, 2003). To be able to protect all consumers and avoid underestimation of the intake, this so-called overage should be integrated into the MSFL in the model. Rasmussen *et al.* also noted this problem. In Denmark the currently accepted practice is to add up to 150% of the declared amount. Our calculated MSFL includes overage.

International applicability of the risk-assessment model

Currently, the European Commission is preparing to set maximum and minimum amounts for vitamins and minerals in both foods and dietary supplements (Directorate E, 2006). The simultaneously setting of both the maximum levels for dietary supplements and for foodstuffs can result in a well based division of micronutrients over dietary supplements and fortified foods. Once the choice has been made which micronutrient is allowed to be added to dietary supplements and/or fortified foods, models like the one presented can be helpful to set the MSFL and AFL for micronutrients in food products.

The applicability of the model for this purpose depends on the availability of the input data. When calculating MSFLs valid for Europe as a whole, the availability of European data is necessary. However, data from a food consumption survey that cover all Member States of the European Union representatively are not available. Such data are not even available for all Member States individually. Furthermore, consumption data available in various Member States are often collected with different methods, in a different time frame, and for different specific population groups and the fraction of energy intake that can be fortified may differ greatly from country to country because of the various traditional diets. This makes it difficult to estimate the total habitual intake for each micronutrient and energy type at a European level.

To overcome these problems, MSFLs in Europe can be set by using the available country-specific calculations and to select the most sensitive country (i.e. the country with the lowest MSFL). The maximum safe level for fortification for this country can then be applied in all Member States.

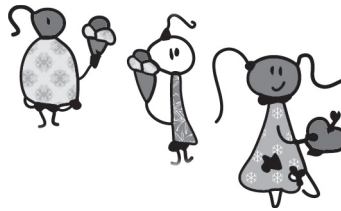
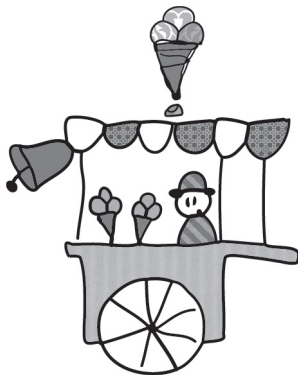
Conclusion

As this Chapter illustrates, our model for risk assessment can be used in The Netherlands to help risk managers to set maximum levels for safe addition of vitamins to foods. This has resulted in two general exemptions, one for folic acid at 100 µg/100 kcal and one for vitamin D at 4.5 µg/100 kcal. The model is flexible and can be adapted to new insights. For example, aspects concerning overage and 'light' products can be included with minor changes in the formula. Monitoring of the total micronutrient intake after

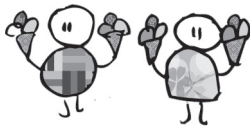
applying a general exemption, as well as monitoring of the fortified fraction of the energy intake and the effect of the exception for light products, is recommended for evaluating the model parameters and AFLs and for making adjustments when needed.

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7



Evaluation of the Dutch general exemption level for voluntary fortification with folic acid

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Abstract

Introduction: Fortification with folic acid was prohibited in The Netherlands. Since 2007, a general exemption is given to fortify with folic acid up until a maximum level of 100 µg/100 kcal. This maximum level was based on a calculation model and data of adults only. The model requires parameters on intake (diet, supplements, energy) and on the proportion of energy that may be fortified. This study aimed to evaluate the model parameters considering the changing fortification market. In addition, the risk of young children exceeding the UL for folic acid was studied.

Methods: Folic acid fortified foods present on the Dutch market were identified in product databases and by a supermarket inventory. Together with data of the Dutch National Consumption Survey-Young Children (2005/2006) these inventory results were used to re-estimate the model parameters. Habitual folic acid intake of young children was estimated and compared to the UL for several realistic fortification scenarios.

Results: Folic acid fortified foods were identified in seven different food groups. In up to 10% of the population, the proportion of energy intake of folic acid fortified foods exceeded 10% - the original model parameter. The folic acid intake from food supplements was about 100 µg/day, which is lower than the intake assumed as the original model parameter (300 µg). In the scenarios representing the current market situation, a small proportion (<5%) of the children exceeded the UL.

Conclusion: The maximum fortification level of 100 µg/100 kcal is sufficiently protective for children in the current market situation. In the precautionary model to estimate the maximum fortification levels subjects with high intakes of folic acid from food and supplements and high energy intakes are protected from too high folic acid intakes. Combinations of high intakes is low in this population. The maximum levels should be monitored and revised with increasing fortification and supplementation practices.

Introduction

Fortification of foods with micronutrients should be safe for the whole population; hence, unacceptable high intakes from all sources (i.e. basic foods, fortified foods, and food supplements) should be prevented. Due to a small range between the recommended daily intakes and tolerable upper intake levels (ULs) in combination with a lack of proof of nutritional need, fortification (other than substitution or restoration) with vitamin A, vitamin D, folic acid, selenium, copper, and zinc is prohibited in The Netherlands (Anonymous, 1996). In 2004, the European Court of Justice decided that this prohibition of fortification contradicted the fundamental principle of 'free movement of goods' in the Treaty Establishing the European Community (Anonymous, 2005a). Food fortification with these micronutrients may only be prohibited if there is harm to public health. This resulted in a more flexible handling of requests of exemption from the Dutch Commodity Act in order to fortify (Anonymous, 2005b).

In 2007, a general exemption was granted for food fortification with folic acid or vitamin D up until a certain maximum fortification level (Anonymous, 2007). For folic acid the maximum allowed fortification level is 100 µg/100 kcal. In case of light-food products (low-energy products) the same fortification level is approved as for their energy dense counterparts. In The Netherlands, a model was used to calculate the maximum safe fortification levels (MSFL) from which the risk manager derived the maximum allowed fortification level (AFL) (Chapter 6). Several input parameters are required for this model: micronutrient intake of diet and dietary supplements, energy intake, and the proportion of the energy intake that can and will be fortified. The intake parameters were estimated based on data of the Dutch National Food Consumption Surveys. However, intake data of dietary supplements were scarce and assumptions had to be made. In addition, the proportion of energy that can and will be fortified was a best educated guess based on knowledge of the Dutch dietary pattern and expected fortification practices. In deriving the AFL of folic acid from the MSFL, data on children were not taken into account because the risk-manager considered that exceeding the UL for children (extrapolated from adults based on masking of vitamin B₁₂-deficiency) is a low risk (Chapter 6).

To warrant safety of the Dutch population, the general exemption has to be evaluated regularly. The AFL might need revision when changes in the model input parameters occur, for instance due to changing dietary pattern or changes in supply of fortified foods. The aim of the present study was to evaluate the Dutch general exemption level for voluntary folic acid fortification two years after it became into force. For the evaluation, an inventory of the current market situation of folic acid fortified foods was made. The model parameters and MSFLs were re-estimated and evaluated using data of the Dutch Food Consumption Survey - Young Children 2005/2006 (DNFCS-

young children) (Ocké *et al.*, 2008) and the results of the market inventory. This article concludes with considerations whether the currently legal maximum allowed fortification levels seems to warrant safe intakes in Dutch young children.

Methods

Inventory of folic acid fortified foods

Folic acid fortified foods available on the Dutch market in early 2009 (Feb–April) were searched for. In The Netherlands, there is no complete central registration of fortified foods available on or introduced to the consumer market. Therefore, the inventory on folic acid fortified foods started by screening three food databases: 1) the Dutch food composition database (NEVO, 2006) extended with additional food product data for recent and ongoing Dutch National Food Consumption Surveys, 2) Innova database (commercial food database) (www.innovadatabase.com), and 3) Compendium dietary products and dietary supplements (www.dieetconsult.nl). Unfortunately, the databases were incomplete, in particular, foods recently launched, foods recently reformulated, and home brand products were missing. To complete the inventory as much as possible, a supplementary supermarket inventory was conducted (March–April 2009). This supermarket inventory was limited to the food groups containing folic acid fortified foods identified in the database search. Eight supermarket chains with the highest Dutch market shares (www.distrifood.nl) were visited, as well as two supermarkets with relatively high contribution of foods in the DNFCs–young children and two supermarkets with a low market share.

Of all folic acid fortified foods, data were collected on product name, brand name, folic acid content, and energy content. Missing data were completed by searching for information on manufacturer websites or contact with manufacturers. All data were collected based on information provided on the label or by manufacturers; no chemical food analyses were conducted. The folic acid content of the fortified foods was compared with the currently permitted maximum levels of the 2007 general exemption (Anonymous, 2007).

Evaluation of model parameters

All model input parameters were re-estimated using data of DNFCs–young children (Ocké *et al.*, 2008) and the results of the inventory for folic acid fortified foods available in The Netherlands. The model input parameters are: the 95th percentile (P95) of habitual energy intake (EI_{95}), the P95 of the habitual folic acid intake from the background

diet (CI_{95}), the P95 of folic acid intake from dietary supplements, and the proportion of the energy intake that can and will be fortified (PFF_n). All analyses were performed with SAS 9.2 (SAS Institute Inc., Cary, NC, USA) unless otherwise stated.

P95 of habitual energy intake (EI_{95})

Data of DNFCs-young children 2005–2006 among 1279 children aged 2–6 yr old (Ocké *et al.*, 2008) were used. Consumption data were collected by means of two food records on independent days (8–13 days in between). The food records were filled in pre-structured diaries by the care taker of the children. To calculate energy intake, data on food consumption was linked with data on food composition (NEVO, 2006). Habitual energy intake was estimated by correcting the intake data for within-person variation using the ISU-method (IML-SIDE) (Nusser *et al.*, 1996). In order to make the sample representative to the Dutch population of young children, data were weighted for socio-demographic factors and season.

P95 of habitual folic acid intake from background diet (CI_{95})

The UL of folic acid is based on the intake of synthetic folic acid only and not on the intake of natural folate (SCF/NDA, 2006). As we were interested in safety and made comparisons with the UL, only the intake of synthetic folic acid should be taken into account. Since synthetic folic acid is only consumed via dietary supplements or fortified foods, the intake of the background diet (i.e. excluding fortification) is zero.

P95 of folic acid intake from food supplements (SI)

The intake of folic acid from dietary supplements was calculated using data from DNFCs-young children (Ocké *et al.*, 2008), briefly described above. In the two food diaries, the use of dietary supplements on that day was also recorded. To calculate folic acid intake from dietary supplements, data on supplement intake was linked with data on dietary supplement composition (Buurma-Rethans *et al.*, 2008). Mean intake over two observed days was calculated and P95 was derived. Due to the infrequent use of dietary supplements and lack of FFQ data no habitual intake could be estimated.

Proportion of energy intake that can and will be fortified (PFF_n)

At the time DNFCs-young children (2005/2006) was conducted, the general exemption for folic acid fortification was not in force. Based on results of the product inventory, four scenarios of food fortification were defined. The scenarios were applied to the consumption data of DNFCs-young children and the proportion of the energy intake of

folic acid fortified foods was calculated on each observed day by dividing the amount of energy consumed from all folic acid fortified foods by the total amount of energy consumed. This proportion was corrected for within-person variation using ISU-method (IML-SIDE and C-SIDE) (Nusser *et al.*, 1996) and weighted for socio-economic factors and seasons.

In the *first scenario* the food composition (i.e. folic acid level) of all foods currently fortified that were consumed during DNFCs-young children was replaced with the current (2009) folic acid level. Foods currently fortified but not consumed in DNFCs-young children were not taken into account. Foods fortified during DNFCs-young children and currently not anymore were regarded as not fortified. Current fortification levels were used for foods fortified during DNFCs-young children and currently fortified with a different level.

The *second scenario* is an expansion of the first scenario. Foods consumed in DNFCs-young children belonging to the same food group and brand as the fortified foods found in the inventory were considered to be fortified. The highest currently legal fortification level found within the same food group and brand was applied.

The *third scenario* is a further expansion of the first and second scenario. In this scenario foods also belonging to the same food group and of other brands consumed in DNFCs-young children were considered to be fortified. Again, the highest currently legal fortification level found in the same food group and brand was applied. One exception was made: bread, which is a staple food in The Netherlands was not taken into account except the specific brand currently applying fortification, as this will have very high influence on the total intake.

The most expanded scenario is the *fourth scenario* in which not only foods belonging to the same food group (all brands), but also foods belonging to similar food groups (Table 7.1) (all brands) were assumed to be fortified. Similar to the above, the highest currently legal fortification level found in the same food group and brand was applied.

Evaluation of the maximum safe fortification level (MSFL)

The MSFL is calculated as follows: $MSFL = (UL - (CI_{95} + SI)) / ((EI_{95} * PFF_n) / 100)$. Using the re-estimated model input parameters (see above) the MSFL was also re-estimated. The re-estimated MSFL was compared with the 2007 MSFL.

Table 7.1 Overview of folic acid fortified foods on the Dutch market (first half 2009), number of foods (number of brands) within different food groups and specification of type of foods that are fortified

Food group	No folic acid fortified foods (no brands)	Type of food	Scenario 4: included similar food groups
Bread	4 (2)	Bread, cracottes	Cream crackers, knackerbröt
Cereal products	62 (15)	Breakfast cereals (cornflakes, muesli), baby porridge	Crueli
Dairy products	6 (2)	Yoghurt drink, instant chocolate/fruit-milk drink	Dairy-fruit drink
Drinks	20 (8)	Fruit soft drink, fruit drink, sports drink, sweetened water	Fruit drink (>2 fruits), fruit lemonade
Fats and oils	19 (8)	(Low-fat) margarine	Regular margarine
Pastry and cookies	26 (7)	Cereal bars, cereal snacks, nutritional biscuits	
Soy products	2 (1)	Drink	

Folic acid intake of young children and exceeding the UL

In order to get insight in the risk of potentially too high folic acid intakes due to voluntary fortification for each scenario and for the reference situation (i.e. DNFCs-young children) the habitual folic acid intake was estimated and compared to the UL for children as set by EFSA (SCF/NDA, 2006) using the cut-point method (IOM, 2000b).

Results

Inventory of folic acid fortified foods

In the product inventory, 139 folic acid fortified foods of 43 different brands were found. These foods were divided into 7 food groups: bread, cereal products, dairy products, drinks, fats and oils, pastry and cookies, and soy products (Table 7.1). The level of folic acid declared on the label varied from 15–500 µg/100 g (or ml); this was equivalent to 3–267 µg/100 kcal. Correction of the declared folic acid amount for natural folate content showed a small decrease in folic acid content to 1–235 µg/100 kcal. Most foods with a higher folic acid content than the legal maximum amount of 100 µg/100 kcal could be considered as light food products ($n=22$). The folic acid contents of those foods were at or below the legal maximum amount for their energy-dense counterparts. The remaining food ($n=1$) with a too high folic acid level belonged to the food group 'drinks'.

Table 7.2 Comparison of the model parameters required to calculate the maximum safe fortification level* of folic acid for Dutch young children (Chapter 6); 2007 vs. 2009

Year	Age category	UL (µg/day)	CI ₉₅ (µg/day)	SI ₉₅ (µg/day)	EI ₉₅ (kcal/day)	MSFL _(PFF_n=0.15) (µg/100 kcal)	MSFL _(PFF_n=0.10) (µg/100 kcal)	AFL (µg/100 kcal)
Original model	2007 [†]	200	0	300	1,890	<0	<0	100
	2007 [†]	300	0	300	1,995	0	0	100
Re-estimation	2009	200	0	100	1,779	56	37	
	2009	300	0	150	1,779	28	19	
	2009	300	0	100	1,941	103	69	
	2009	300	0	150	1,941	77	52	

* $MSFL = (UL - CI_{95} - SI_{95}) / ((EI_{95} * PFF_n) / 100)$
[†] (Chapter 6)

UL: tolerable upper intake level; CI₉₅: 95th percentile of habitual intake of background diet; SI₉₅: 95th percentile of intake of food supplements, EI₉₅: 95th percentile of habitual energy intake, MSFL: maximum safe fortification level, PFF_n: proportion of energy intake that may and will be fortified, AFL: allowed fortification level according to Dutch legislation (Chapter 6).

Evaluation of model parameters

In Table 7.2 both the original input parameters of the model as used to set the MSFL on which the current AFL are based (Chapter 6) and the input parameters based on the recent DNFCS–young children and the inventory are presented (i.e. re-estimation). It should be noted that differences are not only due to, for instance time trends or different consumption patterns, but also due to differences in survey methodologies and different age categories (1–3 yr for the original intake parameters, 2–3 yr for the re-estimated parameters).

The P95 of habitual energy intake is about 50–110 kcal lower in DNFCS–young children (2005/2006) than in the previously used data of DNFCS-3 (1997/1998).

In DNFCS–young children, data on dietary supplement use was available for each recorded day. About 20% of the children used folic acid containing dietary supplements on at least one of the record days. The P95 of the folic acid intake distribution from dietary supplements was 100 µg/day (2-day mean). This is one-third of the best educated estimation used as original input parameter for the MSFL in 2007 (Chapter 6). For users of folic acid containing dietary supplements, the 95th percentile of the intake distribution was 300 µg/day (2-day mean) and intakes up to 800 µg/day were recorded in DNFCS–young children. Our results show that although intakes of 300 µg folic acid per day or higher are realistic among users of dietary supplements for the 95th percentile of the intake distribution of the whole population, this is an overestimation. For this input parameter 100 µg/day or when taking into account some uncertainty among this value 150 µg/day is more realistic.

The third input parameter is the estimation of the proportion of the energy intake that can and will be fortified (PFF_n). The original PFF_n was estimated at 10% (best educated guess). For each of the four scenarios of folic acid fortification, the population distribution of this proportion was calculated (Figure 7.1). In the scenarios most representative for the current situation (1 and 2), up to 10% of the children aged 2–3 yr and up to 5% of the children 4–6 yr had a habitual proportion of the energy intake coming from folic acid fortified foods that was higher than 10%. In the scenarios realistic for the current Dutch situation, a higher PFF_n of 15% was exceeded by up to 3% of the young children (Figure 7.1). In the more extreme scenarios (3 and 4), illustrating an ongoing trend of folic acid fortification in similar food groups, the percentage of the children with more than 10% of the energy intake coming from folic acid fortified foods increased to 53–100% (Figure 7.1). Our results show that a PFF_n of 10% seems an underestimation, especially when taking into account the potential ongoing increase in folic acid fortified foods entering the Dutch market, a proportion of 15% seems more realistic.

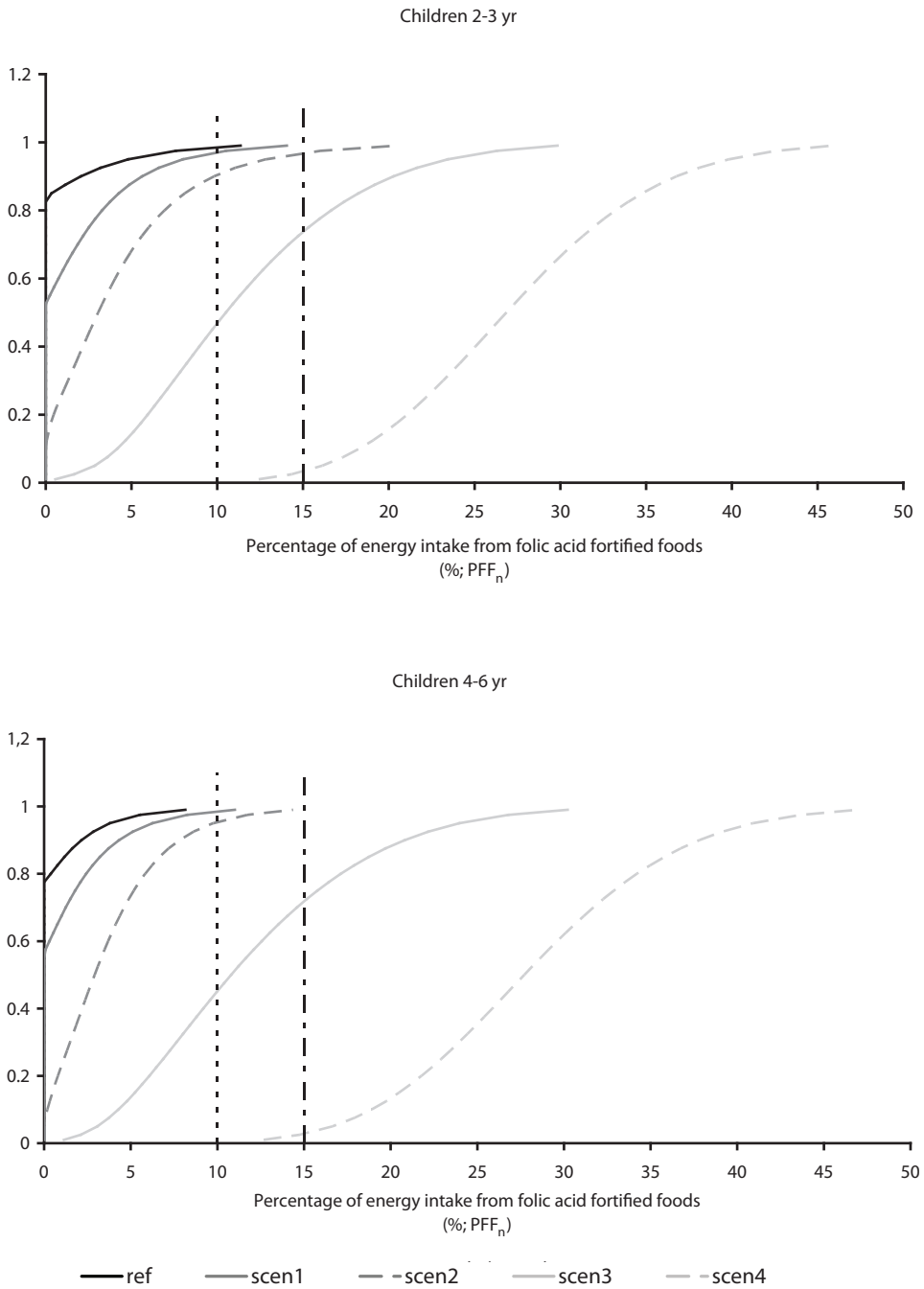


Figure 7.1 Distribution of habitual proportion of the energy intake of folic acid fortified foods among Dutch young children (2-3 and 4-6 yr) for four different fortification scenarios.

Evaluation of calculated maximum safe fortification levels

The maximum safe fortification levels were re-estimated using both 100 and 150 µg/day as folic acid intake from dietary supplements and a PFF_n of both 10 and 15% (Table 7.2). For children 2-3 yr old, the newly calculated maximum safe fortification levels ranged from 19-56 µg/100 kcal and for children 4-6 yr old from 52-103 µg/100 kcal, depending on the assumed model parameters for intake of dietary supplements and PFF_n (Table 7.2). The re-calculated MSFLs are higher than those originally calculated (i.e. ≤0 µg/100 kcal). The current AFL for folic acid of 100 µg/100 kcal is higher than the re-estimated maximum levels for children aged 2-3 yr old. In the most liberal situation (i.e. PFF_n = 15% and intake from dietary supplements = 100 µg folic acid/day) the re-estimated maximum level for children aged 4-6 yr old is similar to the current AFL.

Current and potential folic acid intakes and exceeding of the UL

In the scenarios realistic for the current situation (i.e. 1 and 2) the habitual folic acid intake from *foods* of young children (2-6 yr) did not exceed the UL (Table 7.3). In the more extreme fortification scenarios (i.e. 3 and 4), up to 10% of the children aged 2-3 yr and up to 1% of the children aged 4-6 yr did have habitual folic acid intakes of *foods* above the UL (Table 7.3). Considering the intake of both foods and dietary supplements, the proportion of children exceeding the UL increased in all scenarios. In general, the proportions exceeding the UL were higher in the age category 2-3 yr than 4-6 yr, due to the lower UL. In the scenarios representing the present situation (i.e. 1 and 2) up to 5% of the children had folic acid intakes above the UL. In the more extreme scenarios (i.e. 3 and 4), up to 20% had folic acid intakes above the UL (Table 7.3).

Discussion

We presented an evaluation of the 2007 Dutch general exemption level for voluntary food fortification with folic acid of maximally 100 µg/100 kcal focusing on young children. These maximum levels were estimated using a calculation model and several input parameters to which purpose several assumptions had to be made (Chapter 6). Our study showed that the model assumptions made for the intake of folic acid from dietary supplements are overestimated and that the prediction of the proportion of the energy intake of folic acid fortified foods is too liberal for an increasing market. Re-estimation of the maximum safe fortification level based on data of young children resulted in a higher maximum level compared to the results from 2007. However, the re-estimated maximum levels remain below the currently legal maximum of 100 µg/100 kcal for

Table 7.3 Habitual folic acid intake ($\mu\text{g}/\text{day}$; median and P95) for four different folic acid fortification scenarios and percentage exceeding the UL, Dutch young children 2-6 yr

Age	Source	Reference			Scenario 1			Scenario 2			Scenario 3			Scenario 4		
		Median ($\mu\text{g}/\text{d}$)	P95 ($\mu\text{g}/\text{d}$)	%>UL	Median ($\mu\text{g}/\text{d}$)	P95 ($\mu\text{g}/\text{d}$)	%>UL	Median ($\mu\text{g}/\text{d}$)	P95 ($\mu\text{g}/\text{d}$)	%>UL	Median ($\mu\text{g}/\text{d}$)	P95 ($\mu\text{g}/\text{d}$)	%>UL	Median ($\mu\text{g}/\text{d}$)	P95 ($\mu\text{g}/\text{d}$)	%>UL
2-3 yr	Food	0	20	0	0	43	0	25	105	0	77	180	3	111	229	10
	Food & supplements	0	117	2	6	119	2	36	184	4	91	253	11	129	297	20
4-6 yr	Food	0	25	0	0	48	0	32	93	0	96	199	0	139	252	1
	Food & supplements	0	104	<1	8	119	<1	44	154	<1	113	254	2	154	306	6

children aged 2-3 yr old. For the current Dutch situation, folic acid intake from foods only did not result in too high intakes among young children. However with combined intake from foods and dietary supplements up to 5% of the young children did have habitual folic acid intake above the UL and this was mainly due to the intake of dietary supplements with dosages higher than the UL (data not shown). It is advised to better regulate the amounts of folic acid in dietary supplements for young children. Currently, EU legislation on this topic is under discussion (EC 1925/2006 and 2002/46/EC). Labelling that specific dietary supplements are not suitable due to high dosages will also be helpful. In our inventory one food product had a folic acid content higher than the legal maximum. Although this did not result in too high intakes immediately, it is recommended to enforce the maximum fortification level well. When more and more foods with higher folic acid levels than the maximum safe level will enter the food market, the risk of folic acid intakes above the UL will increase.

Several other models have been published calculating maximum safe fortification levels (Domke *et al.*, 2004a; b; Flynn *et al.*, 2003; Rasmussen *et al.*, 2005). However, to our knowledge, this is the first study evaluating the model and the assumptions few years after the maximum safe fortification levels were adopted in national legislation. The Dutch calculation model is designed to estimate a maximum safe fortification level that will protect virtually the whole population from too high intakes (i.e. precautionary principle). To do this, high population intakes (95th percentile) of the micronutrient from food and dietary supplements and high energy intake are combined. Only a small part of the population will have the combination of all high intakes and therefore be at risk of too high intake. On the other hand, there might also be a small part of the population with higher values for one or more of the model input parameters than applied. To some extent this will not result immediately in the risk of too high intakes. This is also what our study shows because even with a currently legal fortification level which is higher than the calculated maximum level for young children large part of the children have habitual folic acid intakes below their UL.

The current calculation models do not take into account correlations between, for instance, intake of a micronutrient from dietary supplements and from the diet or energy intake and micronutrient intake of each source. In case of strong correlations, they could be considered in modeling the maximum safe fortification level. In our study, correlations between folic acid intake of dietary supplements and energy intake were not found (data not shown). In the scenarios with more folic acid fortified foods (scenario 2-4) there was an increasing statistically significant positive correlation between the energy intake and folic acid intake of fortified foods (data not shown). This is logical as many food groups currently applying folic acid fortification are main energy suppliers (e.g. breakfast cereals, fats and oils).

The original model made use of DNFCS-3 data conducted in 1997–1998 (Chapter 6). The methodology of this survey is different from the DNFCS-young children conducted in 2005/2006 and differences in habitual energy intake between the surveys can partly be explained by these methodological differences. It cannot be stated that the habitual energy intake among young children decreased from 1997–1998 to 2005–2006, but the values are in the same order of magnitude.

A limitation of our study is that the DNFCS-young children was conducted in 2005/2006, just before the new legislation on voluntary folic acid fortification came into force. Our inventory showed that several new folic acid fortified food products entered the market since 2006. To estimate the situation for 2009 and later, four fortification scenarios were designed representing the currently realistic situation and potential future situations proposing an increase in fortification in similar foods. Although the inventory may have resulted in an incomplete overview of the folic acid fortified foods on the Dutch market, we do think that we have identified all main food groups containing folic acid fortified foods. The results for the various scenarios should be interpreted as indicative outcomes.

A second limitation is that the amounts of folic acid were not analytically analyzed, but taken from the label information. So potential overage could not be taken into account. Several studies show that overages in folic acid fortification are common (Samaniego-Vaeslem *et al.*, 2010; Shakur *et al.*, 2009). This would implicate that the figures used in our study are an underestimation of the true folic acid dosages in fortified foods. The folic acid information on the label is the total of folate and folic acid rather than folic acid only. Therefore, it is impossible to estimate the real amounts of folic acid from the label information only. To correct for the natural folate, data from the Dutch food composition database (NEVO, 2006) was used to estimate the amounts of folic acid in the foods by subtracting the natural folate levels found in NEVO from the label information of the total of folate and folic acid. As there is only an UL for folic acid it is needed to differ between both forms, we would therefore recommend labeling folate and folic acid separately.

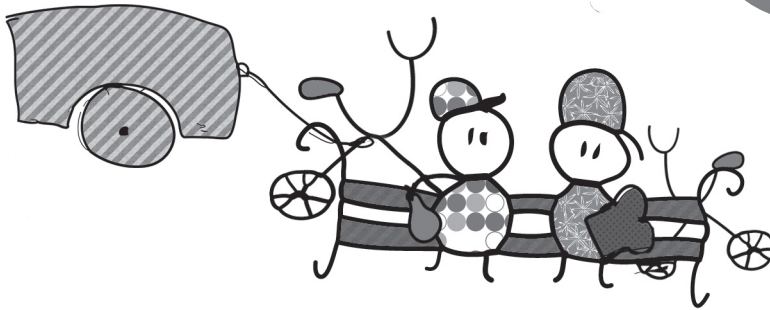
Another limitation is that our study focused on young children and did not take into account other age categories. However, the UL for children is lower than for adults and therefore young children are the most vulnerable group regarding the risk of exceeding the UL. The UL for folic acid is under debate. For children, the UL is extrapolated from the UL for adults, which is based on masking the haematological picture of vitamin B₁₂-deficiency, mainly a problem of the elderly (SCF/NDA, 2006). When physicians are aware that not only the haematological picture has to be taken into consideration diagnosing vitamin B₁₂-deficiency, but also the actual measurement of vitamin B₁₂ status this risk will diminish. Other potential health effects might be

more relevant in setting the UL, but at present there is insufficient scientific data to set the UL for folic acid on other end points (Anonymous, 2010). As soon as it is possible to take other end points into account, the UL for folic acid should be revised, especially for children.

Within the EU legislation it is regulated what micronutrients (and in what chemical form) may be applied in food fortification and supplements, as well as the minimum and maximum levels that may be applied (EC 1925/2006 and 2002/46/EC). However, the actual maximum and minimum levels are still under discussion. Our model (Chapter 6) is accurate in setting a maximum level in foods protecting virtually the whole population given a certain intake of dietary supplements. By changing the 'given' intake of dietary supplements the maximum safe level in fortified foods will change. It is important to realize that it is a risk manager's decision how to divide the free space between the P95 of intake from the background diet (excluding voluntary fortification or supplementation) and the UL between dietary supplements and fortified foods (Verkaik-Kloosterman *et al.*, in press). Models similar to our model (Chapter 6) are also proposed to calculate the maximum amounts of micronutrients that may be applied in fortified foods and dietary supplements. Combining the maximum levels for fortification and dietary supplements calculated with different models should be done with caution, as there are differences in the proportions of the free space assigned to foods or dietary supplements (Dufour *et al.*, 2010). Further, it is a risk manager's choice how safe such calculation model should be, should it protect virtually the whole population or is some level of risk of too high intakes accepted?

This Chapter illustrates the importance of regular evaluation of maximum allowed fortification levels that are adopted in national policy. In setting the maximum safe fortification levels, modeling is needed based on input parameters with regard to food and dietary supplement consumption and predicted fortification practices. Fortification practices might develop differently than predicted. In addition, changes in dietary patterns might occur or better data might become available (like in our situation on intake of dietary supplements). Further, continued monitoring of the actual percentage of the population exceeding the UL is recommended.

8



General discussion

The general aim of this PhD-thesis is to improve, develop and apply statistical models to estimate micronutrient intake distributions, with particular emphasis on three identified issues. These issues are 1) how to estimate current habitual micronutrient intake when (detailed) data are lacking or data from different sources should be combined, 2) how to predict future intakes in order to support policy making, and 3) how to estimate a maximum safe fortification level per food item. This last chapter will focus on the methodological developments and starts with a summary of the main findings. Thereafter the findings, remaining issues and challenges, and the need for future improvements will be discussed in a wider perspective. Topics addressed are the requirement of scenario analyses in relation to policy making, issues relating to the estimation of habitual intake, and evaluation of dietary intake. This general discussion will finish off discussing the results in a public health perspective and presenting an overall conclusion.

Main findings

Three methodological improvements have been made: 1) the combination of the generally applied deterministic approach with probabilistic approaches to be able to take into account uncertainty and variability (Chapters 2-4), 2) the development of a new statistical model to estimate habitual total micronutrient intake aggregated from food and dietary supplements (Chapter 5), and 3) a model calculating maximum safe fortification levels per 100 kcal of a food for the Dutch situation (Chapters 6, 7).

In Chapters 2-4 the generally applied deterministic approach to calculate dietary micronutrient intakes was combined with a probabilistic approach. This combination could take into account uncertainty and variability e.g. in the cases of lacking data or the combination of data from different sources. The combined model was developed from a nutritional science point of view and had the deterministic approach as a basis. This meant the reported food consumption data of the study participants and consequently the data structure remained intact, e.g. the underlying correlations in food consumption like the combination of food products and consumed amounts. For the specific parts of total intake for which uncertainty and/or variability were important issues, a probabilistic approach was applied. For the other parts of total intake a deterministic approach was used. The effect of uncertainty, such as which consumers use a voluntary fortified food in future (Chapter 2), or discretionarily use (iodized) salt (Chapters 3, 4), was quantified by re-sampling a subpopulation as large as the proposed market share for a number of iterations (bootstrapping) and estimating total intake for each iteration. The variation in the population intake distributions between the iterations is a quantification of the uncertainty. With the combined deterministic and probabilistic approach it was possible to estimate the habitual intake distribution, including a quantification of some of the

uncertainty after proposed fortification or reformulation (folic acid: Chapter 2, iodine: Chapters 3, 4, and sodium/salt Chapter 4). Additionally, current habitual iodine intake was accurately estimated (Chapter 3). As far as we know, this method of combining deterministic and probabilistic approaches is a novelty. Combinations of probabilistic and deterministic approaches have been published in the field of food safety. Unlike our approach in which the population is re-sampled by bootstrapping, values from different distributions are combined for many iterations by Monte Carlo simulation to create one new virtual population (Arcella *et al.*, 2003; Rubingh *et al.*, 2003). Although it may be possible to take into account of some correlation (e.g. brand loyalty (Arcella *et al.*, 2003)), such modeling misses the opportunity to keep the whole complex data structure and all potential correlations, even the correlations one is not aware of.

Another important development was the improved statistical model to estimate habitual total micronutrient intake from both food and dietary supplements (Chapter 5). This three-part model takes into account differences in within- and between-person variances in intake from food and intake from dietary supplements as well as differences in intake from foods between users and non-users of dietary supplements are included in this 'first shrink then add' approach. Compared to existing more simple models ('first add then shrink'), issues relating to heterogeneous variances and multi-modality are taken into account in the improved model. Therefore the estimates of this new model are expected to be more valid, especially at the tails of the intake distribution. With a 'first add then shrink' approach the habitual total vitamin D intake is estimated lower than the habitual vitamin D intake from food sources only; for children 4-6 yr this was the case up to the 15th percentile. In the three-part model, following a 'first shrink then add' approach, habitual vitamin D intake at all percentiles was at least as high as, though generally higher, than estimates from food sources only. Additionally, the multi-modal shape was only retained in the three-part model. This all effects the estimation of the proportion of the population with intakes below a cut-point. When estimating proportions of the population with vitamin D intake below set cut-points, a difference of up until 12 percent points was noted when comparing 'first add then shrink' estimations with those of the 'first shrink then add'.

The third development regarded the question as to what levels of a nutrient may be added to foods without putting the consumer at risk. This resulted in a model that yields estimates of the maximum safe fortification level per 100 kcal of a food for the Dutch food pattern (Chapter 6). This model was based on the precautionary principle and therefore results in protection of virtually the entire population, including persons consuming high amounts of micronutrients from different sources. The basic idea of this model was taken from Flynn *et al.* (2003) and Rasmussen *et al.* (2005), but some adaptations were made, e.g. including data for children and dietary supplement consumption data. The use of such calculation models make the decision on maximum

safe fortification levels transparent and in addition scientifically funded by using valid estimates of dietary intake and ULs. The model was applied to estimate maximum safe fortification levels for vitamin A, D, and folic acid. Based on the model results the risk manager decided for a general exemption from the Dutch Commodity Act to permit voluntary fortification with vitamin D or folic acid up until a maximum level of 4.5 µg/100 kcal and 100 µg/100 kcal respectively (Chapter 6).

These three methodological improvements were applied to estimate current and future intake and to estimate maximum safe fortification levels. This was illustrated for several nutrients: vitamin A, D, folate/folic acid, iodine, and sodium/salt. The choice for these nutrients was mainly based upon needs of Dutch policy makers. The methodological improvements are however not solely suitable for the examples illustrated in this PhD-thesis and the basic ideas of these methods can be applied to other nutrients or other research questions. Furthermore, the methods were developed using data from the Dutch National Food Consumption Surveys and Dutch food and supplement composition databases. But again, the methodologies are generic and can be implemented in other countries, even if different types of data are available. This may improve the intake estimations in a similar manner to The Netherlands and therefore support local food and nutrition policy making.

Scenario analysis

Scenario analyses were conducted for voluntary and mandatory folic acid fortification (Chapter 2), salt reduction (Chapter 4), and in setting maximum safe fortification levels (Chapter 6). Scenario analyses were performed to predict future nutrient intake after food reformulation or fortification and to estimate maximum safe fortification levels for potential future voluntary fortification. Using scenario analyses, quantitative insight can be obtained into potential dietary intake changes which would result from changes in food composition or food legislation. This insight could help policy makers in their decision making as well as making it more scientific based and transparent.

Scenario analyses are theoretical exercises only. They provide insight into changes in the exposure distribution in a relatively rapid and cost-efficient way, where otherwise no quantitative insight could be given. Scenario analyses are always built on a number of assumptions. It is therefore important to interpret the results of scenario analyses in light of these assumptions. The more realistic the assumptions are, the more predictive the results.

Questions can be raised on the assumptions made in scenario analyses, which makes them subject to scientific scrutiny and improvement based on a search for data that can support or falsify the assumptions. Firstly, the assumptions are usually rather

simplistic, (e.g. few aspects in the diet change and other dietary components are not influenced) (examples are Chapters 2-5, 7, Hendriksen *et al.*, 2011; Sacco *et al.*, 2009; Sioen *et al.*, 2011; Strom *et al.*, 2011; Temme *et al.*, 2010) whereas in practice dietary habits include complex interactions. In scenario analyses regarding the impact of fortification, it is often assumed that only the food composition will change and that there are no effects on or changes in the dietary pattern. Another example of simplicity is the use of cross-sectional data to predict future intake, time trends in dietary intake are often not extrapolated. Secondly, the percentage of participants or percentage of food products for which a future change will take place is often a "guesstimate" (e.g. Chapter 6). The actual impact of a proposed change will remain unknown until the change has taken place (e.g. Chapter 7). Depending on the issue at hand, it might be worthwhile to get more insight into the feasibility, acceptability or side-effects of certain proposed changes, before actual measures are taken.

Evaluation of the dietary intake after implementation is required to show the actual effect of the policy for which scenarios were the basis and to check the assumptions. This will provide essential information on whether the desired effect has been realized and also show which aspects were modeled correctly or otherwise. If the desired effect has not been realized or some unexpected adverse effect is shown, the results of an evaluation study can be used to e.g. amend the policy and address the problem. In Chapter 7 such an evaluation study is described. Some years after implementation of the general exemption to fortify with folic acid an inventory was made of the current market of folic acid fortified foods and intake was estimated. Besides insight into the actual situation, evaluation studies as well as intervention studies provide insight in the validity of the input parameters in the scenario analyses. This also provides an opportunity to improve the models for future scenario analyses. From our evaluation study it was shown that the assumptions for intake from dietary supplements resulted in an overestimation of intake compared to the situation in 2009, whereas the scenario for the proportion of the energy intake from folic acid fortified foods was underestimated. Overall, it was estimated that less than 5% of the young children had folic acid intakes above the UL.

Estimation of habitual intake distributions

As most of the effects micronutrients have on health are related to long-term intakes, the habitual population intake is of interest rather than the short-term observed intake. For this reason in all chapters of this PhD-thesis habitual intake was estimated from short-term measurements by statistical correction for within-person variation.

A frequently asked question is: what is habitual intake? The answer to this question depends on the research topic at hand and the data available. The generally used

definition is the long-term average intake (Nusser *et al.*, 1996), which is still indefinite. Is long-term a whole life or only a few years or months? In nutritional science, the reference values for nutrients are set for different life stages; for a specific life stage an average requirement is set. Therefore, for comparison with nutrient reference values, a time frame comparable to the life stage seems relevant for the definition of usual intake. Depending on the life stage this usually varies from a few months in infants, to a few years in young children, to a few decades in adults.

Further, the underlying short-term observed data covers a specific time frame. Both the time frame of data collection for the survey as well as the time frame for repeated short-term measurements determine the definition of the estimated habitual intake. Generally, a food consumption survey is conducted over a relatively short time frame e.g. one or a few years. For practical reasons and to prevent drop-out, subjects usually have repeated short-term measurements a few days or weeks apart, rather than randomly assigned days in the whole relevant time frame (Brussaard *et al.*, 2002). The habitual intake estimated for this study population represents the habitual intake in that specific time period for a specific year of age or age-gender category. In this PhD-thesis, data of three DNFCSs were used. DNFCS-3 (1997-1998) and DNFCS-young children (2005-2006) both had a time frame of one year. Habitual intake estimated from this data can be defined as mean intake for a specific life stage (age group) in that year. For DNFCS-3, recording days were consecutive and this might have resulted in some error in the estimation of usual intake due to too high or too low within-person variability (IOM, 2000b). In practice it is not known how important this is for the final estimates, from US data the day-to-day correlation seems generally small (Carriquiry *et al.*, 1995; NRC, 1986). In DNFCS-young children recording days were 8-13 days apart. The repeated observations are relatively close in time, therefore there may have been an underestimation of within-person variation because seasonal effects are not included in the within-person variation. DNFCS-young adults (2003) was conducted in autumn only, so the defined timeframe here is not one year, but only the autumn months. For nutrients or dietary components with seasonal effects, this might have caused bias in the estimates. In general however, seasonal effects in the Dutch diet are relatively small (Büchner *et al.*, 2009; Van Staveren *et al.*, 1986).

Statistical methods to estimate habitual intake assume that the 24-hr recall is an unbiased estimator of the true intake (Dodd *et al.*, 2006; Nusser *et al.*, 1996; Tooze *et al.*, 2006). This would suggest the only bias is the day-to-day variation within repeated measures. Unfortunately this assumption does not appear valid. Several studies compared the intake estimated with 24-hr recalls with measurements of recovery markers for protein or potassium, or a biomarker for energy intake (i.e. doubly labeled water). All these studies show that for these nutrients the intake was underestimated with 24-hr recalls (Crispim *et al.*, 2011; Lissner *et al.*, 2007; Ocké *et al.*, 1997). This

indicates that estimation of habitual energy, protein and potassium intake with the currently available statistical procedures will correct part of the error due to day-to-day variation. However, habitual energy, protein or potassium intake distributions are still somewhat biased compared to the true intake due to remaining systematic and person specific bias. For most other nutrients no recovery biomarkers are available and it is reasonable to assume that with intake estimations based on self-reporting additional bias will remain for these nutrients. It is however not possible to predict how the estimated habitual intake will deviate from the true intake. One could imagine that energy dense foods are underreported, but that foods considered being healthy, like fruit and vegetables, could be over-reported (Miller *et al.*, 2008). Recovery biomarkers, which are more objective measurements of intake, are generally measured over a short time frame, e.g. measurements in collections of 24-hr urine. In line with this, the estimation of habitual intake cannot be validated against true long-term intake, as the latter cannot be measured due to practical constraints. Recovery biomarkers can be used to validate the short-term measurements, but need the same modeling procedures to correct for day-to-day variation to estimate habitual intake. Therefore, statistical methods to estimate habitual intake are 'validated' against simulated 'true' long-term intakes (Tooze *et al.*, 2010; 2006). Simulated 'true' long-term intakes have predispositions on what the true intake distribution should look like, similar as the modeling assumptions, e.g. a distribution that could be transformed to normal. Effort should also be put on to show how the models perform on data less optimal regarding the model assumptions. Dietary assessment will always have sources of error. Studies providing insight into the error structure will help to improve statistical methods, dietary assessment tools, study design, and data collection. In addition this insight may improve the interpretation of the results, or adjustment of results (Van Staveren, 2010).

Methods to estimate habitual intake seem to work well for non-complex situations, but need to be improved for more complex situations. In Chapter 5 of this PhD-thesis a step forward was made with the development of an improved model to estimate habitual intake in a complex situation. The complexity was related to heterogeneous variances and multi-modality. The improved model was developed to estimate habitual total micronutrient intake from foods and dietary supplements. The concepts and approaches underlying this new model could be useful to improve methodologies for other complex problems, e.g. for certain foods with similar complexities of the intake distribution, like foods high in specific nutrients (regularly) consumed by part of the population (e.g. vitamin A in liver (products), or fortified foods). However the complexity of the model should be in proportion with other potential measurement error. In addition, more complex models will not always give different estimates or improved results.

Evaluation of dietary intake

The estimation of intake distributions and the evaluation of dietary intake are inextricably bound up with each other. In this PhD-thesis progress was made on improved estimation of the intake distributions. Development of the methods applied for evaluation of the dietary intake and developments in deriving nutrient reference values were outside the scope of this PhD-thesis. With increased validity and precision of the estimates of dietary intakes there is a need for further improvement of dietary evaluation methods and the nutrient reference values.

Currently dietary intake is evaluated by comparing the intake with a single reference value, like the EAR or UL. These values are set by different scientific bodies and although they are based on the same scientific literature, large differences in these values are present (Aggett, 2007; Doets *et al.*, 2008; Verkaik-Kloosterman *et al.*, in press). The setting of reference values for nutrient requirements is currently not harmonized (Doets *et al.*, 2008). For the UL the differences mainly originate from differences in uncertainty factors applied. The Eurreca project started to harmonize the way micronutrients requirements are set, in order to make the procedure more transparent and to obtain better insight into the causes of differences between European countries (Ashwell *et al.*, 2008; Matthys *et al.*, 2010). Next to, improvements in the procedure to derive reference values, the data on which these values are based should be improved as well. There are several uncertainties and sources of error underlying this data. Additionally, the number of studies providing evidence are generally limited and conducted in specific populations or under specific conditions. A more extensive burden of proof is desirable. Effort is especially needed to set valid reference values for children and elderly. The current reference values are based on small studies or few observations or on values extrapolated from the reference values set for adults (Doets *et al.*, 2008; Prentice *et al.*, 2004). Also, more insight is needed in dose-response relations to more accurately define the risk of adverse health effects due to insufficient or excessive intakes. Currently such data are often not presented (De Jong *et al.*, submitted). Waijers *et al.* proposed to derive dietary reference values for children as a function of age rather than staggered values in fixed age categories (Waijers *et al.*, 2004). In this way, differences in nutrient requirement due to e.g. height and bodyweight over the ages are taken into account more accurately.

A general assumption in evaluating dietary intake against reference values is that the validity of the derived reference value is comparable to the estimated habitual intake. Generally, dietary reference values are derived from studies using different methods measuring dietary intake (e.g. balance studies or epidemiological studies measuring dietary intake with FFQ) compared to the food consumption surveys conducted to estimate habitual population intake distributions. These differences are generally qualitatively considered. However a generally accepted reference method to estimate

dietary intake is desirable. Such a reference method could also be used to calibrate data collected with a different method.

In this PhD-thesis, dietary intake was evaluated against single reference values using a cut-point method. Under several conditions the EAR cut-point method is valid to estimate the proportion of the population with insufficient intakes (Carriquiry, 1999; IOM, 2000b). One condition of the EAR cut-point method is that the variation in intake is larger than the variation in requirement, which is assumed to be 10-15%. In our studies the variation is generally >30% (calculated as $(P50-P5)/P50$), which is indeed higher than the 10-15% variation assumed in the requirement (data not shown). Another condition is that the actual prevalence of inadequate intake is neither very low nor very high; below 8-10% or above 90-92%. If the prevalence is low the EAR cut-point method yields an underestimation of the true prevalence, on the other hand if this prevalence is high the EAR cut-point method is an overestimation of the true prevalence. In chapters 3 and 4 the EAR cut-point method was applied to evaluate the habitual iodine intake. In most of the scenarios presented the proportion with intakes below EAR was less than 10%. Although this proportion may not provide a precise estimate of the prevalence of inadequate intake it does reflect that the prevalence is low. Three other conditions of the EAR cut-point method regard the requirement distribution, that should be symmetrically around the average requirement, should have less between-person variation compared to this variation in the intake distribution, and should have no or only weak correlation with the intake. However, the requirement distribution is unknown for micronutrients. It is therefore impossible to conclude whether the conditions for use of the EAR cut-point method were met and whether the evaluation process of micronutrient adequacy was valid. With some exceptions (e.g. iron) it is generally assumed that the conditions regarding the requirement distribution are met unless there is data to the contrary. More research is needed to acquire insight into the distribution of requirements. It is good to realize that for the alternative method to evaluate dietary intake, the probability method (IOM, 2000b), even more detailed information on the distribution of requirements is required.

The results of the use of a cut-point method for comparison with the UL should be interpreted differently than the comparison with the EAR. The proportion with intakes above the UL is not equal to the proportion with excessive intakes (Carriquiry *et al.*, 2006), but it is the proportion of the population for which adverse health effects cannot be excluded. The interpretation of this result will depend on e.g. the health effects associated with the reference value, and more specifically with the uncertainty in this value. In the derivation of the UL a precautionary principle is applied by using uncertainty factors to warrant safe intakes at levels below the UL. Generally, policy makers use the UL as a cut-point above which intakes should be prevented in order to be sure of safe intakes.

In the Safefoods project an integrated probabilistic risk assessment approach (IPRA) was recently developed. This approach provides insight into the proportion of the population at risk of adverse effects and the severity of these health effects (Van der Voet *et al.*, 2007). In this approach the exposure distribution is combined with the distribution of the dose above which the critical adverse health effect is observed (dose-response). It would appear promising to also implement this approach in the evaluation of nutrient intakes to get better feeling on the severity associated with observed intakes above the UL. This may help policy makers in their decision how to cope with observed intakes above the UL. The EAR cut-point method does provide insight into the prevalence of insufficient intake, it does however not give insight in the severity of health effects. The idea of the IPRA-approach could be a basis for a more detailed evaluation at the low intake level as well.

Public health perspective

Tools like those developed and improved in this PhD-thesis may support the decision making or risk managing process by providing more precise estimates of current intakes, by predicting future intakes related to proposed changes and by estimating maximum safe fortification levels.

The estimation of maximum safe fortification levels (Chapter 6) resulted in implementation of general exemptions on the Dutch Commodity Act to fortify with folic acid and vitamin D up until a maximum level of 100 µg/100 kcal and 4.5 µg/100 kcal respectively (Anonymous, 2007). With the implementation of these general exemptions, evaluation of this regulation was advised to monitor the safety of the exemption carefully. Two years after the implementation an evaluation study on fortification with folic acid was conducted (Chapter 7). This evaluation study showed that with the current fortification practice the intake remained below the UL for the majority of the young children. Less than 5% of the young children had intakes above the UL. These high intakes were mainly due to large folic acid intakes by dietary supplements. Within the legislation of the European Union minimum and maximum levels of nutrients that can be added to foods are being harmonized (Anonymous, 2002a; 2006; Directorate E, 2006). The discussions on the actual levels are still ongoing. In these discussions the Dutch model (Chapter 6) and experiences are considered. The use of a model like the Dutch model, makes the whole process of selecting safe fortification levels transparent and scientifically sound. For European legislation, data from different European countries should be used as model input data to estimate maximum safe fortification levels. This will give insight into inter-country differences in 'free-space' available for fortification and in the estimated maximum fortification levels.

The framework to estimate the impact of proposed voluntary or mandatory fortification on micronutrient intake (Chapter 2) was applied to give the Health Council of The Netherlands insight into the effect of potential solutions to improve folate and vitamin D intake in The Netherlands. This insight supported the Health Council of The Netherlands in their advice to the Ministry of Health, Welfare, and Sports (Health Council, 2008b; Weggemans *et al.*, 2009a). Additionally, the Health Council of The Netherlands published a report on the maintenance of an optimal iodine intake in which preliminary results from Chapter 3 and 4 of this PhD-thesis were used to discuss the effects of lowering salt iodine content and of lowering salt content of foods (Health Council, 2008c). Fortification is generally seen as one of the options to improve nutrient intakes, next to change of dietary patterns and use of dietary supplements. In mandatory fortification practices a large part of the population will be reached as the vehicle to fortify is generally a food consumed by a large percentage of the population, e.g. bread, margarine. Such mandatory fortification practice is administered by the authorities to improve the intake of a specific nutrient in the population, whereas otherwise a public health problem regarding inadequate intake would occur (Allen *et al.*, 2006). Scenario analysis as illustrated in Chapter 2 is useful to quantify the effect of a proposed mandatory fortification strategy and to provide insight into the change of the whole intake distribution; considering both the improvement of intake at the low intake side and the potential risk of exceeding the UL at the high intake side of the distribution. Voluntary fortification encouraged by authorities in agreement with a large part of the food industry, can be regarded as similar to mandatory fortification as most of the manufacturers will fortify the specific foods and only a small number will not. Worldwide truly voluntary fortification (i.e. not specifically encouraged by authorities) is more and more allowed and applied and a market driven process (Rosenberg, 2007). To warrant safe population intakes, authorities do regulate voluntary fortification (Anonymous, 1996; 2006; 2007). In practice, only a small proportion of all foods (often even of specific brands only) are voluntary fortified with some micronutrients (Flynn *et al.*, 2009). As a result the inequality in nutrient intake within a population will become larger as only (regular) consumers of these specific fortified foods will have increased nutrient intakes (Flynn *et al.*, 2008). The question remains whether those in need of additional nutrient intake are the users of these fortified foods (Hoey *et al.*, 2007). Completely voluntary fortification may therefore be of no use as a tool to prevent public health problems; particularly when relatively few foods are fortified. It may even result in introducing problems with both inadequate and excessive intakes in a population.

The authorities have the task to protect public health. In practice, this means the authorities should mainly focus on establishing safe intakes. This seems logical from a toxicological point of view as chemicals and contaminants are not required for human

life and are only potentially harmful. A nutrient is another type of compound however. Both insufficient and excessive intakes may be associated with harmful effects. Protection of public health regarding nutrient intake is not only preventing excessive intakes, but also the prevention of insufficient intakes. For prevention of excessive intakes there are legislations regarding maximum levels for fortification and dietary supplements (Anonymous, 1996; 2002a; 2006; 2007; Flynn *et al.*, 2009). The prevention of insufficient intakes is generally regarded as a person's own responsibility to choose the 'healthy' diet. However this choice may be influenced intentionally with publicity campaigns e.g. '200 g of vegetables and 2 pieces of fruit' and 'the balance-day'. Due to population-wide problems with inadequate intake, even with a 'varied' diet, few specific nutrients are an exception. In The Netherlands, iodine and vitamin D are the exceptions and the authorities have agreements with the food industry which allow and encourage them to fortify specific foods (salt and (low-fat) margarine respectively) with specific amounts of these nutrients. These agreements encourage fortification, but do not obligate. In The Netherlands, there is no mandatory fortification as freedom of choice by consumers is apparently considered more important than prevention of inadequate intakes.

With regard to the difference in protection of the population for excessive or insufficient intakes it is important to consider the difference in concept between the EAR and UL. The proportion with intakes below the EAR is generally assumed to be a good predictor of the proportion of the population with inadequate intakes, although additional insight in nutritional status and associated health effects are more conclusive. The proportion of the population with intakes below the UL is not at risk of adverse health effects due to excessive intakes. For the proportion of the population with intakes above the UL, adverse effects due to excessive intakes cannot be excluded. There is however an uncertainty factor applied on the NOAEL (or LOAEL) derived from scientific data to derive the UL. To improve the nutrient intake more efficiently it would be important to consider the severity and dose-response of the adverse health effects associated with both too low and too high intakes. If the focus is on optimal public health, a balance between the risks associated with insufficient intakes and those associated with excessive intakes must be made and these results will help to prioritize the important issues (Chambers *et al.*, 2010; Hoekstra *et al.*, 2008). This is especially important for nutrients for which population intakes below the EAR and above the UL are observed and nutrients with a small range between EAR and UL (like vitamin D, folate, selenium, copper). In some situations it might be possible to shift the population intake distribution in such a way that too low and too high intakes can both be prevented, whereas in other situations acceptance of some risk of too high intakes might be needed to prevent the (larger) harmful effects of insufficient intakes, or the other way around.

Estimates of current or potential future habitual micronutrient intake distributions are valuable in the estimation of consequences to public health by changes in dietary micronutrient intake. The estimations of folate-equivalent intake for different scenarios of folic acid fortification of bread presented in Chapter 2, were applied in a quantitative benefit-risk assessment to estimate the overall health gain or loss in the population for each fortification scenario (Hoekstra *et al.*, 2008). Salt reduction scenarios described in Chapter 4 were used to quantify the effects on blood pressure and cardiovascular diseases (Hendriksen *et al.*, in preparation). Additionally models estimating the health effects of a change in micronutrient intake can be extended by considering the costs of intervention (e.g. fortification or reformulation) and the costs saved by public health gain (e.g. Bentley *et al.*, 2009; Bibbins-Domingo *et al.*, 2010; Dalziel *et al.*, 2010).

Although the final decision making is generally (scientific) evidence-based, food and nutrition policy making and risk management consider other issues besides the scientific ones, such as (supposed) acceptability.

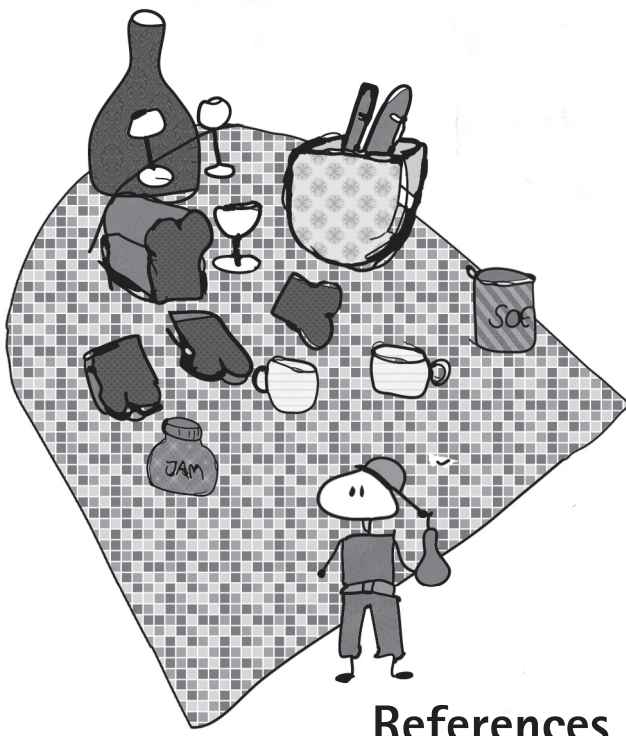
Conclusion

Three methodological improvements to estimate current or future micronutrient intake or maximum safe fortification levels were developed and applied. The methodological improvements and the resulting intake estimations are essential for nutritional and food policy making. They provide improved and more precise quantitative insight into current and potential future micronutrient intakes that was not possible with the generally applied methods. Subsequently, this also improves the nutritional evaluation of the dietary intake and as a consequence improves the insight in potential problems regarding micronutrient intake. Furthermore, scenario analyses provide quantitative insight into proposed changes or maximum safe fortification levels under specific conditions. Explicit description and quantification of these conditions, as well as of uncertainty and/or variability make scenario analyses a transparent tool that will provide useful information for food and nutrition policy making or advice on policy making.

As mentioned on several occasions in this general discussion, there are still several issues left for future improvement. In summary; in scenario analyses the current rather simplistic assumptions could be more sophisticated by considering a) interactions between potential changes in part of the diet and other dietary habits and b) extrapolation of the results according to observed time trends. Secondly, statistical models are used to estimate habitual intake from short-term measurements. It is known that, because a 24-hr recall is a biased estimator of true intake, the estimated habitual intake distribution retains some bias. Studies providing insight into the error structure

may improve the dietary assessment, study design, data collection, statistical method, and the interpretation of the results. Furthermore, methods to estimate habitual intake cannot cope with complexities in the observed data, e.g. multimodality, heterogeneous variances, very skewed distributions. In this PhD-thesis an improved model was presented to estimate habitual total intake from food and dietary supplements. In future research, improved methodologies could be developed for other examples of complex observed data. Finally, in addition to improvements in estimating the intake distributions, improvements could also be made in the derivation of the dietary reference intakes and the method for evaluation of the dietary intake.

Some of the results and methods described in this PhD-thesis are already in use in Dutch as well as European food and nutrition policy making, or advice on policy making. This shows that improved methodologies which were developed in this PhD-thesis are already of immediate value.



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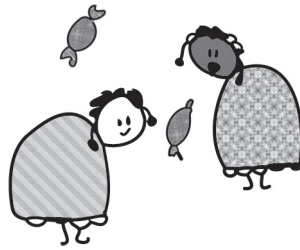
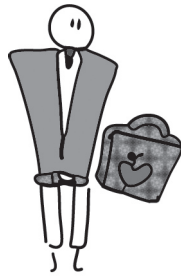
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Summary

Adequate and safe micronutrient intake is important. Inadequate as well as excessive intake should be prevented as both can be associated with negative consequences for health. Ideally, the population intake distribution should lie between insufficient and excessive. Estimates of dietary intake are generally compared to (inter)nationally set dietary reference values in order to predict the proportion of the population with inadequate or at risk for excessive intakes. This information may be used to assist in correcting micronutrient intake levels. Methods to correct intake levels could include advice and education to improve the diet, advice to take or avoid the use of dietary supplements, and fortification of foods by manufacturers on a mandatory or voluntary basis. In nutritional science a deterministic approach to estimate the population micronutrient intake is commonly used. However, this deterministic approach is not always appropriate. In this PhD-thesis three issues relating to estimation of population micronutrient intake were addressed in order to improve this estimation: 1) how to estimate current habitual micronutrient intake when (detailed) data is lacking or data from different sources should be combined, 2) how to predict future intakes in order to support policy making, and 3) how to estimate a maximum safe fortification level per food item. The aim of this PhD-thesis is to further develop and apply statistical models to estimate micronutrient intake distributions which can cope with these issues.

In Chapter 2 a general framework to simulate the potential future intake of a micronutrient after proposed mandatory or voluntary fortification is presented. This framework consists of six steps: 1) definition of scenarios with fortification strategies, 2) identification of carrier products, 3) definition of fortification levels, 4) creation of virtual (i.e. scenario related) food or supplement composition data, 5) combination of virtual composition data with food and dietary supplement consumption data, and 6) simulation to get the total habitual intake distribution. The framework was illustrated by simulation of the effects of both mandatory and voluntary folic acid fortification on the habitual folate-equivalent intake distribution from foods only. Uncertainty in the potential use of voluntary fortified foods was taken into account by probabilistic modeling.

The general framework was also applied to estimate the current iodine intake and to simulate the iodine intake for scenarios based on proposed changes in the Dutch iodine policy (Chapter 3) and changes in salt content of foods due to reformulation (Chapter 4). A problem in the estimation of current iodine and sodium intake from the Dutch food consumption survey is the lack of detailed data on the discretionary use of (iodized) salt. Another problem is the lack of data on the actual use of iodized salt in industrially processed foods. Estimates for the proportion of subjects using discretionary (iodized) salt and the proportion of industrially processed foods containing iodized salt were obtained from additional data sources. As it is unknown which subjects actually use discretionary salt or industrially processed foods containing

iodized salt the commonly used deterministic calculation method was combined with probabilistic approaches, in order to take into account the uncertainty. The habitual iodine and sodium intake distributions estimated with our model were comparable with results of studies measuring urinary excretion of iodine or sodium. The model showed that habitual iodine intakes were adequate and safe in large part of the Dutch population. However reduction of the currently permitted highest salt iodine level to the currently allowed lowest level, resulted in an estimation of insufficient intakes for ~10% of young children. Reduction of salt is required to reduce the risk of elevated blood pressure and subsequent cardiovascular diseases. On the other hand, salt is the main vehicle for iodine fortification in The Netherlands. In Chapter 4, the effect of salt reduction on the iodine intake was quantified using the model described in Chapter 3. It was shown that a 50% reduction in salt use in industrially processed foods as well as discretionary use of salt would be required for the average habitual salt intake of adults to be within the maximum level of 6g/day recommended by the Dutch Health Council. With this large salt reduction up to 10% of the Dutch population will have inadequate iodine intakes when the current legal salt iodine levels were applied.

In addition to food, dietary supplements are a potential source of micronutrient intake and must be taken into account when estimating habitual micronutrient intakes. Habitual intake is estimated from short-term measurements by statistical correction of the observed intake distribution for within-person variation. The within-person and between-person variation could be very different for intake from foods as compared to intake from dietary supplements. In addition, the total intake distribution could be multi-modal due to a different distribution for users and non-users of dietary supplements. In Chapter 5 a three-part model is proposed to estimate habitual total intake from food and dietary supplements. With this three-part model habitual intake from food is estimated separately from dietary supplements and these intake distributions are also estimated separately for users and non-users of dietary supplements. The habitual total micronutrient intake is estimated by convolution of the three separately estimated habitual intake distributions (a so-called 'first shrink then add' approach). The model was developed on the basis of the method developed by researchers of the USA National Cancer Institute to estimate habitual intake, using data from the Dutch national food consumption survey among young children. It was illustrated by the estimation of habitual total vitamin D intake. The three-part model using the 'first shrink then add' approach was compared with a more simple 'first add then shrink' approach. With this 'first add then shrink' approach habitual total vitamin D intake at the lower percentiles of the intake distribution were estimated to be lower than those estimated for the intake from food only, which is not internally consistent. With the three-part model this inconsistency did not occur. Further, the multi-modal shape observed in the 'raw' data was only retained with this three-part model.

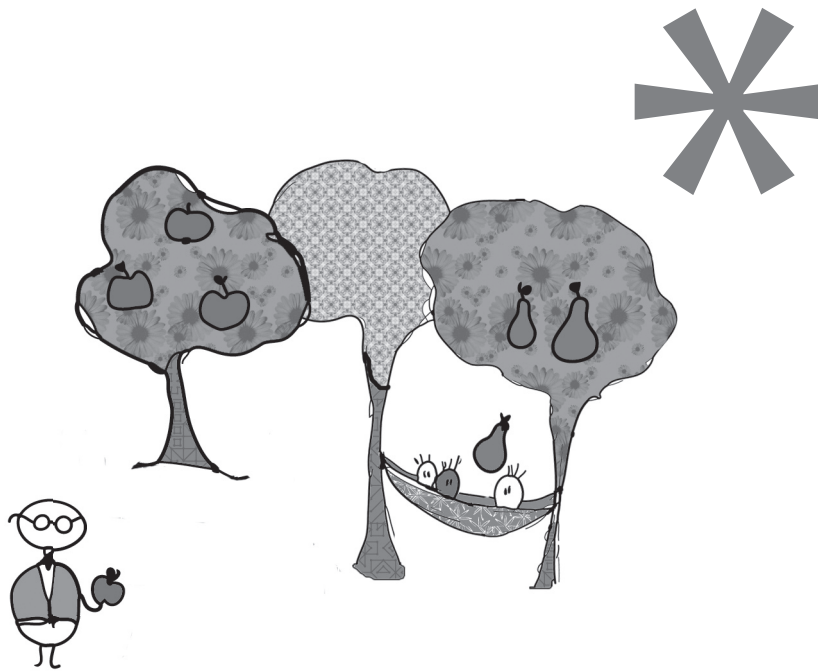
In Chapter 6 estimated distributions of habitual intake were used as input in a model to estimate maximum safe levels for voluntary fortification. This model is an adapted version of the models of Flynn et al. and Rasmussen et al. and was applied to data of the Dutch population. Maximum safe fortification levels were calculated by first estimating the 'free space' that is available for fortification. This 'free space' for a specific micronutrient was calculated by subtracting the 95th percentile of habitual intake from non-voluntary fortified foods and a reasonable high level from dietary supplements from the age-specific tolerable upper intake level. To estimate the maximum safe fortification level per 100 kcal, this 'free space' was divided over the part of the energy intake that can and will be fortified. This model was applied on vitamin A, D, and folic acid. The calculated maximum safe fortification levels were respectively 0 µg/100 kcal, 3.0 µg/100 kcal, and 0 µg/100 kcal. After consultation of stakeholders in the Regular Consultation on the Commodity Act, the risk manager decided to decrease the fraction of the energy intake that can and will be fortified from 15% to 10% and decided to only consider data of adults for folic acid. This resulted in a general exemption from the Dutch Commodity Act for vitamin D (4.5 µg/100 kcal) and folic acid (100 µg/100 kcal). As data from children were not taken into account in the general exemption for folic acid, two years after the general exemption came into force an evaluation study was conducted (Chapter 7). An inventory of the folic acid fortified foods available on the Dutch market was made. In the total 139 folic acid fortified foods available on the Dutch market, only one had a level of folic acid higher than the legally permitted amount.

Evaluation of the model parameters with data from the Dutch food consumption survey young children showed that the reasonably high intake level from dietary supplements in the original model was overestimated, though the percentage of the energy intake as proposed by the risk manager (10%) was an underestimation.

The combination of a large percentage of energy intake from folic acid fortified foods and high folic acid intakes from dietary supplements and fortified foods was uncommon amongst young children. In the evaluation study, less than 5% had intakes above the tolerable upper intake level. This was mainly due to high folic acid intakes from dietary supplements.

In Chapter 8 the main findings are summarized. In this PhD-thesis three methodological improvements have been made: 1) combination of the generally applied deterministic approach with probabilistic approaches to be able to take into account uncertainty and variability (Chapters 2-4), 2) development of a new statistical model to estimate habitual total micronutrient intake aggregated from both foods and dietary supplements (Chapter 5), and 3) a model calculating the maximum safe fortification level per 100 kcal of a food for the Dutch situation (Chapters 6, 7). Additionally, issues regarding

scenario analysis, estimation of habitual intake distributions, and evaluation of dietary intake were reflected in the general discussion. The results from this PhD-thesis were placed in a public health perspective. For each issue addressed implications for future research were considered. It is concluded that the methodological improvements have resulted in more accurate estimations of habitual intake distributions, which are essential for nutritional and food policy making. Furthermore, scenario analyses provide quantitative insight in proposed changes or in maximum safe fortification levels under specific conditions. Although several more refinements are possible, some of the results and methods described are currently used in Dutch and European food and nutrition policy making or in advice on policy making. This shows these methodologies are of immediate value to the practice of policy development and support.



Samenvatting

Een voldoende hoge maar wel veilige inname van vitamines en mineralen, gezamenlijk ook wel micronutriënten genoemd, is belangrijk. Zowel een te lage als een te hoge inname zou voorkomen moeten worden, aangezien dit negatieve gevolgen kan hebben voor de gezondheid. Om een inschatting te maken van het deel van de bevolking met een te lage dan wel een te hoge inname worden schattingen van de inname uit de voeding vergeleken met (inter)nationaal vastgestelde referentiewaarden. Vervolgens kan geprobeerd worden om een eventueel geconstateerde te lage of te hoge inname in de bevolking te corrigeren, bijvoorbeeld door voorlichting over verbetering van het voedingspatroon of door advies ten aanzien van het gebruik van voedingssupplementen. Daarnaast kan vrijwillige of verplichte verrijking van voedingsmiddelen door fabrikanten een rol spelen bij het verbeteren van de inname van micronutriënten.

In de voedingswetenschap is een deterministische aanpak bij de schatting van de micronutriëntinname in de bevolking gebruikelijk. Hierbij wordt gebruik gemaakt van puntschattingen en kunnen onzekerheden en variatie in de gegevens niet worden meegenomen. Deze deterministische aanpak is echter niet altijd geschikt. Om de schatting van de innameverdeling van micronutriënten in de bevolking te verbeteren zijn in dit proefschrift drie onderzoeksvragen opgesteld: 1) hoe is de huidige micronutriëntinname te schatten als (gedetailleerde) gegevens ontbreken of gegevens uit verschillende bronnen gecombineerd moeten worden, 2) hoe kan de toekomstige inname geschat worden om daarmee het beleid te ondersteunen en 3) hoe kan een veilig maximaal verrijkniveau per voedingsmiddel worden vastgesteld. Dit onderzoek heeft tot doel om statistische modellen (verder) te ontwikkelen en toe te passen om zo de innameverdeling van micronutriënten in de bevolking te schatten voor situaties waar op zijn minst één van de hierboven genoemde uitdagingen geldt.

In Hoofdstuk 2 wordt een algemeen raamwerk gepresenteerd om door middel van simulatie een inschatting te maken van een mogelijk toekomstige innameverdeling van micronutriënten. Hiermee kan inzicht worden gegeven in mogelijke veranderingen in de innameverdeling. Deze veranderingen kunnen bijvoorbeeld ontstaan door het invoeren van verplichte of het toestaan van vrijwillige verrijking. Het raamwerk bestaat uit zes stappen: 1) het definiëren van scenario's met verrijkningsstrategieën, 2) het vaststellen van de te verrijken voedingsmiddelen, 3) het vaststellen van de verrijkningsniveaus, 4) het aanmaken van virtuele (dit wil zeggen scenariogerelateerde) gegevens ten aanzien van de samenstelling van voedingsmiddelen, 5) het combineren van deze virtuele samenstellingsgegevens met gegevens over de voedselconsumptie en 6) simulatie om tot de totale gebruikelijke innameverdeling te komen. Het raamwerk wordt geïllustreerd aan de hand van het effect van verplichte en vrijwillige foliumzuurverrijking op de gebruikelijke innameverdeling.

Met behulp van waarschijnlijkheidsmodellering is de onzekerheid ten aanzien van mogelijk toekomstig gebruik van vrijwillig verrijkte voedingsmiddelen meegenomen.

Het hierboven beschreven algemene raamwerk is ook toegepast om een schatting te maken van de huidige jodiuminname (Hoofdstuk 3). Een probleem bij het schatten van de huidige jodiuminname op basis van gegevens van de Nederlandse voedselconsumptiepeiling is het gebrek aan gedetailleerde gegevens over het huishoudelijk gebruik van (gejodeerd) keukenzout. Een andere beperking is het gebrek aan gegevens over het gebruik van gejodeerd zout in industrieel bewerkte voedingsmiddelen. Daarom zijn op basis van gegevens uit andere bronnen schattingen gemaakt van het percentage van de bevolking dat gejodeerd keukenzout huishoudelijk gebruikt en van het deel van de industrieel bewerkte voedingsmiddelen dat gejodeerd zout bevat. Omdat het onbekend is welke personen in de voedselconsumptiepeiling keukenzout huishoudelijk gebruiken of wie voedingsmiddelen consumeren die gejodeerd zout bevatten, is de algemeen gebruikte deterministische berekeningsmethode gecombineerd met waarschijnlijkheidsmethoden om deze onzekerheden mee te nemen. De gebruikelijke jodiuminname, zoals geschat met ons rekenmodel, was vergelijkbaar met resultaten van studies waarin de uitscheiding van jodium in de urine werd gemeten. De schattingen die met het rekenmodel gemaakt zijn, laten zien dat de gebruikelijke jodiuminname voldoende is voor een groot deel van de Nederlandse bevolking.

Naast het schatten van de huidige jodiuminname werden ook schattingen gemaakt van de jodiuminname voor verschillende scenario's van mogelijke veranderingen in de Nederlandse jodiumwetgeving (Hoofdstuk 3). Het model om de huidige jodiuminname te schatten was hierbij het uitgangspunt. Op dit moment zijn twee joderingsniveaus van zout toegestaan. Verlaging van het momenteel toegestane hoge joderingsniveau, dat onder andere geldt voor brood, tot het huidig toegestane lage niveau zal bij ongeveer 10% van de jonge kinderen tot een te lage jodiuminname leiden.

Verlaging van de zoutinname is noodzakelijk om het risico op verhoogde bloeddruk en daarmee samenhangend het risico op hart- en vaatziekten te verlagen. Maar aan de andere kant is gejodeerd zout de belangrijkste jodiumbron voor de Nederlandse bevolking. In Hoofdstuk 4 is het effect van verlaging van de zoutinname op de jodiuminname gekwantificeerd. Hierbij is gebruik gemaakt van het model uit Hoofdstuk 3. Uit de schattingen bleek dat een zoutreductie van 50% in zowel industrieel bewerkte voedingsmiddelen als bij het huishoudelijk gebruik van keukenzout nodig is om voor volwassenen een gemiddelde gebruikelijke zoutinname te realiseren van ongeveer 6 g/dag. Dit is gelijk aan de maximale zoutinname die wordt geadviseerd door de Gezondheidsraad. Bij deze grote verlaging van de zoutinname en de huidige joderingsniveaus zal dit, afhankelijk van de leeftijdsgroep, bij $\leq 10\%$ van de Nederlandse bevolking tot een te lage jodiuminname leiden.

Naast voedingsmiddelen zijn ook voedingssupplementen belangrijke bronnen voor de inname van micronutriënten. Bij de schatting van de micronutriëntinname moeten daarom beide bronnen worden meegenomen. De gebruikelijke inname wordt veelal geschat op basis van korte-termijnmetingen in combinatie met statistische correctie van de waargenomen innameverdeling voor dag-tot-dagvariatie. De variatie in inname tussen personen en de dag-tot-dagvariatie in inname van één persoon kunnen beide verschillend zijn voor de inname van micronutriënten uit voedingsmiddelen en de inname uit voedingssupplementen. Bovendien kan de innameverdeling van de totale inname uit voedingsmiddelen en -supplementen meerdere toppen hebben door een verschillende innameverdeling voor gebruikers en niet-gebruikers van voedingssupplementen. In Hoofdstuk 5 wordt een driedelig model beschreven voor de schatting van de gebruikelijke totale micronutriëntinnameverdeling uit voedingsmiddelen en voedingssupplementen. Met dit model wordt de gebruikelijke inname eerst apart geschat voor a) de inname uit voedingsmiddelen voor niet-gebruikers van voedingssupplementen, b) de inname uit voedingsmiddelen voor gebruikers van voedingssupplementen en c) de inname uit voedingssupplementen door gebruikers hiervan. De drie gebruikelijke innameverdelingen worden vervolgens gecombineerd tot één gebruikelijke innameverdeling voor de totale inname uit beide bronnen voor de gehele bevolking ("eerst correctie dan toevoegen"). De basis voor dit model is een methode om de gebruikelijke inname te schatten die is ontwikkeld door onderzoekers van het 'National Cancer Institute' in de Verenigde Staten. Er is gebruikgemaakt van gegevens van de Nederlandse voedselconsumptiepeiling onder jonge kinderen. Het model wordt geïllustreerd aan de hand van vitamine D. Het nieuwe model ("eerst correctie dan toevoegen") is daarbij vergeleken met een eenvoudigere procedure waarbij de inname uit de verschillende bronnen eerst wordt opgeteld en vervolgens wordt gecorrigeerd voor binnen-persoonsvariatie ("eerst toevoegen dan correctie"). Met deze laatste procedure is de schatting van de gebruikelijke totale vitamine D inname bij de laagste percentielen van de innameverdeling lager dan wanneer de gebruikelijke inname uit alleen voedingsmiddelen wordt geschat, wat niet kan kloppen. Bij het nieuwe driedelige model was dit probleem opgelost. Bovendien bleef met het nieuwe model de meertoppige vorm van de innameverdeling, die ook is te zien in de ruwe data, bewaard.

Gebruikelijke innameverdelingen zijn in Hoofdstuk 6 gebruikt als input in een rekenmodel om veilige maximale niveaus voor vrijwillige verrijking te schatten. Dit rekenmodel is een aangepaste versie van modellen die eerder gepubliceerd zijn door Flynn *et al.* (2003) en Rasmussen *et al.* (2006). Ons model is toegepast op gegevens van de Nederlandse bevolking. De veilige maximale verrijkingsniveaus werden voor iedere leeftijdsgroep apart bepaald door eerst de zogenaamde 'vrije ruimte' te schatten die beschikbaar is voor vrijwillige verrijking. Voor een specifiek

micronutriënt is deze 'vrije ruimte' berekend als het verschil tussen de aanvaardbare bovengrens van inname en de som van a) het 95^{ste} percentiel van de gebruikelijke innameverdeling uit voedingsmiddelen (exclusief eventueel bestaande vrijwillige verrijking), en b) een hoge inname uit voedingssupplementen. Deze 'vrije ruimte' is vervolgens verdeeld over het deel van de energie-inname die mogelijk verrijkt kan en zal worden (schatting van 15%), om zo tot een veilig maximaal verrijkingsniveau per 100 kcal voedingsmiddel te komen. Het rekenmodel is toegepast voor vitamine A, D en foliumzuur. Rekeninghoudend met de leeftijdsgroepen die het grootste risico lopen op een te hoge inname, resulteerde dit in een veilig maximaal verrijkingsniveau van respectievelijk 0, 3, en 0 µg/100 kcal. Na bespreking met belanghebbenden in het Regulier Overleg Warenwet besloot de risicomanager (beleidsmaker) om uit te gaan van een lager deel van de energie-inname die mogelijk verrijkt kan en zal worden; namelijk 10%. Bovendien werden gegevens met betrekking tot kinderen niet meegenomen in het vaststellen van het veilige maximale verrijkingsniveau voor foliumzuur. Uiteindelijk leidde dit tot een algemene ontheffing van de Nederlandse Warenwet voor vrijwillige verrijking met vitamine D en foliumzuur tot een maximum van respectievelijk 4,5 en 100 µg/100 kcal.

Omdat de gegevens over foliumzuurinname bij kinderen niet zijn meegenomen bij het vaststellen van het veilige maximum verrijkingsniveau is 2 jaar na het van kracht worden van de algemene ontheffing een evaluatiestudie uitgevoerd (Hoofdstuk 7). Binnen deze evaluatiestudie is een inventarisatie gemaakt van de met foliumzuurverrijkte voedingsmiddelen die beschikbaar zijn op de Nederlandse markt. In totaal werden 139 foliumzuurverrijkte voedingsmiddelen gevonden. Eén van deze producten had een foliumzuurgehalte dat hoger lag dan het in de vrijstellingsregeling wettelijk vastgestelde maximum van 100 µg/100kcal. Daarnaast zijn ook de modelparameters geëvalueerd waarbij gebruik is gemaakt van gegevens van VCP-jonge kinderen. De schatting van de hoge foliumzuurinname uit voedingssupplementen in het originele model (Hoofdstuk 6) bleek een overschatting. Het deel van de energie- inname dat geconsumeerd wordt als foliumzuurverrijkte voedingsmiddelen was in de afleiding van het huidige wettelijke maximum onderschat (Hoofdstuk 6). Bij het rekenmodel is er van uitgegaan dat personen met een hoge foliumzuurinname uit verrijkte voedingsmiddelen in combinatie met een hoge foliumzuurinname uit supplementen en een groot deel van de energie-inname dat uit foliumzuurverrijkte voedingsmiddelen bestaat, ook nog een totale foliumzuurinname zullen hebben die veilig is. Deze combinatie van hoge inname uit verschillende bronnen kwam onder jonge kinderen echter niet veel voor. Een klein deel, minder dan 5%, van de jonge kinderen had een totale foliumzuurinname die hoger lag dan de aanvaardbare bovengrens van inname. Dit werd voornamelijk veroorzaakt door een zeer hoge foliumzuurinname uit supplementen.

In Hoofdstuk 8 zijn de belangrijkste bevindingen van dit proefschrift samengevat tot de drie voornaamste methodologische verbeteringen: 1) de combinatie van een deterministische aanpak met waarschijnlijkheidsmethoden om zo onzekerheden en variatie in gegevens mee te kunnen nemen in de schatting van de inname (Hoofdstukken 2-4), 2) het ontwikkelen van een nieuw statistisch model om de gebruikelijke totale micronutriëntinname te schatten uit voedingsmiddelen en -supplementen samen (Hoofdstuk 5) en 3) een model om een veilig maximaal verrijkinsniveau af te leiden per 100 kcal voedingsmiddel voor de Nederlandse situatie (Hoofdstukken 6 en 7). Daarnaast zijn methodologische aspecten met betrekking tot scenarioanalyse, de schatting van gebruikelijke innameverdelingen en de evaluatie van voedselconsumptie besproken in de algemene discussie (Hoofdstuk 8). Ook zijn de resultaten in een volksgezondheidsperspectief geplaatst. Voor elk onderwerp dat in de discussie is besproken zijn enkele suggesties gedaan voor toekomstig onderzoek. In scenarioanalyses worden op dit moment vrij eenvoudige aannames gedaan, interacties tussen mogelijke veranderingen in een deel van het voedingspatroon of de voedingsmiddelen en de andere voedingsgewoonten worden nu nog niet meegenomen. Daarnaast zou in vervolgonderzoek trends in de tijd meegenomen kunnen worden. Bij het schatten van de gebruikelijke inname worden gegevens verkregen uit korte-termijnmetingen gecorrigeerd met behulp van statistische modellen. Een aanname is dat de korte-termijnmetingen goede schattingen geven van de werkelijke inname, het is echter bekend dat dit niet het geval is. Onderzoek naar de verbanden tussen de werkelijke inname en de korte-termijnmetingen kunnen de studieopzet, gegevensverzameling, statistische methoden, maar ook de interpretatie van de resultaten verbeteren. Verder zijn de huidige statistische modellen om de gebruikelijke inname te schatten niet uitgerust voor gecompliceerde situaties, bijvoorbeeld meertoppigheid, heterogene varianties en erg scheve verdelingen. In Hoofdstuk 5 is een verbeterd model gepresenteerd voor zo'n gecompliceerde situatie. In de toekomst zou dit model uitgebreid kunnen worden voor andere gecompliceerde situaties. Tot slot, behalve verdere verbeteringen in de schatting van de innameverdeling, zijn er ook mogelijkheden voor verbeteringen in de afleiding van de referentiewaarden en de methoden waarmee de inname wordt vergeleken met deze referentiewaarden.

De discussie eindigt met de conclusie dat de methodologische verbeteringen hebben geleid tot preciezere schattingen van de gebruikelijke innameverdelingen. Dit is essentieel voor het maken van beleid op het gebied van voeding en voedingsmiddelen. Daarbij geeft scenarioanalyse, onder bepaalde aannames, kwantitatief inzicht in de effecten van voorgestelde veranderingen of het vaststellen van veilige maximale verrijkinsniveaus. Hoewel er nog verschillende verbeteringen mogelijk zijn, is een deel van de resultaten en methoden gebruikt in het maken van of het adviseren voor

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en optimisme ben ik vooral achteraf gaan waarderen. Cathy, fijn dat jij straks als paranimf naast me zal staan. In de tijd dat het idee van promoveren nog vorm moest krijgen hebben we hier regelmatig over van gedachten gewisseld. Deze gesprekken hebben mij enorm geholpen om het vertrouwen te krijgen dat het zou gaan lukken. Ook de vele gesprekken daarna over van alles en nog wat, met name in de trein op het traject Utrecht C.S. en Bilthoven, waren (en zijn) erg waardevol.

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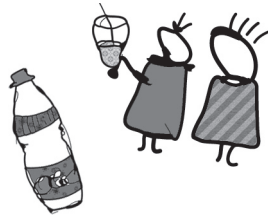
Met name de afgelopen anderhalf jaar heeft de afronding van mijn proefschrift veel 'eigen tijd' gevraagd. Mama en papa, jullie zijn altijd zeer geïnteresseerd in wat ik doe en willen dat ook graag begrijpen. Dank voor de vele voedingsgerelateerde krantenberichtjes. En ook ontzettend veel dank voor het zeer regelmatige oppassen op jullie kleindochter (o wat een straf...), zodat ik boven achter de 'puter' kon. Florentijn, het is fijn dat ook jij straks als paranimf aan mijn zijde zal staan. Ik heb je kritische blik erg gewaardeerd, net als de leuke gesprekken die we kunnen hebben. Zou ik nu eindelijk meer tijd krijgen om spelletjes te spelen? Fabian, ook jij bedankt voor de interesse in mijn proefschrift. Jij hebt het allemaal al meegemaakt, dat schept een band. En natuurlijk ook een woord van dank voor de rest van de familie en mijn schoonfamilie voor jullie interesse en de nodige afleiding.

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Janneke
Bilthoven, 18 mei 2011



About the author

Curriculum vitae

(English)



Janneke Verkaik-Kloosterman (1978, The Netherlands) is a researcher who studies the topic of Nutrition with great enthusiasm from a wide scope. She makes use of her curiosity to find out how or why things are the way they are, or work the way they do. She uses her creativity to find new solutions. This had already begun during her pre-university education ('VWO' at the 'Katholieke Scholengemeenschap Hoofddorp' 1990-1997) where for her biology finals she compared the microbiological composition of yoghurt and a yoghurt-like product. For her physics finals she studied the tractive power of chewing gum. It was no surprise that after obtaining her 'VWO' diploma, Janneke began studying 'Nutrition and Health' at the then Agricultural University in Wageningen.

During this study she chose three main subjects: Epidemiology, Toxicology and Nutritional Science. Additionally, she extended her curriculum with molecular biology and didactics. For the latter, she completed several weeks teaching practice at the 'Hogeschool van Amsterdam' for the training 'Nutrition and Dietetics'. For her first major, she studied the role of a specific genetic variation in the association between smoking, nutrition and an early stage of colorectal cancer at the division 'Human nutrition and epidemiology' of Wageningen University. The effects of flavonoids and dioxin on gene expression were the research topics of her second major. She performed this research at the section 'Toxicology' of Wageningen University and 'Plant Research International'. As part of her third major she improved her laboratory skills at the division 'Human nutrition and epidemiology' at Wageningen University and additionally studied the uptake of heme iron by colon cells at the 'Institute for Nutrition and Food Technology' (INTA) in Santiago, Chili. In 2003 Janneke graduated *cum laude* and obtained her Master of Science degree.

Since 2004, Janneke works as a nutritional scientist at the Centre for Nutrition and Health of the National Institute for Public Health and the Environment (RIVM) in Bilthoven (The Netherlands). From 2008 she is also project manager on several projects about micronutrients and food fortification. At the RIVM she has worked (and is still working) on a wide range of various research topics. Some key words regarding her work at the RIVM are (in alphabetic order): benefit-risk assessment, consumer behavior, development of methods, dietary supplements, estimation of nutrient intake, evaluation of dietary intake, folic acid, food fortification, functional foods, iodine, micronutrients, nutritional status, salt, scenario analysis, sustainability, and vitamin D. Furthermore she was and is involved in European projects like 'QALIBRA' and the 'ILSI Europe' expert group 'mapping low micronutrient intake across Europe'. Her work on the development of methods to estimate dietary intake, on scenario analysis, and on food fortification resulted in this PhD-thesis.

(Nederlands)

Janneke Verkaik-Kloosterman (1978, Nederland) is een onderzoeker die zich met groot enthousiasme vanuit verschillende invalshoeken met het onderwerp voeding bezighoudt. Hierbij maakt ze gebruik van haar nieuwsgierigheid om er achter te komen hoe iets zit of waarom iets gaat zoals het gaat. Ze gebruikt haar creativiteit om vernieuwende oplossingen te zoeken. Dit begon al tijdens haar VWO-opleiding ('Katholieke Scholengemeenschap Hoofddorp' 1990-1997) waar ze voor haar eindexamen biologie de microbiologische samenstelling van yoghurt en een yoghurtachtig product vergeleek en voor haar eindexamen natuurkunde de trekkracht van kauwgom bestudeerde. Het was dan ook geen verrassing dat Janneke na het behalen van haar VWO-diploma met de opleiding 'Voeding en Gezondheid' aan de toenmalige 'Landbouwniversiteit Wageningen' startte.

Tijdens deze studie was ze breed georiënteerd en koos ze voor drie afstudeerrichtingen, namelijk epidemiologie, toxicologie en voedingsleer. Daarnaast verdiepte ze zich ook in moleculaire biologie en didactiek. Voor dit laatste liep ze een aantal weken stage bij de opleiding 'Voeding en Diëtetiek' van de 'Hogeschool van Amsterdam'. Tijdens haar eerste afstudeervak bij de afdeling 'Humane voeding en epidemiologie' van de Wageningen Universiteit deed ze epidemiologisch onderzoek naar de rol van genetische variatie op het verband tussen roken, voeding en voorstadia van darmkanker. Haar tweede afstudeervak deed ze bij de sectie 'Toxicologie' van de Wageningen Universiteit en bij 'Plant Research International'. Ze bestudeerde hier de effecten van flavonoïden en dioxine op genexpressie. Voor haar derde afstudeervak leerde ze een aantal laboratoriumtechnieken bij de afdeling 'Humane voeding en epidemiologie' van de Wageningen Universiteit. Vervolgens onderzocht ze de opname van heemijzer door darmcellen bij het 'Instituto de nutrición y tecnología de los alimentos' (INTA) in Santiago, Chili. In 2003 studeerde zij *cum laude* af.

Vanaf 2004 is Janneke als voedingskundig onderzoeker werkzaam bij het Centrum voor Voeding en Gezondheid (CVG) van het Rijksinstituut voor Volksgezondheid en Milieu (RIVM) in Bilthoven. Vanaf 2008 is ze ook projectleider op diverse projecten over microvoedingsstoffen en verrijking van voedingsmiddelen. Bij het RIVM werkte ze, en werkt ze nog steeds, aan een breed scala aan onderwerpen. Een aantal trefwoorden met betrekking tot haar werk bij het RIVM zijn (in alfabetische volgorde): benefit-risk assessment, berekenen van de innaming van nutriënten, consumentengedrag, duurzaamheid, evaluatie van de inneming, foliumzuur, 'functional foods', jodium, methodeontwikkeling, microvoedingsstoffen, scenarioanalyse, supplementen, verrijking van voedingsmiddelen, vitamine D, voedingsstatus en zout. Daarbij was en is ze betrokken bij diverse Europese projecten waaronder 'QALIBRA' en de 'ILSI Europe' expert werkgroep 'mapping low micronutrient intake across Europe'. Haar werkzaamheden op het gebied van methodiekontwikkeling bij het schatten van de inneming, scenarioanalyses en verrijkte voedingsmiddelen groeiden uit tot dit proefschrift.

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Overview of completed training activities

Description	Organiser & location	Year
Disipline specific activities		
<i>Courses</i>		
1 st international advanced course exposure assessment in nutrition research	Graduate school VLAG, Wageningen (NL)	2010
Nutrition and lifestyle epidemiology	Graduate school VLAG, Wageningen (NL)	2009
Animal agriculture and food safety risk analysis (module 2)	Vose Consulting, Gent (BE)	2008
Methods and techniques for survey studies	CBS, UvA, RIVM, Bilthoven (NL)	2008
Animal agriculture and food safety risk analysis (module 1)	Vose Consulting, Gent (BE)	2006
<i>Conferences & meetings</i>		
1 st international vitamin conference	Technical University of Denmark (DTU), Copenhagen (DK)	2010
Mini-symposium 'will novel protein foods beat meat?'	Graduate school VLAG, Wageningen (NL)	2010
Symposium 'integrated probabilistic risk assessment (IPRA)'	RIVM, Utrecht (NL)	2008
Functional foods symposium	FiFood Ingredients Europe, Amsterdam (NL)	2008
Workshop 'the micronutrient landscape of Europe'	ILSI Europe, Gubbio (IT)	2008
Symposium 'sodium reduction in foods: a matter of desire or ability?'	NVVL/FNLI, Wageningen (NL)	2008
Symposium 'developments in functional foods in Europe – International impact and significance'	ILSI international, Portomaso (Malta)	2007
6 th international conference on dietary assessment methods (ICDAM)	Copenhagen (DK)	2006
Nutritional forum of the Dutch Academy for nutritional sciences (NAV) – 'the court and judgement on scientific evidence'	Dutch Academy for nutritional sciences (NAV), Utrecht (NL)	2011
Nutritional forum of the Dutch Academy for nutritional sciences (NAV) – 'sustainable nutrition'	Dutch Academy for nutritional sciences (NAV), Utrecht (NL)	2008
Nutritional forum of the Dutch Academy for nutritional sciences (NAV) – 'publication pressure'	Dutch Academy for nutritional sciences (NAV), Utrecht (NL)	2007
Annual meeting of the Nutritional science community	NWO, Deurne (NL)	2008, 2007, 2006
Annual meeting of the Nutritional science community	NWO, Papendal (NL)	2005
<i>Training periods at other institutes</i>		
Visit to Prof. A. Carriquiry – C-SIDE training	IOWA State University, Ames (USA)	2006

Description	Organiser & location	Year
General courses & workshops		
Workshop 'improved communication on risks and results	RIVM, Bilthoven (NL)	2011
Personal branding	Novitijd, Bilthoven (NL)	2010
Workshop Endnote	RIVM, Bilthoven (NL)	2010
Starter's course R	RIVM, Bilthoven (NL)	2010
Workshop SAP for RIVM project managers	RIVM, Bilthoven (NL)	2010
Writing for RIVM professionals	Language centre VU, Bilthoven (NL)	2008
Workshop estimation of habitual intake	RIVM, Bilthoven (NL)	2008
Speed reading	Purple Monkey, Bilthoven (NL)	2007
The benchmark dose approach and dose-response modelling	IRAS/RIVM, Utrecht (NL)	2007
Working together in projects	Horizon training & development, Bilthoven (NL)	2006
Scientific writing in English	Language centre VU, Bilthoven (NL)	2005
Refurbish courses SAS (introduction, logistic regression, linear regression)	RIVM, Bilthoven (NL)	2006, 2004
Optional courses & activities		
Biometris research meeting 'modelling food intake and health'	Biometris, Wageningen (NL)	2010
Discussion meeting 'two times per week fish: feasible for human and fish?'	NVVL, Schiedam (NL)	2008
Ingredients for success: functional foods and other healthy products	VMT, Maarsse (NL)	2005
Nutrition and medicines: how do they interact?	Nascholing Medische Professie (NMP), Nieuwerkerk a.d. IJssel (NL)	2005
Symposium 'functional foods: nutrition and health'	Platform Life Sciences Noord Nederland, Leeuwarden (NL)	2004
Functional foods	Elsevier conferences, Leiden (NL)	2004
Preparation research proposals	RIVM, Bilthoven (NL)	2004-2010
RIVM Centre for nutrition and health lecture series	RIVM, Bilthoven (NL)	2004-2011
RIVM Centre for nutrition and health strategy meetings	RIVM, Utrecht (NL)	2007, 2005
RIVM Centre for nutrition and health review meetings	RIVM, Bilthoven (NL)	2004-2011

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