Part 3

Risk Management in Relation to Food and Its Components

chapter sixteen

Introduction to risk management

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16.1 Introduction

Part 1 of this textbook describes the ways in which consumers are exposed to dietary substances. Adverse effects and their underlying mechanisms of dietary substances are dealt with in Part 2. In Part 3, the information given in Parts 1 and 2 is integrated for managing toxicological risks due to food intake. Background information is provided to recognize and identify potential toxicological risks associated with dietary intake in present-day society. Some examples of health risks from food and its components will be given, and the importance of prevention, intervention, and control will be explained. In addition, a number of possibilities to reduce these risks will be described. Finally, an overview of the contents of the other chapters of Part 3 will be given.

Table 16.1 Ranking of food hazards, as perceived by the general public

1	Additives and food processing residues
2	Environmental contaminants (pollutants)
3	Nutritional imbalance
4	Naturally occurring toxins
5	Microbiological contamination

Table 16.2 Ranking of food hazards based on objective scientific criteria

1	Nutritional imbalance
2	Microbiological contamination
3	Naturally occurring toxins
4	Environmental contaminants (pollutants)
5	Additives and food processing residues

16.2 Public risk perception vs. expert risk opinion

Recently, the general public's interest in the quality of food has increased considerably. Also, more attention to this issue is paid by the press, in particular when hazards associated with contaminants and additives are concerned.

The five principal categories of food hazards are listed in Table 16.1 in order of importance according to the opinion of the general public.

The highest risk is believed to be associated with additives and contaminants, and the lowest with microbiological contamination. But is this ranking by the general public realistic? Section 16.3 discusses several examples which show that the ranking order of food hazards based on objective scientific criteria is completely different (see Table 16.2).

While, according to the general public, the toxicological risks from additives and contaminants are at the top of the list, the expert opinion scores them relatively low. The reverse applies to the toxicological risks from nutritional imbalance and microbiological contamination. The health risks acknowledged by experts are based on accepted scientific criteria. The next section describes the process of risk assessment in which the toxicological risks due to food intake are established on the basis of scientific data. Further, risk assessment will be discussed as the basic element of risk management.

16.3 Risk assessment, risk evaluation, and risk management

16.3.1 Risk management

Risk management is a complex process, based on information from various sources. A schematic overview of this process is presented in Figure 16.1.

First, the risk posed by a food component must be assessed, preferably in an objective and quantitative way. To do so, toxicological and epidemiological information is needed. Based on this information, guide values for components are determined. This is then followed by risk evaluation, in which the results of risk assessment are weighed against certain issues, such as those of socio-economical and political interest. Public perception also plays a role.

This process results in setting a standard. Such a standard is an important tool for risk management. Using the standard as a yardstick, the toxicological risks from food components are evaluated. If a standard is exceeded, the situation may become hazardous, and appropriate measures should be taken. These measures may concern risk intervention

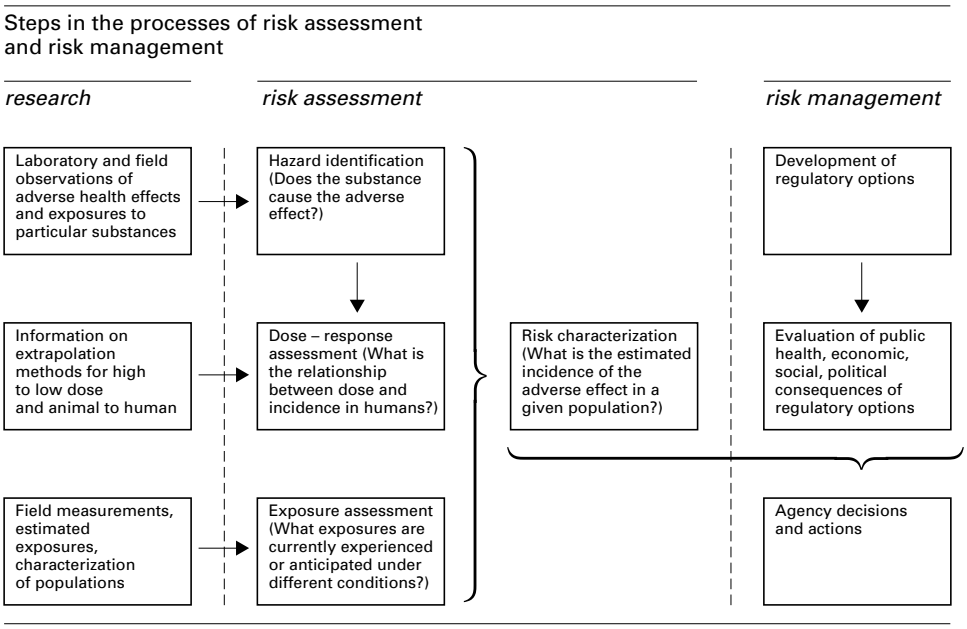

Figure 16.1 Framework for risk assessment and risk management. (Source: Grant and Jarabek, 1990.)

(relief of the risk situation) and risk prevention. In some cases, potential risks are regularly controlled or monitored by the authorities. It should be noted that risk management is also the concern of food producers, scientists, and consumers.

16.3.2 Methods of risk assessment

To assess the health risks from food components, information on the components, exposure to the components (see Part 1), the consumer, and the interactions between the components and the consumer (see Part 2) is needed. It should be noted that in many cases interactions with other dietary or environmental substances are also involved. Quantitative risk assessment therefore includes the following items:

- exposure assessment: daily intake of the components, duration and pattern of use;
- characterization of the relationship between exposure (dietary intake) and response (toxicity);
- elucidation of mechanisms;
- extrapolation of results from experimental animals to *humans*, and subsequently to *sensitive human populations*, the so-called high-risk groups;
- extrapolation from experiments, usually with high doses, to the real-life situation with exposure through the diet;
- extrapolation from short-term to *long-term exposure*;
- quantitative risk estimation, taking into account the estimated exposure (dietary intake) and the expected response (toxicity);
- estimation of the maximum allowable levels, guide values to be used in health policy. For foods, the Acceptable Daily Intake (ADI) (see Section 17.3.2 and 17.3.3) is applied.

Intermezzo

Calculation of guide values (ADI, TDI, PTWI), For non-carcinogenic components, the ADI is derived from the no-observed-adverse-effect level (NOAEL) (see Section 17.3.2 and Section 19.2.2) determined in experimental animals. NOAEL is divided by safety factors (e.g., 10 for taking into account the extrapolation from animals to humans, and 10 for taking into account a susceptible human subpopulation, such as infants), resulting in an integral safety factor of 100.

The guide value is not called ADI for all food components. For environmental pollutants, such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, the guide value is known as the tolerable daily intake (TDI) (see Section 17.4 and 17.4.1 and Section 21.4.4.3): such pollutants are not added to food intentionally, and are therefore "tolerable" rather than "acceptable." Contamination with lead is another example. For this element, the guide value is called the provisional tolerable weekly intake (PTWI). The toxic effects of lead are measured in relation to the lead blood concentration and not to the intake. PTWI is based on the observation that at a certain level of weekly intake, intake is balanced by elimination, and therefore no accumulation in the body will take place. Provisional means that the available safety data do not warrant a final conclusion.

For *carcinogenic components*, ADI is not derived from a NOAEL. In the US, for example for substances indicated as carcinogens, and especially for components initiating cancer, a zero-risk approach is followed. To this purpose, a so-called "calculated mortality" procedure is used, involving linear extrapolation to a virtual low risk level (e.g., 10^6 over a lifetime). It is assumed that carcinogenesis starts with a cell mutation, and that the risk of cancer development is related to the daily dose of the component concerned to the power m. M corresponds to the number of hits of the carcinogenic component that is necessary for the initiation of cancer. Generally, for m the value 1 is used: this is a conservative model in which exposure to a component and cancer incidence are linearly related. Using information on the carcinogenic dose of a component in animal experiments, the daily dose can be estimated that would induce extra cancer incidence in humans. Currently, the maximal tolerable extra cancer risk is estimated at 10^{-6} per lifetime.

The information necessary for quantitative risk assessment should be provided by toxicological studies and epidemiological studies. For the toxicological screening of additives and contaminants, standardized protocols have been developed. It should be borne in mind that for many components not all necessary information on exposure, toxicity, and dose–response relationships is available. The next section gives a few examples of risk assessment, evaluation, and management.

16.3.3 Examples of risk assessment, risk evaluation, and risk management

The examples in this section underline the importance of risk assessment, evaluation, and management. Furthermore, they will show the lack of necessary information and its implications for risk assessment and ranking of risks. In fact, these examples explain the ranking order of food hazards as shown in Table 16.2. In each example, the following items will be addressed: toxicity of the substance concerned, its daily intake and the duration of use, the sensitivity of the consumer, and the existence of high-risk groups.

16.3.3.1 Additives and processing residues

According to the general public, the toxicological risks associated with the intake of food additives and food processing residues are high. In particular, sweeteners, antioxidants, dyes, and preservatives are substances that have recently received large negative publicity.

In contrast, more objective scientific criteria prove the toxicological risk from additives to be minimal. For most of these substances extensive information on toxicity is available; acute and subacute toxicity as well as chronic toxicity, including mutagenicity, carcinogenicity and teratogenicity, have been investigated. Epidemiological (human) data, however, are scarce.

16.3.3.1.1 *Saccharin. Risk assessment — Toxicity.* Saccharin is a sweetener which, at very high doses, has been shown to cause bladder tumors in experimental animals. Generally, for components suspected to be carcinogenic, the risk is estimated from so-called "calculated mortality" (see Section 16.3.2), the linear extrapolation to a virtually low risk level. However, the doses at which bladder tumors were shown to develop in experimental animals were very high. The carcinogenicity of saccharin appeared to be due to the formation of bladder stones, rather than to genotoxicty (interaction at DNA-level). Therefore, the use of saccharin has been approved in the U.S. and Europe, and the ADI calculation using the calculated mortality procedure was not applied. For safety reasons, the maximum daily intake was advised to be 2.5 mg/kg body weight. No epidemiological study has shown that cancer incidence and mortality are related to the use of saccharin.

Risk assessment — Intake. In general, the daily intake of saccharin is below the ADI. Soft drinks are allowed to contain a maximum of 200 mg saccharin/kg. The average use of soft drinks is 300 g/day, which means a maximum of 70 mg saccharin/day. However, the daily saccharin intake by diabetic patients may be several times higher than that of non-diabetics.

Risk assessment — Sensitivity. There is no evidence for an increased sensitivity of specific subpopulations. Diabetic patients may be a high-risk group owing to their extensive intake, rather than high sensitivity.

Risk evaluation. Saccharin most probably does not pose an important health risk to humans. It has been calculated that a cancer risk may only develop at a daily saccharin dose present in 800 cans of soft drink (equivalent to the sweetness of 25 kg of sugar). This agrees with the fact that no increased cancer risk for diabetic patients has been observed in epidemiological studies.

Risk management. Saccharin is already the subject of risk management. Its use in foods is regulated by several food acts. Saccharin-containing sugar substitutes should be labeled with the warning not to use more than 80 mg/day. Saccharin is prohibited in baby food. Authorities are also involved in risk management by checking the observation of food regulations and by giving proper dietary advice and information to diabetics. Scientists take part in saccharin risk management, for example, by investigating the need for diabetics to use sugar substitutes.

For most additives the situation is very similar: extensive toxicological information is available, and legislation on use is provided for. To this end, so-called "positive lists" are made up, i.e., an additive not on this list is not allowed to be used unless explicitly stated otherwise by law. In fact, additives are considered to be the safest food components. The toxicological risks from this category are believed to be minimal. However, there are a few examples of additives for which the evaluation of toxicological risks is more difficult. This is mainly due to interactions with other toxic substances, such as contaminants.

16.3.3.1.2 *Nitrite (and nitrate).* Nitrite is an important preservative. It is used in the production of cheese and meat products. Nitrite inhibits the growth and development of *Clostridia* bacteria. Exposure to the contaminant nitrate mainly occurs by drinking water and consumption of leafy vegetables.

Risk assessment — Toxicity. Toxic effects of nitrite include methemoglobinemia, leading to disturbances in oxygen supply, and hypertrophy of the adrenal zona glomerulosa.

Nitrite can also react with secondary amines to form N-nitrosamines, which have proved to be carcinogenic in several experimental animals. The toxic effects of nitrate originate from its bacterial reduction to nitrite in the oral cavity. Some epidemiological studies have suggested that in subjects with gastric lesions a higher risk of gastric tumors may be associated with a high nitrate intake. However, such effects have not been observed in non-patients, so that the evidence is limited.

The no-observed-adverse-effect level (NOAEL) of nitrite as calculated from the results of chronic toxicity studies in rats is 10 mg $NaNO_2$ or 6.7 mg NO_2^- per kg body weight. Since there is a difference in the reduction of nitrate to nitrite between rats and humans, the NOAEL of nitrate is calculated from the NOAEL of nitrite. Estimating the conversion of nitrate to nitrite at 5%, the NOAEL for adults is: $100/5 \times 10$ mg/kg body weight = 200 mg $NaNO_3$ per kg body weight or 146 mg NO_3^- per kg body weight. Currently, the ADI values are 5 mg $NaNO_3$ per kg body weight (3.65 mg NO_3^- per kg body weight) and 0.2 mg $NaNO_2$ per kg body weight (0.13 mg NO_2^- per kg body weight).

Endogenous nitrosamine (dimethyl- and diethylnitrosamine) formation has been demonstrated in human volunteers on a diet rich in fish and nitrate-containing products. Using the conservative one-hit model with linear extrapolation for carcinogenic substances (see Section 16.3.2) the acceptable daily dose for prevention of a lifetime tumor incidence of 10^{-6} can be calculated. For dimethylnitrosamine, this value amounts to $16–186 \times 10^{0}$ mg/day, and for diethylnitrosamine to $11–14 \times 10^{0}$ mg/day.

Risk assessment — Intake. According to the Dutch Food Act, addition of nitrate to foods other than cheese, melted cheese, and meat products is not allowed. For these products maximum acceptable limits are indicated, e.g., a maximum of 500 mg KNO_3 and 200 mg KNO_2 per kg meat. For baby foods, a maximum of 50 mg NO_3^- per kg dry matter is allowed. Leafy vegetables such as spinach contain high concentrations of nitrate by nature. Standards given in the Dutch Food Act are a maximum of 3500 mg NO_3^- per kg in summer, and 4500 mg NO_3^- per kg in winter.

A recent survey has shown that the average daily nitrate intake in the Netherlands ranges from 1.25 mg/kg body weight for men aged 65 to more than 3.6 mg/kg body weight for 1 to 3 year olds. These data were arrived at by combining information from a dietary survey in a large representative subpopulation with information on the nitrate content of various food products. Particularly among children, an excessive nitrate intake (higher than ADI) occurred quite frequently (20 to 40%). The intake of nitrite is probably lower than the amount of nitrite formed endogenously, and is estimated at 2.3 mg NO_2^- per day. Water accounted for 4% of the nitrate intake, while leafy vegetables such as spinach accounted for about 45% of the total estimated intake.

Risk assessment — Sensitivity. Infants are more sensitive to nitrite, resulting in nitrite-induced methemoglinemia, often leading to oxygen supply problems. Also in babies, nitrate is more extensively reduced to nitrite.

Risk evaluation and management. The toxicological risk of the preservative nitrite itself is probably low. Its use is regulated, as is the use of other additives like saccharin.

A major cause for concern is the fact that for many people in general and many children in particular the intake of nitrate is larger than the ADI. In the future, more attention should be paid to the reduction of nitrate emission, e.g., in the form of fertilizer, into the environment. This is the concern of the authorities; the agricultural sector in particular is responsible for this. The health effects of high nitrate intake by children as well as the validity of the current ADI levels need to be examined in more detail. The effects of food preparation on the nitrate content and the consumption of leafy vegetables, especially in winter, ask for attention. Public advice concerning this issue should be considered.

16.3.3.2 Environmental contaminants

In general, contaminants are believed by the consumer to pose high risks to health. According to the experts, however, environmental contaminants only rank fourth on the list of food hazards, as shown in Table 16.2.

Concerning polychlorinated dibenzo-*p*-dioxins and biphenyls — the subject of the next example — the public paid much attention to the high levels found in milk from cows grazing in the vicinity of waste incinerators. However, the guide values for contaminants are based on cumulative, life-long exposure. Therefore, the life-long duration of individual exposures should be taken into consideration when estimating the risks from such high levels of contaminants.

16.3.3.2.1 *Polychlorinated dibenzo-p-dioxins and biphenyls.* Dioxins are emitted by waste incinerators. They are also known as by-products in pesticides. *Polychlorinated biphenyls* (PCBs) are well-known environmental contaminants, originating from their earlier use in transformers, and more recently in heat insulation.

Risk assessment — Toxicity. As far as the toxicity of dioxins is concerned, the congener 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is known best. Wasting syndrome (weight loss) is a characteristic acute toxic effect of TCDD in animals. TCDD is not mutagenic. It induces to a large extent the biotransformation enzymes in the liver. Therefore, it is assumed to have a tumor-promoting effect. One epidemiological study reported an association between TCDD exposure and cancer occurrence in a group of workers in a chemical industry. In animals, also immunotoxic and teratogenic effects have been observed. Humans which were exposed to TCDD, e.g., as a result of an occupational accident, developed chloracne. Dioxins and PCBs can have similar biological effects. However, they differ in the intensity of their effects. Therefore, the so-called TCDD equivalent (TEQ) was introduced, relating the toxicity of all dioxins and PCBs to that of TCDD.

When rats were submitted to a lifetime exposure of 1000 pg TCDD per kg body weight, the effects in the liver were minimal. This dose was considered to be a "marginal-effect-level" from which the TDI was calculated using a safety factor of 250. Therefore, the Dutch TDI was 4 pg TCDD or TCDD equivalents per kg body weight. Recently, however, the WHO assessed the TDI at 10 pg TEQ per kg body weight. This value was obtained by using a toxicokinetic approach for humans, resulting in a NOAEL of 1000 pg TCDD per kg body weight. A safety factor of 100 was applied to calculate TDI. This TDI is identical to a lifetime maximum of 255.5 ng TEQ per kg body weight for 70 years.

Risk assessment — Intake. The daily exposure of the general population is estimated on the basis of data on the intake of foods by a representative subpopulation in combination with data on the dioxin and PCB contents of foods as determined by chemical analyses. Using this approach, the daily exposure is estimated to be about 130 pg TEQ, i.e., 2 pg TEQ per kg body weight for adults and 7 pg TEQ per kg body weight for infants. More than 95% of this exposure results from the intake of animal fat. Dairy products are estimated to account for 30 to 50% of the total exposure. Recently, life-long exposure was estimated at 70 ng/kg body weight for dioxins and structurally related substances.

Risk assessment — Sensitivity. About 1% of the children younger than 6 years are estimated to have an exposure of more than 10 TEQ per kg body weight per day. In this respect, the dioxin and PCB contents of breast milk are also of importance. Dairy milk has been shown to contain 2 to 4 pg TEQ per g fat. For breast milk, this is about 35 pg/g fat, implying that breast-fed infants are exposed to about 250 pg TEQ per kg body weight.

Risk evaluation and management. The exposure of breast-fed infants is only four times lower than the marginal-effect-level for rats. Therefore, the TEQ of breast milk certainly needs attention. On the other hand, it should be noted that the TDI levels are cumulative

values, calculated on the basis of the results of a number of studies. This implies that conclusions are not allowed if, as is the case for breast-fed babies and children, these limits are exceeded during short periods of time. As far as risk evaluation is concerned, it should also be noted that from a nutritional point of view, for small babies breast milk has definite advantages over cow's milk. Therefore, breast-feeding should certainly not be discouraged. Other management measures, such as reduction of dioxin and PCB formation and emission, and checking of foods, are preferred.

Other groups with potentially higher exposures are, for example, industrial workers or individuals consuming milk and cheese from polluted areas near waste incinerators. Industrial safety, and food control should prevent toxic exposure of these groups.

16.3.3.3 Nutritional imbalance

As shown in Table 16.1, the consumer does not consider the risks associated with nutritional imbalance to be very important. However, since the beginning of this century it has become clear that the occurrence of several important chronic disorders, such as cardiovascular diseases and cancer, is affected by nutrients which form a substantial part of the diet. Epidemiological studies are particularly useful in bringing these risks to light. As a result, experts generally rate the risk of nutritional imbalance to be one of the highest of all food aspects. Several national nutritional councils have published extensive reports on the macro- and micronutrient contents of foods. For each nutrient, the so-called recommended dietary allowance (RDA) is given, also in relation to high-risk groups such as infants, children, pregnant women, and the elderly. These RDAs guarantee that the intake by 95% of the population is sufficient from a nutritional point of view. In addition, all major nutritional councils have prepared dietary recommendations for overall health maintenance. These guidelines are based on knowledge of the effects of nutrients and foods on the occurrence of chronic diseases, such as cardiovascular diseases and cancer.

Intermezzo

Guidelines for a healthy diet.

1. Pay attention to dietary variation.
2. Use dietary fats, in particular saturated fatty acids, in moderate amounts, and ensure a sufficient intake of polyunsaturated fatty acids.
3. Use dietary cholesterol moderately.
4. Ensure a liberate intake of complex carbohydrates and dietary fiber, and avoid frequent and high consumption of simple sugars.
5. Use alcohol in moderate amounts.
6. Use dietary salt in moderate amounts.

In the Netherlands, a large number of dietary surveys have shown that the macronutrient intake by the general population through the common diet does not match these guidelines. At present, the *average* daily energy intake by the population agrees with the recommended value, indicating that the energy intake of many people is too high (that is why the estimated prevalence of overweight individuals is about 20%!). The average fat intake is much higher than the recommended values, and this excess intake is estimated to be responsible for an extra 15% mortality due to coronary heart disease. In other Western countries, the picture as far as energy intake is concerned, is very much the same as that in the Netherlands. Also, sodium intake is high. The chronic "toxic" dose leading to hypertension in humans is about 60 g/day. Using a safety factor of 100, the ADI would be

10 mg NaCl per kg body weight. However, the usual intake by many Western populations is about 10 g/day, which is about 17 times the ADI. This means that the actual safety factor for salt (±6) is much lower than 100, the value commonly used for the determination of ADI levels for additives and contaminants (see Section 16.3.2). This is one of the reasons why the risks from nutritional imbalance are rated highest by the experts. The following example will show the toxicological risks from an important nutrient, dietary fat.

16.3.3.3.1 *Dietary fat.* Dietary fat is the main energy source in the human diet. The combustion of 1 g of fat results in the production of 37 kJ (or 9 Kcal). Dietary fatty acids are usually classified as follows:

- saturated fatty acids (SFAs), i.e., fatty acids with 4 to 18 C atoms. Well-known examples, occurring in large quantities in the diet, are palmitic acid (C16:0, i.e., number of carbon atoms:number of double bonds) and stearic acid (C18:0);
- monounsaturated fatty acids (MUFAs), fatty acids like oleic acid (C18:1), the main constituent of olive oil;
- polyunsaturated fatty acids (PUFAs), containing two or more double bonds, e.g., linoleic acid (C18:2). PUFAs are essential dietary components. The polyunsaturated fatty acids can be distinguished into n-6 and n-3 acids, referring to the location of the first double bond. Especially, fish oils are rich in n-3 PUFAs (see Chapter 6.2.1.1).

Risk assessment — Toxicity. Unsaturated fatty acids are susceptible to oxidation. The oxidation products may have several adverse effects, e.g., tumor induction. In addition, depletion of the anti-oxidant pool in the body may occur, and in some cases vitamin E deficiency may develop. Erucic acid (C22:1) is found in rapeseed oil and has been shown to induce cardiopathy (myocardial fibrosis) in experimental animals. For the combination of erucic and linolenic acid (C18:3, n-3), a NOAEL of 1% of vegetable oil intake has been suggested. However, it should be noted that the epidemiological evidence for these effects is limited.

A recent epidemiological study has suggested that PUFAs are associated with an increased risk of chronic non-specific lung disease (CNSLD). For CNSLD, a relative risk of 1.6 was observed comparing a linoleic acid daily intake equivalent of more than 5.6% of the total energy intake with an intake of less than 4% of energy. Since the prevalence of high linoleic acid intake was 25%, this results in a population attributable risk (see Part 2, Chapter 15) of 13%.

The recommended intakes of fatty acids are usually expressed in terms of energy percentages. For SFAs, a range of 0 to 10% of the energy intake is advised, while for PUFAs, a range of 3 to 7% of the energy intake is recommended. Since the total fat intake is recommended not to exceed 30% of the energy intake, the remainder can be provided by MUFAs.

Risk assessment — Intake. An extensive survey among a representative sample of the Dutch population has shown that in 1987/1988 the average daily intake of dietary fatty acids was 97 g/day. The intake of SFAs was 40 g/day (16.3% of the energy intake), and the intake of PUFAs 16 g/day (6.4% of the energy intake). The daily intake of erucic acid is estimated at less than 1% of the energy intake.

Risk assessment — Sensitivity. No information on the sensitivity of particular subpopulations to dietary fatty acids is available. On the other hand, it is known that infants may suffer from deficiency of the diet in essential fatty acids, possibly resulting in reduced neurological functions.

Risk evaluation and management. Toxic effects of several MUFAs and PUFAs have been observed, but at doses much higher than the usual intake. Therefore, these specific fatty

acids probably do not cause a great health hazard, although their suggested role in the development of other chronic diseases such as CNSLD should be carefully considered in the future. In addition, it should be noted that this example clearly shows a dilemma with regard to risk management. One of the possibilities to reduce the intake of unsaturated fatty acids is to discourage the population's consumption of PUFA-rich food. This will not be useful if, instead, the consumption of SFA-rich foods increases, as this will enhance the risk of hypercholesterolemia and coronary heart disease. In fact, the adverse effects of SFAs on public health have been estimated to be more important than the potential detrimental role of unsaturated fatty acids in the induction of tumors and CNSLD. Also, positive effects of n-3 PUFAs have been reported.

Typically, there is an optimum for nutrient intake. Deficiencies as well as toxic effects need to be prevented. Public advice on nutrition in general, and fatty acids in particular, must be balanced and careful. This example illustrates a second difficulty in nutrition education: what is consumed is food rather than nutrients or food components. Fish, with the potentially beneficial n-3 PUFAs, may also contain small amounts of environmental contaminants such as dioxins and mercury. Therefore, pros and cons of fish consumption need to be weighed before univocal public advice can be given.

Besides authorities (guidelines, food labeling, public advice) and consumers (dietary habits), scientists and food producers also should be aware of these dilemmas. The recommended changes in dietary habits of the general public (see Section 16.3.3.3) will not result from public advice only. Food labeling may help, but also alternative food products should be developed and become available. A price policy would also contribute to behavioral change in people.

Intermezzo

Examination of cardiovascular toxicity, a necessity? In general, the toxicological evaluation of substances includes acute, subacute, and chronic toxicity testing. Teratogenicity, mutagenicity, and carcinogenicity are studied. Only for a small number of substances (e.g., lead, cadmium) are cardiovascular effects considered. This is remarkable. For example, the total mortality in the Netherlands in 1989 was 9.1 per 1000 for men and to 7.9 per 1000 for women. For men, 30% of mortality was due to cancer, for women this was 25%. However, the contribution of cardiovascular disease to total mortality was larger: 41% for men, and 43% for women. For both men and women, acute myocardial infarction was the most important cause of death (17 and 13% of total mortality respectively). This indicates that for a complete evaluation of the health risk due to substances, a standardized cardiovascular or atherosclerotic screening is also necessary.

16.3.3.4 Naturally occurring toxins

For most naturally occurring toxins information is scarce. Also, information on their presence in food is usually lacking, which makes risk assessment difficult. Recently, the scientific interest in the potential toxic effects of naturally occurring toxins has increased. This concerns in particular mycotoxins, phytotoxins and phycotoxins. The lack of information may be one reason for the low ranking of hazards from these food components by the general public (Table 16.1). On the other hand, perhaps in combination with the fact that one of the most potent carcinogenic substances, aflatoxin, is a natural toxin, it may also explain the relatively high ranking of naturally occurring toxins by the experts (Table 16.2).

Aflatoxin is a mycotoxin occurring in peanuts and cereals originating from hot, humid countries. In developed countries, consumers may be exposed to aflatoxin as a result of

international trade and the presence of the contaminated cereals in cattle feed.

Risk assessment — Toxicity. Many animals have been shown to develop hepatic tumors after exposure to aflatoxin B1. Several epidemiological studies on hepatic cancer have suggested that aflatoxin is involved in the etiology of this disease, in combination with hepatitis B virus. Aflatoxin M1 is also carcinogenic, but is less potent than aflatoxin B1. Such as for other carcinogenic substances, the cancer risk is derived from the "calculated mortality" procedure as described in Section 16.3.2.1. According to the Dutch Food Act, the content of aflatoxin B1 in foods is not allowed to exceed 5 μg/kg. The maximum content of aflatoxin M1 in milk is set at 0.05 μg/kg, because of its frequent use. Aflatoxin is not allowed to be present in groundnuts *(Arachis hypogaea)* at all or in any products prepared from them.

Risk assessment — Intake. A recent analytical survey reported that aflatoxin may be present in small quantities in peanuts, peanut products, buckwheat, and nutmeg. In baby foods, the average content appeared to be 0.06 μg/kg. Aflatoxin M1 was also found in cow's milk, but the standard level was not exceeded. Aflatoxin levels are higher in winter than in summer, due to the addition of cattle feed concentrate.

Risk evaluation and management. Apparently, in the Western countries the exposure to aflatoxins has increased due to the import of tropical products. Until now, however, no detrimental effects have been reported, and no elevated aflatoxin levels in food have been found. Surveillance of foods remains necessary, however, among others because the use of tropical products in cattle feed is expected to increase.

To prevent the occurrence of aflatoxin in these products, food processing in developing countries should be improved and controlled. In other words, Good Agricultural Practice (GAP) should be applied. The problem is monitored by organizations like the Food and Agricultural Organization (FAO). Unfortunately, however, local funds and equipment are often still lacking.

16.3.3.5 Bacterial contamination

The general public rates the risk due to microbiological contamination as minimal. According to objective scientific criteria, this risk ranks much higher on the list of toxicological risks from foods.

Many bacterial species produce toxins. These can be divided into two main groups:

- toxins formed after consumption of contaminated food, causing gastrointestinal disorders. These disorders have a long incubation period, as the toxins are only produced after multiplication of the microorganisms inside the host. Examples of this type of infection are *Salmonella* poisoning and cholera;
- toxins produced in the food before intake. The symptoms appear shortly after consumption, and the patients are not contagious. A well-known example is the induction of enterotoxic effects, caused by the consumption of food contaminated by *Staphylococcus aureus*.

Risk assessment — Toxicity. *Staphylococcus aureus* produces several toxins, classified as enterotoxins A to E. The toxins (mostly A) are responsible for acute food poisoning. The symptoms (diarrhea, vomiting) are mild, and occur shortly after the meal (1 to 6 hours). Therefore, most epidemics are not recognized.

Risk assessment — Intake. *S. aureus* can survive in foods with high salt concentrations and in briefly cooked protein foods. Epidemics are usually caused by contamination of ham, pastries with cream, or milk products.

Risk assessment — Sensitivity. Infants, sick people, and elderly people are groups whose reduced resistance may make them more sensitive to the toxins.

Risk evaluation and management. Based on the official data on the number of acute food poisonings, the risk would seem low. Only few cases are registered annually. However, the official records of microbiological contaminations do not represent the actual situation. A population survey has shown that in the case of diarrhea only 25% of the subjects consult a general practitioner. This means that identification of the pathogenic bacteria only takes place in a small subpopulation. The percentage of all cases of food poisoning that are officially recorded is estimated at only 1 to 5%. This suggests that microbiological contamination of food is a larger public health problem than generally assumed. Prevention of these intoxications is therefore important. Special attention should be paid to the production of foods. It is important to do this according to the guidelines known as Good Manufacturing Practice. Factors such as hygiene, temperature, pH, and water activity need to be controlled regularly by the industry as well as by governmental agencies. However, it should be noted that 75% of the contaminations occur where food is prepared, such as restaurants, hospitals, nursing homes, catering companies, and kitchens at home. Again, control by governmental agencies is necessary. In addition, it is important that the consumer is made aware of proper food handling. Especially, cooling and heating of food need attention, and public advice and education will be needed.

16.4 Important issues in risk management

The examples discussed in the preceding subsections serve two purposes. The first aim was to give an impression of the toxicological risks associated with food intake by the population. As shown in Tables 16.1 and 16.2, the perception of the toxicological risks from different food components differ between the public and the experts. The examples discussed show that in reality the highest risks do not originate from food additives and contaminants, as perceived by the public, but from nutritional imbalance and microbiological contamination. In fact, the risks due to additives are minimal. The difference in ranking between consumers and scientists is a cause for concern, especially as risk prevention and control is also partly the responsibility of the consumer.

As shown by the examples, the perception of toxicological risks by the public is different from the real situation. As will be discussed in Chapter 22, the public's perceptions of food risks are affected by information from the media. Also, psychological factors play a role. Self-inflicted risks, such as risks associated with food habits, are more easily accepted than risks coming from other sources (food producers). This may be due to the idea that risks posed from outside cannot be managed. These issues need to be taken into account, when public advice and behavioral health education are parts of the risk management process, as in the case of microbiological contamination.

The second purpose of the above examples is to introduce briefly the upcoming chapters. In Chapter 17, the basic requirements for risk assessment will be described in more detail. Attention will be paid to the standard toxicological protocols, and the nationally and internationally required toxicological data. Also, the importance of information on biotransformation and toxicokinetics will be stressed (see also the remarks on polychlorinated dibenzo-*p*-dioxins and biphenyls).

As described in the example on nitrite and nitrate, the calculation of the ADI values requires extrapolation from experimental animals to sensitive human populations. Chapter 18 deals with the factors affecting and hindering extrapolation, such as species differences and variation, and measurement errors, in more detail. New possibilities, involving toxicological modelling, will be discussed.

As shown in Figure 16.1, standard setting is a main step in the process of risk management. In Chapter 19, the principles, possibilities, and limitations of standard setting are

described. Standard setting is not only based on risk assessment. As shown in the example of dietary fat, it also involves careful weighing against other issues, such as political and socio-economical interests. Special attention will be paid to harmonization of standard-setting procedures on national as well as international level. The latter has been shown to be important in the example of aflatoxin, as the standard setting in tropical countries affects the potential exposure to aflatoxin in other countries.

Up to now, epidemiological data are only rarely used as additional information for risk evaluation and standard setting. This is due to methodological limitations, such as low sensitivity and difficulties in characterizing the exposure of participants. As mentioned in the example of saccharin, an epidemiological study on cancer risk differences between diabetics, who are likely to use more saccharin, and healthy subjects revealed no statistically significant differences. As will be shown in Chapter 20, this study is one of a few examples of epidemiological studies that have contributed to risk assessment. It is expected that the input of epidemiology on risk management will increase in the coming years, as more possibilities become available for the use of so-called biomarkers to characterize exposure and disease. This is a fortunate development, as an advantage of epidemiological studies is their direct relevance to the human situation.

Chapter 21 provides a detailed overview of risk assessment, risk evaluation, and risk management.

16.5 Summary

The public perception of toxicological risks from foods differs from the experts' opinion. Several examples show that nutritional imbalance and microbiological contamination pose the highest food-related risks, followed by naturally occurring toxins and environmental contaminants. The risks from additives are only minimal.

These results are based on quantitative risk assessment, an important step in the risk management process. After identification of the risk, an evaluation against other interests (economical, social, political) takes place, before management measures are issued. The examples show that the responsibility for risk management, i.e., control and prevention of health risk, is shared by authorities, scientists, and food producers, as well as consumers.

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