Dietary Fat

1. Background Information and Definitions

1-1. Definitions and Classifications

Fats are compounds that are insoluble in water but soluble in organic solvents(1). The nutritionally important fats include fatty acids, neutral fat, phospholipids, glycolipids, and sterols. Fatty acids consist of a carboxyl group at the end of a hydrocarbon chain (composed solely of hydrogen and carbon), and have a total number of carbon atoms ranging from 4 to 36. The presence of a carboxyl group allows fatty acids to be metabolized *in vivo* and used as an energy source or cell membrane component. Fatty acids can be saturated - without a double bond between carbon atoms, monounsaturated - with just one double bond in the fatty acid chain, and polyunsaturated - with more than one double bond in the fatty acid chain. Polyunsaturated fatty acids are further differentiated into n-3 fatty acids (third carbon atom from the methyl end) and n-6 fatty acids (sixth carbon atom from the methyl end), based on the position of the first double bond from the methyl end. Unsaturated fatty acids with double bonds are geometric isomers, which are classified into trans and cis isomers. A majority of the unsaturated fatty acids that exist in the natural world are cis isomers; only a few trans isomers exist. Neutral fat can be formed of one, two, or three fatty acids combined with glyceride to form a monoacylglycerol, diacylglycerol, or triacylglycerol (triglyceride, triglycerol, neutral fat). Phospholipids are lipids containing phosphoric acid attached with one or two ester bonds. Glycolipids are lipids in which one or more monosaccharides are attached to a lipid moiety with a glycosidic bond.

Cholesterol is an amphiphilic molecule with a hydrocarbon chain and steroid skeleton composed of a ring of four carbons. We examined dietary cholesterol as a dietary fat.

2. DRIs for Dietary Fat

2-1. Characteristics of Reference Setting

The DRIs for total fat, saturated fatty acids, n-6 fatty acids, and n-3 fatty acids were established. The primary role of the macronutrients (fat, carbohydrates, and proteins) is to supply energy to the cells. If the body weight, and physical activity level (PAL) do not change, the energy intake remains largely within a fixed range. Therefore, when the fat intake increases (or decreases), the intake of carbohydrates decreases (or increases). Therefore, the DRIs for fat need to be set taking into account carbohydrate and protein intakes. This is why the DRIs for fat are shown as a percentage of total energy intake, i.e., the energy ratio (%energy: %E), for the tentative dietary goals (DG) for the prevention of lifestyle-related diseases (LRDs) of individuals aged 1 year or older. The DG of infants is shown as %E. Saturated fatty acids are also shown as %E from the standpoint of preventing LRDs. However, the DGs for n-6 and n-3 fatty acids, which are essential fatty acids, are shown as absolute amounts (g/day) not influenced by total energy intake. When body weight correction is necessary, the reference body weight of

each sex and age group was used. The n-3 fatty acids examined were alpha-linoleic acid derived from edible cooking oil, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) derived from fish.

2-2. Total Fat (Total Fat Energy Ratio)

2-2-1. Basic Matters and Intakes

2-2-1-1. Basic Matters

In the DRIs for fat, the total fat energy ratio was set as the DG for those aged 1 year or older, and adequate intake (AI) for infants.

2-2-1-2. Intakes

The median dietary fat intake ratio of Japanese people aged 30–49 years, based on the results of the 2010 and 2011 National Health and Nutrition Survey (NHNS)[(2)], is 25.8%E in men and 28.3%E in women. The fat energy ratio decreases with age. Meanwhile, the median total energy intake of Japanese people aged 30–49 years is 2,078 kcal in men and 1,635 kcal in women. Based on the United States Department of Agriculture's *Continuing Survey of Food Intakes by Individuals* (CSFII, 1994–1996, 1998), the median ratio of fat in those aged 31–50 years is 33.7%E in men and 32.8%E in women. Therefore, the fat energy intake of Japanese people is lower than that of Americans.

2-2-2. To Avoid Inadequacy

2-2-2-1. Infants (Methods Used to Set the AI)

Breast milk was considered to be an ideal source of nutrients for infants. Therefore, the total fat energy ratio of breast milk[(3,4)] and the average milk intake was calculated (0.78 L/day)[(5,6)] and set as the AI. Infants aged 0–5 months obtain their nutrients from breast milk (or infant formula), but from the age of 6 months, they begin taking baby food, and between ages 6 and 11 months, they obtain their nutrients from both breast milk (or infant formula) and baby food. This period is regarded as the transition period to early childhood, so the average AIs (medians) of 0–5-month-old infants and 1–2-year-old infants were used.

The fat concentration of breast milk consumed by 0–5-month-old infants is 3.5 g/100 g, and, thus, the energy derived from fat in 100 g of breast milk is 3.5 g × 9 kcal = 31.5 kcal/100 g. The total energy in 100 g of breast milk is 65 kcal, which yields a fat energy ratio of 48.46%, as shown below. The AI was rounded to be set at 50%E.

Fat energy ratio (%E) = 31.5/65 = 48.46%E

In addition, the fat intake, per day, of infants aged 0–5 months is 27.8 g/day when the fat concentration of the breast milk of Japanese women (35.6 g/L) and the average milk intake (0.78 L/day) are multiplied.

The average AI of infants aged 0–5 months, as obtained from the above formula and

median (male and female average) intake from the 2010 and 2011 NHNS of infants aged 1–2 years, was taken for infants aged 6–11 months. When calculated as follows, a fat energy ratio of 37.9%E was obtained, which was rounded to an AI of 40%E.

Fat energy ratio (%E) = [48.46 + (27.2 + 27.6) /2] /2 = 37.9%E

Furthermore, the fat intake per day of infants aged 6–11 months was 29.1 g. This was obtained by taking the average of the fat intake of infants aged 0–5 months (27.8 g/day) and the median (male and female average) intake from the 2010 and 2011 NHNS of infants aged 1–2 years.

2-2-3. For the Prevention of the Development and Progression of LRDs

2-2-3-1. Association with LRDs

Intake of a low-fat/high-carbohydrate diet increases postprandial blood glucose levels and fasting triacylglyceride levels (neutral fat), and decreases blood high-density lipoprotein (HDL) cholesterol levels[7,8]. No studies have shown that this kind of a diet in healthy individuals increases the risk of arteriosclerosis, obesity, or diabetes; however, if these patterns of blood lipid levels persist over a long period of time, the risk of coronary heart disease increases. The data of a large number of interventional studies were reviewed in the US-Canada DRIs[7]. These data were used to conduct a regression analysis of the associations between fat or carbohydrate energy ratio, blood HDL cholesterol, total cholesterol/HDL cholesterol, and triglycerides. As a result, it was determined that, to achieve an appropriate blood concentration of these nutrients, a dietary fat energy ratio of at least 20%E is optimal. Additionally, extremely low-fat diet may impair the absorption of fat-soluble vitamins (particularly vitamins A and E)[9], and since there is a positive correlation between the fat and protein contents of food, the intake of sufficient protein may be made difficult. Fat has the highest energy density, and thus it is assumed that the intake of energy is unlikely to be adequate when the intake of fat is low. Therefore, an intake of at least 10–15%E is considered appropriate for adults[10].

Unlike a low-fat/high-carbohydrate diet, a high-fat/low-carbohydrate diet increases HDL cholesterol levels, and decreases fasting triacylglyceride levels. However, low-density lipoprotein (LDL) cholesterol levels, postprandial free fatty acid levels, and postprandial triglyceride levels increase[11,12]. Furthermore, it is of concern that the risk of total mortality and type 2 diabetes may increase, as taking a high-fat/low-carbohydrate diet results in an inadequate intake of minerals contained in cereals, and a higher intake of protein[13].

In a meta-analysis of cohort studies published in 2013[14], the consumption of diets with a large intake of fat, compared to carbohydrates, increased the likelihood of total mortality 1.3-fold. Other cohort studies suggested that total mortality may be influenced by the type of lipid. The Nurses' Health Study and Health Professionals' Follow-up Study found that total mortality increased in groups with a high intake of animal-derived foods, whereas the total mortality was decreased in groups with a high intake of plant-derived foods[15]. However, a meta-analysis of interventional studies over more than six months (excluding studies on n-3

fatty acids)[16], did not reveal a decrease in total mortality or the prevalence of cardiovascular disease even when total lipid intake was reduced, which was different from the results of the above-mentioned cohort studies.

With regards to the prevention of obesity, a meta-analysis (including 33 interventional studies) conducted in 2012, targeting primarily non-obese individuals, demonstrated that the body weight decreased when the total fat intake reduced[17]. Specifically, the body weight decreased by 0.19 kg for every 1%E reduction in the total fat intake. However, it should be noted that a low-carbohydrate diet (fat: 30%E, carbohydrates: 40%E) had a stronger effect on weight loss than a low-fat diet (fat: 20%E, carbohydrates: 55–60%E) in a group of obese individuals with high blood insulin levels and strong insulin resistance[18]. In populations with a small number of obese individuals, such as those in Japan, there is concern that the risk of obesity, metabolic syndrome, diabetes, and coronary heart disease may increase when the fat energy ratio rises. A large-scale interventional study in postmenopausal women found that the development of diabetes was significantly reduced when a decrease in the total fat intake and weight loss were observed[19]. A high-fat diet increases the intake of saturated fatty acids, and saturated fatty acids raise serum LDL cholesterol levels, which further increase the risk of coronary heart disease. For this reason, the U.S. National Cholesterol Education Program Step I Diet and Step II diets stipulate that a fat energy ratio less than 30% is appropriate[20]. According to a report on a meta-analysis of 37 interventional studies that assessed this National Cholesterol Education Program[21], a lipid energy intake of less than 30% resulted in decreased serum total cholesterol, LDL cholesterol, triglyceride and total cholesterol/HDL cholesterol levels, and body weight.

2-2-3-2. Children and Adults (Methods Used to Set the DG)

The DG for saturated fatty acids was set at 7%E or less. The median (AI) intakes of n-6 and n-3 fatty acids in Japanese people are 4–5%E and approximately 1%E, respectively, and the median intake of monounsaturated fatty acids is at least 6%E[2], leading to a fatty acid total of 18–19%E. Triacylglycerides and phospholipids contain glycerol in addition to fatty acids, and account for approximately 10% of all fat. Taking into account glycerol moieties, the lipid energy ratio is 20%E (= 18 ÷ 0.9) to 21%E (= 19 ÷ 0.9). This was rounded to 20%E to be set as the value below the DG range.

Moreover, considering obesity, diabetes prevention, and mortality (reports of cohort studies), an energy ratio less than 30%, which is viewed as a low fat energy ratio in Western countries, is recommended. For this reason, the lipid energy ratio was set at 30%E, which is above the DG. In the US-Canada DRIs[7], because 30%E is considered difficult to achieve in typical individuals due to the current intake status, the value is set at 35%E instead.

2-3. Saturated Fatty Acids

2-3-1. Basic Matters and Intake Status

2-3-1-1. Basic Matters

Saturated fatty acids include caprylic acid (8:0), capric acid (10:0), lauric acid (12:0), myristic acid (14:0), palmitic acid (16:0), and stearic acid (18:0). Saturated fatty acids are consumed from foods, and can be synthesized from acetyl coenzyme A (CoA) which is an intermediate metabolite of carbohydrate and protein. Therefore, no estimated average requirement (EAR), recommended dietary allowance (RDA), or AI can be set. However, saturated fatty acids are an important source of energy, and are necessary to maintain an appropriate energy ratio and ensure an appropriate fatty acid intake ratio. In addition, interventional studies suggest that lowering the intake of saturated fatty acids can reduce the risk of myocardial infarction. Therefore, a DG was set accordingly.

2-3-1-2. Dietary Intake Status

The median intakes of Japanese people aged 30–49 years, based on the results of the 2010 and 2011 NHNS[(2)], are 15.2 g/day and 13.8 g/day, respectively, and the energy ratios are 6.6%E and 7.6%E in men and women, respectively. The median intakes in Americans aged 31–50 years are 31.4 g/day and 20.3 g/day, and the energy ratios are 11.4%E and 11.0%E in men and women, respectively[(7)]. Therefore, the intake of Japanese people is approximately 40% lower than that of Americans, in terms of the energy ratio.

2-3-2. For the Prevention of the Development of LRDs

2-3-2-1. Association with LRDs

A meta-analysis of cohort studies found that, when saturated fatty acids were substituted with polyunsaturated fatty acids, the hazard ratio for coronary heart disease decreased to 0.87; however, when monounsaturated fatty acids or carbohydrates were substituted, the ratios increased to 1.19 or 1.07, respectively. The lack of a strong correlation between saturated fatty acid intake and myocardial infarction may be attributed to the fact that different effects may be induced depending on the type of saturated fatty acid, and the risk of coronary heart disease varies depending on the intake of foods containing saturated fatty acids[(22)]. The intake of saturated fatty acid derived from dairy products prevents the development of cardiovascular disease, whereas the intake of saturated fatty acid derived from meats is a risk factor for cardiovascular disease[(23)]. A cohort study in Japanese people aged 45–74 years (the Japan Public Health Center-based Prospective [JPHC] study)[(24)], found a positive correlation between saturated fatty acid intake and myocardial infarction. The hazard ratio for myocardial infarction increased to 1.24 in the intermediate quintile group (saturated fatty acid intake: 16.3 g/day, 7.2%E) and 1.39 in the largest quintile group (saturated fatty acid intake: 24.9 g/day, 10.9%E), compared to the lowest quintile group (saturated fatty acid intake: 9.6 g/day, 4.4%E). Many interventional studies in Western countries have shown that reducing

saturated fatty acid intake lowers the prevalence of coronary heart disease, the degree of arteriosclerosis, and LDL cholesterol levels. For example, a meta-analysis that pooled interventional studies (including primary and secondary prevention) found that, when saturated fatty acids are substituted with polyunsaturated fatty acids, and polyunsaturated fatty acid intake (including both n-6 and n-3 fatty acids) is increased to an average of 14.9%E, the relative risk of myocardial infarction (including death) decreases by 19%, compared to the control group (average polyunsaturated fatty acid intake of 5.0%E).

Pertaining to the relationship between diabetes and obesity, observational studies have demonstrated a positive association between diabetes and saturated fatty acid intake; however, these studies did not find any association between diabetes and saturated fatty acid intake when adjusted for body mass index (BMI)[25,26]. However, cross-sectional studies that examined the relationship between saturated fatty acid intake and insulin resistance, which is a cause of diabetes, found a positive correlation between saturated fatty acid intake and insulin resistance even after BMI adjustment[27–29]. Interventional studies have also revealed that insulin resistance occurs when a diet high in saturated fatty acids is consumed[30,31]. Interventional studies comparing monounsaturated fatty acids demonstrated that insulin sensitivity decreases, and insulin secretion increases when the saturated fatty acid intake is increased[30,32]. Therefore, these results suggest that an increased intake of saturated fatty acids causes obesity and insulin resistance (independent of obesity), thereby increasing the risk of diabetes.

Meanwhile, cohort studies in Japanese people revealed that the risk of stroke, particularly cerebral hemorrhage-related mortality or morbidity, increased in those with a low saturated fatty acid intake[24,33–36]. The recently published JPHC study found that there is a negative linear correlation between saturated fatty acid intake and cerebral hemorrhage or lacunar infarction, whereby the risks of cerebral hemorrhage and lacunar infarction are reduced as the saturated fatty acid intake increases[24]. The hazard ratio for cerebral hemorrhage increased to 0.84 in the intermediate quintile group (saturated fatty acid intake: 16.3 g/day, 7.2%E) and 0.61 in the largest quintile group (saturated fatty acid intake: 24.9 g/day, 10.9%E), compared to the lowest quintile group (saturated fatty acid intake: 9.6 g/day, 4.4%E).

However, animal experiments have not shown that cerebral hemorrhage can be prevented by an increased saturated fatty acid intake[37]. Therefore, it is not known if decreases in saturated fatty acid intake may increase the risk of cerebral hemorrhage. Animal protein intake adjustments are insufficient in cohort studies and increased morbidity from diseases such as cerebral hemorrhage may be caused by decreased animal protein intake associated with a reduced saturated fatty acid intake. In fact, a meta-analysis that examined the relationship between the intake of dairy products and stroke found that the relative risk of cerebral hemorrhage decreased to 0.75 in the group with the largest intake of dairy products, compared to the group with the lowest intake[38].

2-3-2-2. Adults (Methods Used to Set the DG)

A positive correlation between saturated fatty acid intake and serum (or plasma) total cholesterol concentration has long been known from Keys's[39] and Hedsted's[40] formulas. In addition, a meta-analysis of 27 interventional studies revealed results that are very similar to those of another meta-analysis of a large number of studies[8,41]. This also applies to LDL cholesterol levels[8,41]. However, a meta-analysis that examined serum cholesterol levels according to the number of carbon atoms in saturated fatty acids found significant rises in the levels of lauric acid, myristic acid, and palmitic acid (12–16 carbon atoms), but observed no significant change in the stearic acid levels (18 carbon atoms) [8]. It has been pointed out that even among saturated fatty acids, the effect on serum cholesterol levels differs according to the number of carbon atoms in them. Therefore, an excessive intake of saturated fatty acids (all saturated fatty acids, regardless of the number of carbon atoms) is assumed to be a risk factor for arteriosclerosis, and, particularly, myocardial infarction. Nevertheless, a meta-analysis summarizing the results of 21 cohort studies (16 that examined the incidence of myocardial infarction) that examined the relationship between saturated fatty acid intake and the incidence of cardiovascular disease found no significant correlation with myocardial infarction[42]. However, serum total cholesterol levels were adjusted in seven of these studies; it has been suggested that over-adjustment may apply to this case at the time of statistical calculation, and, therefore, the relationship between saturated fatty acid intake and cardiovascular disease may not be correctly assessed[43]. Two cohort studies were performed in Japanese people: one observed no significant correlation with myocardial infarction mortality[36], while the other observed a significant positive correlation with the incidence of myocardial infarction[24]. Incidentally, according to a pooled analysis examining the data of 11 cohort studies on the difference in the risk of myocardial infarction or death when saturated fatty acids, accounting for a fixed total energy intake of 5%E, are switched to the respective amount of fatty acids or carbohydrates, both the incidence of and mortality associated with myocardial infarction are significantly decreased when saturated fatty acids are substituted with polyunsaturated fatty acids[44].

This series of results suggests that, to prevent both the development and progression of arteriosclerosis, particularly myocardial infarction, it is important to not only restrict the intake of saturated fatty acids, but also to simultaneously increase the intake of polyunsaturated fatty acids.

Considering these reports and the feasibility of the amount of and improvement in each citizen's intake, the ideal intake in adults in each country is set at less than 10%E[45]. In addition, the American Heart Association (2006 and 2009) and American Diabetes Association (2008) set a ratio of less than 7%E[45]. Furthermore, in some cases, guidelines are limited to a qualitative description stating the ratio should be kept "as low as possible" without providing a specific value[45]. The saturated fatty acid intake in Japanese people is relatively low compared to that of people in Western countries. The intake was approximately 7.3%E in all participants in the 2011 NHNS (calculated from the average energy intake [1,840 kcal] and average

saturated fatty acid intake [14.85 g]), and 6.9%E when the population was limited to those aged 20 years and older. The health benefits of consuming an amount of saturated fatty acids that is higher than the above-stated value is not clear, with the exception of a possible reduction in the risk of stroke.

With regards to the reduction in the risk of stroke, many cohort studies in Japanese people found that those with a low saturated fatty acid intake are at an increased risk of death or morbidity from stroke, particularly cerebral hemorrhage[24,33–36]. However, it is not clear if an increased saturated fatty acid intake can prevent cerebral hemorrhage[37]. For this reason, it has not been elucidated whether the correlations in the above-mentioned cohort studies are due to saturated fatty acid intake, or due to the intakes of other nutrients or living habits that show a correlation with saturated fatty acid intake. A negative correlation was demonstrated between saturated fatty acid intake and cerebral hemorrhage in a meta-analysis, but it was not significant[42]. There are few reliable data indicating that a low saturated fatty acid intake is a direct risk factor for some LRDs and other diseases. Based on these findings, a reference value, which indicates an enhanced risk of LRDs if the value falls below it, has not been set in the DRIs of other countries or similar guidelines[45]. Furthermore, restricting saturated fatty acids intake can lead to the restriction of total fat intake, resulting in an inadequate intake of essential fatty acids. Therefore, caution must be exercised in setting DRIs.

Based on the facts mentioned above, the DG for saturated fatty acids was set at 7%E or less.

2-3-2-3. Children (Methods Used to Set the DG)

Arteriosclerosis has long been known to manifest in childhood, progress throughout early adulthood, and cause coronary heart disease from middle age[46]. Several cohort studies in Western countries reported that carotid artery intima-media thickening increases when individuals with high LDL cholesterol levels during childhood (age 4–18 years) enter adulthood (age 18–42 years)[47–49]. Low saturated fatty acid intakes during childhood decrease childhood LDL cholesterol levels[50–52]. Meanwhile, an excessive intake of saturated fatty acids during childhood can cause coronary heart disease and obesity in middle age. Therefore, a DG of 7%E or less for saturated fatty acids is considered best even during childhood. However, there are only a few descriptive epidemiological studies focusing on the intakes and sources of saturated fatty acids during childhood, studies examining the relationship between saturated fatty acid intake during childhood and arteriosclerosis-related diseases in adulthood, and studies examining the safety of reducing saturated fatty acid intake during childhood (in terms of growth impairment, etc.). Therefore, it was decided not to set a DG for children at this time.

2-4. n-6 Fatty Acids

2-4-1. Basic Matters and Intake Status

2-4-1-1. Background Information

Linoleic acid (18:2n-6), gamma-linoleic acid (18:3n-6), and arachidonic acid (20:4n-6) are some n-6 fatty acids. Gamma-linoleic acid and arachidonic acid are metabolites of linoleic acid. Since n-6 fatty acids cannot be synthesized from acetyl-CoA *in vivo*, they must be consumed orally. Ninety-eight percent of the n-6 fatty acids consumed by Japanese people is linoleic acid. Few studies have investigated the effect of the consumption of gamma-linoleic acid or arachidonic acid alone on the human body.

2-4-1-2. Dietary Intake Status

Based on the results of the 2010 and 2011 NHNS[2], the median n-6 fatty acid intake of Japanese people aged 30–49 years is 10.0 g/day in men and 8.4 g/day in women, and the energy ratio is 4.3%E in men and 4.6%E in women. In Americans aged 31–50 years, the median linoleic acid intake is 16.1 g/day in men and 11.1 g/day in women, and the energy ratio is 5.9%E in men and 6.0%E in women[7]. Therefore, the linoleic acid intake of Japanese people is about 30% lower than that of Americans in terms of energy ratio.

2-4-2. To Avoid Inadequacy

2-4-2-1. Factors to be Considered in Estimating Requirements

A deficiency of n-6 fatty acids is observed in those who receive total parenteral nutrition, and the deficiency disappears on administering 7.4–8.0 g/day or 2%E of linoleic acid[53–56]. However, no data are available for the setting of the EAR of healthy adults. No studies have reported on conditions such as dermatitis which are thought to be caused by n-6 fatty acid deficiency in healthy adults who lead free daily lives. A DG for n-6 fatty acids was set in light of the possible need for n-6 fatty acids other than linoleic acid.

2-4-2-2. Methods of Determining AI

(1) Infants

Breast milk was considered an ideal source of nutrients for infants; therefore, the AI was determined from the fat content of breast milk[3,4] and the average milk volume (0.78 L/day)[5,6]. Infants aged 0–5 months obtain their nutrients from breast milk (or infant formula). From the age of 6 months, infants begin taking baby foods. Thus, infants aged 6–11 months obtain their nutrients from both breast milk (or infant formula) and baby food. This is regarded as the transition period to early childhood, so the average AIs (medians) of 0–5-month-old infants and 1–2-year-old infants were used.

The AI of infants aged 0–5 months was found by multiplying the n-6 fatty acid concentration of breast milk (5.16 g/L) and the average milk intake (0.78 L/day).

n-6 fatty acids: AI (g/day) = 5.16 g/L × 0.78 L/day = 4.02 g/day

For infants aged 6–11 months, the average AI of infants aged 0–5 months and median (male and female average) intake from the 2010 and 2011 NHNS[2] of infants aged 1–2 years were taken. The AI was calculated as follows:

n-6 fatty acids: AI (g/day) = [4.0 + (4.7 + 4.5) /2] /2 = 4.3 g/day

(2) Children and Adults

The median n-6 fatty acid intake, calculated from the results of the 2010 and 2011 NHNS, was set as the AI for those aged 1 year and older.

(3) Pregnant and Lactating Women

The median n-6 fatty acid intake of pregnant women, calculated from the results of the 2007 to 2011 NHNS[57], is 9 g/day. Thus, the AI was set at 9 g/day because it was considered a value that would not cause fetal developmental problems.

Lactating women are assumed to secrete breast milk containing the average fat components of the breast milk of Japanese women. The median n-6 fatty acid intake of lactating women, calculated from the results of the 2007 to 2011 NHNS[57], is 9 g/day. This value has not been found to cause essential fatty acid deficiencies in a majority of lactating women, and is considered the amount that can be secreted of breast milk containing sufficient n-6 fatty acids. The AI was, therefore, set at 9 g/day.

2-4-3. Preventing the Development of LRDs

2-4-3-1. Association with LRDs

Studies on coronary heart disease include an interventional study that compared blood lipids in Western countries. This interventional study found that LDL cholesterol decreased the most when polyunsaturated fatty acids (primarily n-6 fatty acids), instead of carbohydrates, were consumed compared to when other fats were consumed instead of carbohydrates[8]. LDL cholesterol levels also decrease when n-6 fatty acids are consumed instead of saturated fatty acids[58]. However, the results of observational studies with coronary heart disease as an endpoint are inconsistent[59,60]. In the Nurses' Health Study[64] the largest quintile for linoleic acid intake (7.0%E) had the lowest risk of coronary heart disease; however, recent studies found no correlation with n-6 fatty acid intake[61–64]. Many interventional studies have found that the prevalence of coronary heart disease is reduced when saturated fatty acids are substituted with polyunsaturated fatty acids, although no interventional studies have substituted proteins or carbohydrates with polyunsaturated fatty acids. Therefore, it is not clear whether this decrease in the prevalence of coronary heart disease is due to a reduced intake of saturated fatty acids or an increased intake of polyunsaturated fatty acids[65]. A meta-analysis of interventional studies published in 2013 (in both healthy individuals and post-myocardial infarction patients) analyzed the effects of n-3 and n-6 fatty acids separately[66]. This analysis revealed that a mixed intake of n-3 and n-6 fatty acids reduced the rate of death from myocardial infarction by 19%, while the intake of linoleic acid alone increased mortality by 33%. Meanwhile, a meta-analysis of interventional studies published in 2010 (in both healthy individuals and post-myocardial

infarction patients)[67] analyzed nonfatal myocardial infarction, as well as fatal cases and found that a mixed intake of n-3 and n-6 fatty acids reduced the risk of myocardial infarction by 22%, whereas an intake of n-6 fatty acids alone increased this risk by 13%.

A prospective nested case control study of stroke in Japanese people compared a group with a serum lipid linoleic acid ratio of 34% (linoleic acid intake equivalent to approximately 13.3 g/day) with a group with a ratio of 22% (linoleic acid intake equivalent to approximately 9.5 g/day), and found that the odds ratio for stroke decreased to 0.43. However, some cohort studies that examined n-6 fatty acid intake and stroke prevalence did not demonstrate a correlation[68,69].

Although the Nurses' Health Study[70] found a weak negative correlation between vegetable oil intake and diabetes, the types of fat contained in vegetable oil were not clarified. A recent study did not show any correlation between n-6 fatty acid intake and diabetes[71].

Pertaining to cancer, a recent cohort study[72] and some case control studies[73,74] revealed a positive correlation between n-6 fatty acid intake and breast cancer[75].

Linoleic acid is more easily oxidized than oleic acid, which is a monounsaturated acid. The risks of consuming large quantities (10%E or higher) of linoleic acid have not been elucidated[7]. As linoleic acid produces prostaglandin and leukotriene[76], which cause inflammation, the safety of consuming it in large quantities is a matter of concern. The increased breast cancer and myocardial infarction morbidities associated with an excessive intake of linoleic acid may be attributed to the ease of oxidation and the inflammatory action of linoleic acid.

However, despite the above-stated risks associated with excessive n-6 fatty acid intake, no DG was set due to the lack of studies in Japanese people.

2-5. n-3 Fatty Acids

2-5-1. Background Information and Intake Status

2-5-1-1. Background Information

Alpha-linoleic acid (18:3n-3) derived from edible cooking oil, and EPA (20:5n-3), docosapentaenoic acid (DPA; 22:5n-3) and DHA (22:6n-3) derived from fish are some n-3 fatty acids. A small amount of alpha-linoleic acid is converted to EPA and DHA in the body.

These fats cannot be synthesized *in vivo,* and deficiencies result in conditions such as dermatitis[77,78]. For this reason, an AI was set.

Apart from the physiological actions of n-3 fatty acids competing with those of n-6 fatty acids, as it is thought that they may also have independent actions, reference intakes were set for n-3 fatty acids themselves as opposed to a ratio of n-3 to n-6 fatty acids. Epidemiological studies also support this approach. The Nurses' Health Study[79] of women found that the preventive action of alpha-linoleic acid against coronary heart disease is not influenced by linoleic acid intake. In addition, the Health Professional Study[80] of men demonstrated that the preventive action of alpha-linoleic acid or EPA and DHA against coronary heart disease was

not influenced by n-6 fatty acid intake, either.

Moreover, given the environmental contaminants contained in fish, such as mercury and dioxins, and the global shortage of fish resources, the intake of alpha-linoleic acid will become difficult and different sources must be considered in the future. This is why alpha-linoleic acid and fish-derived n-3 fatty acids were both investigated. The AI was set from the standpoint of preventing deficiencies, although it is difficult to distinguish alpha-linoleic acid from fish oil. Reference intakes were, therefore, set for the n-3 fatty acids contained in both alpha-linoleic acid and fish oil. Since many studies have used EPA and DHA intakes in their epidemiological data, EPA and DHA intakes were examined together to find the fish-derived n-3 fatty acid intake.

2-5-1-2. Dietary Intake Status

The median n-3 fatty acid intake of Japanese people aged 30–49 years, based on the results of the 2010 and 2011 NHNS[(2)], was 2.1 g/day in men and 1.6 g/day in women, and the energy ratio was 0.89%E in men and 0.86%E in women. In Americans aged 31–50 years, the median n-3 fatty acid intake is 1.8 g/day in men and 1.2 g/day in women, and the energy ratio is 0.64%E in men and 0.66%E in women[(7)]. The n-3 fatty acid intake of Japanese people is; therefore, approximately 1.3-fold higher that of Americans, in terms of energy ratio.

According to calculations based on the results of the 2005 and 2006 NHNS used in the DRIs (2010), the median EPA and DHA intake of Japanese people aged 30–49 years is 0.32 g/day in men and 0.23 g/day in women, and the energy ratio is 0.14%E in men and 0.12%E in women. In Americans aged 31–50 years, the median EPA and DHA intake is 0.086 g/day in men and 0.063 g/day in women, and the energy ratio is 0.031%E in men and 0.034%E in women[(7)]. The EPA and DHA intake of Japanese people is, therefore, increased by approximately 4-fold compared to that of Americans, in terms of energy ratio, which is quite significant. No major difference was observed between the median alpha-linoleic acid intakes of American people and Japanese people.

There is a large bias in the intake distribution of fish oil. Marked differences are observed in the average and median intakes of EPA, DHA, and DPA, and, therefore, it is unclear whether the median is a typical value reflecting the habitual intake of fish oil in the population. This kind of bias is not seen in the intake distribution of alpha-linoleic acid.

2-5-2. To Avoid Inadequacy

2-5-2-1. Factors to be Considered in Estimating Requirements

An AI was set for n-3 fatty acids due to the presence of n-3 fatty acid deficiency[(81)]. Of the patients who could not consume food orally due to enterectomy, encephalopathy, etc., the effects of administered n-3 fatty acid (alpha-linoleic acid + fish oil) were reported in patients who had developed scaly dermatitis, hemorrhagic dermatitis, nodular dermatitis, or growth impairment, and whose n-6 fatty acid intake had been maintained to a certain degree, but n-3

fatty acid intake had been extremely low. With the increase in the blood n-3 fatty acid ratio, skin symptoms were improved through the administration of 0.2–0.3%E n-3 fatty acid[82,83], and increases in weight were observed through the administration of 1.3%E n-3 fatty acid[77]. However, because both alpha-linoleic acid and fish oil are administered in many studies, it is unclear which lipid(s) improved symptoms. It may be necessary to consider n-3 fatty acids other than alpha-linoleic acid, EPA and DHA, and, accordingly, an AI was set for n-3 fatty acids.

2-5-2-2. Methods of Determining AI

(1) Infants

Breast milk was considered to be an ideal source of nutrients for infants, and, therefore, the AI was determined from the fat content of breast milk[3,4], and the average milk intake (0.78 L/day)[5,6]. Infants aged 0–5 months obtain their nutrients from breast milk (or infant formula), and from the age of 6 months, they begin taking baby foods. Infants aged 6–11 months obtain their nutrients from both breast milk (or infant formula) and baby food. Since this is the transition period to early childhood, the average AIs (medians) of 0–5-month-old infants and 1–2-year-old infants were used.

The AI of infants aged 0–5 months was found by multiplying the n-3 fatty acid concentration of breast milk (1.16 g/L) and the average milk intake (0.78 L/day).

n-3 fatty acids: AI (g/day) = 1.16 g/L × 0.78 L/day = 0.90 g/day

For infants aged 6–11 months, the average AI of infants aged 0–5 months, and median (male and female average) intake from the 2010 and 2011 NHNS[2] of infants aged 1–2 years were taken. The AI was found as follows.

n-3 fatty acids: AI (g/day) = [0.9 + (0.7 + 0.8) /2] /2 = 0.8 g/day

(2) Children and Adults

The median total n-3 fatty acid intake, calculated from the results of the 2010 and 2011 NHNS[2], was set as the AI for those aged 1 year and older.

(3) Pregnant and Lactating Women

Arachidonic acid and DHA are important constituent fatty acids of the nervous tissue. DHA is present in large quantities *in vivo*, particularly in the nerve synapses and photoreceptors of the retina. A larger number of n-3 fatty acids are required to create these organs in fetuses during pregnancy[84]. The median n-3 fatty acid intake of pregnant women, calculated from the results of the 2007 to 2011 NHNS[57], is 1.8 g/day; thus, this value was considered as that which would not cause fetal developmental problems. Consequently, the AI for n-3 fatty acids was set at 1.8 g/day during pregnancy. Lactating women are assumed to secrete breast milk containing the average fat components of the breast milk of Japanese women. The median n-3 fatty acid intake of lactating women, calculated from the results of the 2007 to 2011 NHNS[57], is 1.8 g/day. This value has not been found to cause essential fatty acid deficiencies in a majority of lactating women, and is considered to be the secretable amount of breast milk with sufficient n-3 fatty acids; therefore, this was set as the AI.

DRIs for Dietary Fats

(Percentage of total dietary fat in total energy (fat energy ratio): % energy)

Gender	Males		Females	
Age etc.	AI	DG [1] (median [2])	AI	DG [1] (median [2])
0-5 months	50	—	50	—
6-11 months	40	—	40	—
1-2 years	—	20-30（25）	—	20-30（25）
3-5 years	—	20-30（25）	—	20-30（25）
6-7 years	—	20-30（25）	—	20-30（25）
8-9 years	—	20-30（25）	—	20-30（25）
10-11 years	—	20-30（25）	—	20-30（25）
12-14 years	—	20-30（25）	—	20-30（25）
15-17 years	—	20-30（25）	—	20-30（25）
18-29 years	—	20-30（25）	—	20-30（25）
30-49 years	—	20-30（25）	—	20-30（25）
50-69 years	—	20-30（25）	—	20-30（25）
70+ years	—	20-30（25）	—	20-30（25）
Pregnant women			—	—
Lactating women			—	—

[1] Ranges are expressed as approximate values.

[2] Medians indicate the median values for the given range. They do not indicate most desirable values.

DRIs for Saturated Fatty Acid (% energy)

Gender	Males	Females
Age etc.	DG	DG
0-5 months	—	—
6-11 months	—	—
1-2 years	—	—
3-5 years	—	—
6-7 years	—	—
8-9 years	—	—
10-11 years	—	—
12-14 years	—	—
15-17 years	—	—
18-29 years	≤ 7	≤ 7
30-49 years	≤ 7	≤ 7
50-69 years	≤ 7	≤ 7
70+ years	≤ 7	≤ 7
Pregnant women		—
Lactating women		—

DRIs for n-6 Fatty Acid (g/day)

Gender	Males	Females
Age etc.	AI	AI
0-5 months	4	4
6-11 months	4	4
1-2 years	5	5
3-5 years	7	6
6-7 years	7	7
8-9 years	9	7
10-11 years	9	8
12-14 years	12	10
15-17 years	13	10
18-29 years	11	8
30-49 years	10	8
50-69 years	10	8
70+ years	8	7
Pregnant women		9
Lactating women		9

DRIs for n-3 Fatty Acid (g/day)

Gender	Males	Females
Age etc.	AI	AI
0-5 months	0.9	0.9
6-11 months	0.8	0.8
1-2 years	0.7	0.8
3-5 years	1.3	1.1
6-7 years	1.4	1.3
8-9 years	1.7	1.4
10-11 years	1.7	1.5
12-14 years	2.1	1.8
15-17 years	2.3	1.7
18-29 years	2.0	1.6
30-49 years	2.1	1.6
50-69 years	2.4	2.0
70+ years	2.2	1.9
Pregnant women		1.8
Lactating women		1.8

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