SCIENTIFIC OPINION

Scientific Opinion on the essential composition of total diet replacements for weight control[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2,3]

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ABSTRACT

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver a scientific opinion on the essential composition of total diet replacements for weight control. Total diet replacements for weight control are intended to induce a substantial energy deficit in overweight or obese adults who wish to lose weight and replace the whole diet in the context of energy-restricted diets for weight reduction. In this opinion, the Panel proposed a minimum protein content based on a Population Reference Intake for protein adjusted for the overweight or obese (75 g/day), a minimum carbohydrate content based on the obligatory glucose demands of the brain (30 g/day) and minimum contents of linoleic acid (11 g/day), α-linolenic acid (1.4 g/day) and micronutrients based on reference values established either by the Panel or by other scientific or authoritative bodies. Derived from the minimum content of macronutrients, the Panel proposed a minimum energy content of total diet replacements for weight control of 2 510 kJ/day (600 kcal/day). The Panel also advised on potential conditions and restrictions of use for these products.

KEY WORDS

total diet replacement, weight control, very low calorie diet, VLCD, low calorie diet, LCD, composition

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SUMMARY

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver a scientific opinion on the essential composition of total diet replacements for weight control. Total diet replacements for weight control are intended to induce a substantial energy deficit in overweight or obese adults who wish to lose weight and replace the whole diet in the context of energy-restricted diets for weight reduction.

The guiding principle for providing advice on the essential composition of total diet replacements for weight control should be that products are safe and suitable when consumed as a sole source of nutrition for several weeks to months by overweight or obese adults in the context of energy-restricted diets for weight reduction. In order to avoid nutrient deficiencies, these products should, therefore, provide at least the Population Reference Intake or the Adequate Intake for adults of all indispensable nutrients. As Dietary Reference Values are generally established for healthy, normal-weight individuals, specific consideration has been given by the Panel in this opinion whether there was an increase in nutrient requirements in the overweight or obese or (rapid) weight loss leads to an increased nutrient loss and thus a higher requirement. The Panel also considered the extent to which different diet compositions impact on losses in fat-free mass, and on other adverse effects of weight loss diets, such as gallstone formation. The effectiveness of a product in terms of extent of weight loss was not in itself considered an appropriate determinant for the necessary composition of total diet replacements for weight control.

Protein

The Population Reference Intake of 0.83 g/kg body weight per day cannot be directly applied to overweight or obese individuals considering that the Population Reference Intake was derived for healthy, normal-weight individuals with corresponding body composition. It is established that protein requirements are closely linked to fat-free mass and that in the overweight or obese the percentage of fat-free mass related to whole body weight is lower than in normal-weight persons because of a higher percentage of fat mass in relation to body weight. Accordingly, protein requirements for the overweight or obese should be related to fat-free mass. As both protein requirements and resting energy expenditure are mainly related to fat-free mass, the Panel proposes to correct the Population Reference Intake established for a normal-weight person by the quotient of the resting energy expenditure of overweight or obese individuals and the resting energy expenditure of a normal-weight reference subject. This correction translates into a minimum quantity of 75 g high-quality protein (i.e. Protein Digestibility-Corrected Amino Acid Score of 1.0) per day, which should be provided by total diet replacements for weight control. The value is supported by results from nitrogen balance studies, which have shown that obese subjects tended to return closer to nitrogen equilibrium, and somewhat faster, when 70-100 g protein per day was consumed as part of an energy-restricted diet than when smaller amounts of protein were consumed. It is also supported by results showing that protein turnover is either maintained or only slightly decreased during caloric restriction provided a quantity of protein of between 50 g and 100 g/day is supplied in the diet.

With respect to the maximum protein content of total diet replacements for weight control, the Panel proposed to derive it from the maximum protein intakes considered as safe (i.e. equal to twice the Population Reference Intake) for an overweight 40-year-old woman with a body mass index of 25 kg/m^2. This derivation results in a maximum quantity of 105 g protein per day in total diet replacements for weight control. This value is similar to the highest protein intakes investigated in the published studies with no apparent adverse effects.

Glycaemic carbohydrates

Some studies seem to indicate that with a high protein supply of 100 g/day carbohydrates are not needed to achieve the desired effect of near-neutral nitrogen balance. However, the absence of carbohydrates in total diet replacements for weight control may carry a higher risk of severe ketoacidosis. Other studies on very low-calorie diets providing $\leq$ 2 510 kJ (600 kcal) per day with a

lower protein intake, of between 50 and 70 g/day, and supplying carbohydrates in amounts of around 70 g/day have indicated that these intakes are of advantage with respect to nitrogen loss compared with a carbohydrate supply of around 10 g/day. Considering that up to 80 % of the energy requirement of the brain of around 2 092 kJ/day (500 kcal/day) can be supplied by ketone bodies, there remains a demand for, about 25-30 g of glucose that can be produced via gluconeogenesis from glycerol and amino acids or be supplied by the diet. In order to keep the need for gluconeogenesis low, the Panel proposed a minimum content of digestible carbohydrates of 30 g/day.

Dietary fibre

Owing to the lack of scientific evidence, the Panel considered that an absolute minimum requirement for fibre in overweight and obese subjects during weight loss cannot be established, the more so as both constipation and diarrhoea have been reported during the use of total diet replacements. Therefore, the Panel cannot propose a minimum dietary fibre content in total diet replacements for weight control.

Fat

Although the addition of essential fatty acids to total diet replacements for weight control may not be needed owing to their release from tissue stores during weight loss, the Panel considered that total diet replacements for weight control should provide at least the Adequate Intake for linoleic acid and α-linolenic acid established for energy-adequate diets. This recommendation is based on the consideration that the fatty acid content of adipose tissue and the rate of adipose tissue loss may vary between individuals; thus, there is considerable uncertainty as to whether body stores can completely cover requirements. Therefore, the Panel proposed that total diet replacements for weight control should provide at least 11 g linoleic acid and 1.4 g α-linolenic acid per day.

The available evidence is insufficient to establish a minimum fat content in total diet replacements for weight control beyond their content of essential fatty acids. The above proposed minimum content of linoleic and α-linolenic acid leads to a minimum amount of total fat provided by total diet replacements for weight control of around 20 g/day, as oils used to supply these fatty acids have a maximum essential fatty acid content of 55-75 % of total fatty acids.

There is no evidence for proposing a maximum fat content in total diet replacements for weight control.

Energy

The minimum energy content of total diet replacements for weight control can be derived from the minimum macronutrient content of such diets. Considering that the Panel proposed that total diet replacements for weight control should provide at least 75 g protein per day, 30 g carbohydrates per day and linoleic and α-linolenic acid in amounts which sum up to around 20 g fat per day, a minimum energy content of 2 510 kJ (600 kcal/day) could be derived.

From a scientific point of view, there is no evidence to establish a threshold below which a diet could be considered to be very low in energy content.

Micronutrients

The minimum content of micronutrients in total diet replacements for weight control has generally been derived by the Panel from the Population Reference Intakes or Adequate Intakes for micronutrients based either on previous opinions of the Panel or in the absence of such advice on reference values given by the Scientific Committee on Food or other scientific or authoritative bodies. For none of the micronutrients was it considered that there was an increase in nutrient requirements in the overweight or obese or an increased requirement owing to rapid weight loss induced by total diet replacements for weight control when consumed for a single short period of time.

Conditions and restrictions of use

The Panel emphasises that the compositional advice given in the present opinion solely applies to total diet replacements for weight control which are to be used by otherwise healthy overweight or obese adults with the intention of weight loss. They are not intended for use in normal-weight adults, infants, children, adolescents, pregnant or lactating women and the elderly. They may also not be appropriate for overweight or obese populations with one or more medical conditions, such as, but not limited to, diabetes, gout, thyroid disease, kidney disease, liver disease, cardiovascular disease and gallstones. The appropriateness of the use of total diet replacements for weight control by individuals other than overweight or obese adults, such as obese adolescents or obese pregnant women, or by individuals with a medical condition, should be established on a case-by-case basis by a physician and may require continued medical and dietetic supervision.

The Panel noted that there is no scientific evidence which supports the current provisions that labelling of low-calorie diets should inform consumers that low-calorie diets should not be used for more than three weeks without medical supervision. However, none of the studies which investigated adverse metabolic consequences of total diet replacements had a duration of more than three months. In particular, studies which investigated critical endpoints, such as the effect of total diet replacements for weight control on calcium loss and bone health, have not been conducted for periods longer than eight weeks. While the available evidence does not give rise to any concern with respect to bone health in adults when total diet replacements for weight control are consumed for a single period of up to eight weeks, there are no data on the impact of the increased calcium losses on bone health when these products are used over prolonged periods of time or repeatedly for short periods. In addition, the compositional advice given by the Panel is based on the assumption that total diet replacements for weight control are used for a single short period of time and the nutrient content may not necessarily be appropriate when these products are consumed for prolonged or repeated short periods of time.

Finally, the Panel also noted the importance of an adequate fluid intake during energy restriction in line with the Adequate Intakes for adult men and women, i.e. 2.5 L and 2.0 L/day, respectively. The reference values for total water intake include water from drinking water, beverages of all kind and from food moisture.

TABLE OF CONTENTS

BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

Directive 2009/39/EC of the European Parliament and of the Council on foodstuffs intended for particular nutritional uses[4] lays down general rules on the composition of such foods that are specially designed to meet the particular nutritional requirements of the persons to whom they are intended, including "*certain categories of persons who are in a special physiological condition and who are therefore able to obtain special benefit from controlled consumption of certain substances in foodstuffs*".

One of the measures adopted under Directive 2009/39/EC is Commission Directive 96/8/EC on foods intended for use in energy-restricted diets for weight reduction[5] that is based on the opinion of the Scientific Committee for Food (SCF) from 1990.[6] On the basis of this opinion Directive 96/8/EC has established compositional and labelling requirements for foods intended for use in energy-restricted diets for weight reduction and presented as such. These are defined as "*specially formulated foods which, when used as instructed by the manufacturer, replace the whole or part of the total daily diet*". More specifically, the Directive sets rules on products presented as a replacement for the whole of the daily diet which contain between 3 360 kJ (800 kcal) and 5 040 kJ (1 200 kcal) (so-called 'products for low calorie diets, or LCDs') and on products presented as a replacement for one or more meals of the daily diet with an energy content between 840 kJ (200 kcal) and 1 680 kJ (400 kcal).

Directive 96/8/EC did not establish requirements for total diet replacement for weight control containing less than 3 360kJ (800kcal). At that time this kind of products was not extensively used in the internal market and it was not considered opportune to establish harmonised requirements at EU level. The Directive referred to this kind of products and underlined that relevant specific rules would be adopted at a later date. Since many years an increasing number of foods normally containing less than 3 360 kJ (800 kcal) and replacing the whole of the daily diet are placed on the market as 'products for very low calorie diets' (so-called 'VLCDs').

Regulation (EU) No 609/2013 of the European Parliament and of the Council on food intended for infants and young children, food for special medical purposes, and total diet replacement for weight control[7] revises the legal framework applicable to food for particular nutritional uses. It repeals Directive 2009/39/EC and Directive 96/8/EC.

On one side, it foresees that specific rules on statements made on meal replacement products for weight control should be regulated solely under Regulation (EC) No 1924/2006 of the European Parliament and the Council on nutrition and health claims.[8] This with the goal to eliminate any potential confusion between 'meal replacement products' and other foods for normal consumption bearing health claims for weight control according to Article 13(1) (c) of Regulation (EC) No 1924/2006.

[4] Directive 2009/39/EC of the European Parliament and of the Council of 6 May 2009 on foodstuffs intended for particular nutritional uses, OJ L 124, 20.5.2009, p. 21.

[5] Commission Directive 96/8/EC of 26 February 1996 on foods intended for use in energy-restricted diets for weight reduction, OJ L 55, 6.3.1996, p. 22, as amended by Commission Directive 2007/29/EC of 30 May 2007, OJ L 139, 31.5.2007, p. 22.

[6] Report of the Scientific Committee for Food on foods intended for weight control diets, Opinion expressed on 19 October 1990.

[7] Regulation (EU) No 609/2013 of the European Parliament and of the Council of 12 June 2013 on food intended for infants and young children, food for special medical purposes, and total diet replacement for weight control and repealing Council Directive 92/52/EEC, Commission Directives 96/8/EC, 1999/21/EC, 2006/125/EC and 2006/141/EC, Directive 2009/39/EC of the European Parliament and of the Council and Commission Regulation (EC) No 41/2009 and (EC) No 953/2009, OJ L 181, 29.6.2013, p.35.

[8] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods, OJ L 404, 30.12.2006, p. 9.

On the other, it includes total diet replacements for weight control under its scope[9] and foresees that certain specific provisions are set for LCDs on the basis of the relevant provisions of Directive 96/8/EC, and for VLCDs.

In order to comply with the requirements of Regulation (EU) No 609/2013 it is considered necessary to request EFSA to provide a scientific opinion on total diet replacements for weight control. Such an opinion should review the scientific data existing on total diet replacements for weight control and provide scientific advice to the Commission on the essential requirements for these products. More specifically, this would amount to an update of the SCF opinion from 1990 for LCDs and to an advice on VLCDs. The opinion should also include any information, if considered appropriate by EFSA, on the use of LCDs and VLCDs, which can be relevant for the Commission when considering to set additional requirements related to the use of the products covered by this opinion. This could be for example restrictions of use for specific categories of consumers who should avoid use of the product, or information on their appropriate use.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Article 29(1) (a) of Regulation (EC) No 178/2002,[10] the European Commission asks EFSA to:

- Provide advice on the essential compositional requirements for total diet replacements for weight control as defined by Regulation (EU) No 609/2013. This should in particular take into account that:
    - the currently existing rules of Directive 96/8/EC on the compositional requirements of so-called products for 'low calorie diets', based on the opinion of the Scientific Committee for Food from 1990, need to be updated and
    - compositional requirements for products marketed as 'very low calorie diets' need to be established.
- Provide any information (such as for example potential restrictions of use for specific categories of consumers,) if considered appropriate, which can be relevant for the Commission when considering to set additional requirements related to the use of the products covered by this opinion.

[9] It defines them as "food specially formulated for use in energy-restricted diets for weight reduction which, when used as instructed by the food business operator, replaces the whole daily diet".
[10] OJ L 31, 1.2.2002, p. 1.

ASSESSMENT

1. Introduction

Total diet replacements for weight control are intended to induce a substantial energy deficit in overweight or obese adults who wish to lose weight and replace the whole diet in the context of energy-restricted diets for weight reduction.

Total diet replacements for weight control have been regulated in the European Union (EU) by Directive 96/8/EC.[11] They should provide between 3 360 kJ (800 kcal) and 5 040 kJ (1 200 kcal) per day and are commonly denominated as low-calorie diets (LCDs). Products containing fewer than 3 350 kJ (800 kcal) and which are intended to replace the whole diet, also denominated as very low-calorie diets (VLCDs), can be found on the market but are not regulated yet in the EU. To propose essential compositional requirements for total diet replacements for weight control is part of the Terms of Reference, as is to advise on conditions and potential restrictions of use of these products.

Regulation (EU) No 609/2013[12] requires the European Commission to lay down specific composition and information requirements for total diet replacements for weight control, including foods with very low energy content. Total diet replacements for weight control are defined in Regulation (EU) No 609/2013 as "food specially formulated for use in energy-restricted diets for weight reduction which, when used as instructed by the food business operator, replaces the whole daily diet" (Article 2(2)(h)).

This opinion only covers formulated products intended as a sole source of nutrition for weight control.

2. Definitions

For this opinion the following definitions apply:

- *LCDs* are formulated foods which, when used as instructed by the manufacturer, replace the whole diet (total diet replacements) and provide between 800 kcal and 1 200 kcal per day. LCDs have been regulated by Directive 96/8/EC and are defined by Codex-Stan 181-1991.[13] The energy content, expressed in kilojoules, differs slightly between the Directive and the Codex Standard. The minimum and maximum energy contents of LCDs defined in the Codex-Stan 181-1991 and regulated in the Directive 96/8/EC are 3 350 and 5 020 kJ, and 3 360 and 5 040 kJ, respectively.
- *VLCDs* are formulated foods which, when used as instructed by the manufacturer, replace the whole diet (total diet replacements) and provide less than the minimum amount of energy provided by LCDs (i.e. 3 360 kJ (800 kcal) per day). No compositional criteria have been laid down in EU legislation. However, VLCDs have been defined by a Codex Standard (Codex-Stan 203-1995[14]) which sets a minimum daily energy intake of 1 880 kJ (450 kcal) to be provided by these products.
- *Population Reference Intake (PRI)* is the level of (nutrient) intake that is adequate for virtually all people in a population group.
- *Average Requirement (AR)* is the level of (nutrient) intake that is adequate for half of the people in a population group, given a normal distribution of requirement.

[11] Commission Directive 96/8/EC of 26 February 1996 on foods intended for use in energy-restricted diets for weight reduction. OJ L 55, 06/03/1996, p. 22–26.
[12] Regulation (EU) No 609/2013 of the European Parliament and of the Council of 12 June 2013 on food intended for infants and young children, food for special medical purposes, and total diet replacement for weight control and repealing Council Directive 92/52/EEC, Commission Directives 96/8/EC, 1999/21/EC, 2006/125/EC and 2006/141/EC, Directive 2009/39/EC of the European Parliament and of the Council and Commission Regulation (EC) No 41/2009 and (EC) No 953/2009, OJ L 181, 29.6.2013, p. 35–56.
[13] Codex-Stan 181-1991 (Codex Alimentarius), 1991. Codex Standard for formula foods for use in weight control diets.
[14] Codex-Stan 203-1995 (Codex Alimentarius), 1995. Codex Standard for formula foods for use in very low energy diets for weight reduction.

- *Adequate Intake (AI)* is the value estimated when a PRI cannot be established because an AR cannot be determined.
- *Tolerable Upper Intake Level (UL)* is the maximum level of total chronic daily intake of a nutrient (from all sources) judged as unlikely to pose a risk of adverse health effects to humans.

3. Background

In the 1970s, prolonged consumption (four months on average) of very low-calorie weight reduction regimens consisting entirely or largely of protein resulted in more than 60 deaths owing to cardiac complications (Sours et al., 1981). This was mainly a consequence of the low biological value of protein in the products consumed at that time. Since then, protein quality in VLCDs has improved and is no longer a reason for concern. A few case reports of death have been linked to the consumption of VLCDs since the 1980s in the United States of America (USA) with the use of diets providing 1 381 kJ/day (330 kcal/day) (Wadden et al., 1983; Tsai and Wadden, 2006).

European clinical practice guidelines for the management of obesity in adults (Tsigos et al., 2008) state that "the use of VLCDs may form part of a comprehensive programme undertaken by an obesity specialist or other physician trained in nutrition and dietetics; however their administration should be limited for specific patients and for short periods of time; VLCDs are unsuitable as a sole source of nutrition for infants and children, adolescents, pregnant or lactating women and the elderly". Similar guidelines are available in the USA (NIH, 1998; Jensen et al., 2014).

Although initial weight loss is greater with VLCDs than with LCDs, as shown in a meta-analysis of six randomised controlled trials (RCTs) (Tsai and Wadden, 2006), in which subjects lost, on average (± standard deviation (SD)), 16.1 ± 1.6 vs. 9.7 ± 2.4 % of their initial body weight after a mean of 12.7 ± 6.4 weeks of diet intervention, the difference in weight loss was not found to be sustained at follow-up assessments one year after completing the diet if the diet intervention was the only measure taken (6.3 ± 3.2 vs. 5.0 ± 4.0 %), owing to a higher regain in body weight in those subjects who had consumed the VLCD. If subjects are involved in active follow-up programmes this weight regain seems to be attenuated to a certain extent as reported in a meta-analysis of nine RCTs (Saris, 2001). These findings are also supported by a recent study in 204 obese subjects, which showed that, although the time needed to achieve a similar weight loss was longer when a diet with a 1 674-2 092 kJ (400-500 kcal) energy deficit per day was consumed than when a VLCD was consumed providing between 1 883 kJ (450 kcal) and 3 347 kJ (800 kcal) per day, weight regain was similar in both groups (around 70 % after 144 weeks) (Purcell et al., 2014).

Even though, on a theoretical basis, greater weight loss could be expected with a more pronounced caloric restriction, studies which compared VLCDs providing around 1 674 kJ (400 kcal) per day with VLCDs of around 3 347 kJ (800 kcal) per day generally did not show any additional benefit in terms of weight loss of energy intakes below 3 347 kJ (800 kcal) per day (Davies et al., 1989; Foster et al., 1992; Rössner and Flaten, 1997; Moreno et al., 2006; Lin et al., 2009).

4. Metabolic consequences of weight loss

Weight loss in overweight or obese individuals leads to an improvement of almost all co-morbidities, including reduction in blood pressure, improvement of the lipid profile and improvement of the indices of diabetes mellitus type 2. This is independent of the dietary weight loss strategy used. However, large reductions in body weight may also result in the loss of bone mass and a higher risk of gallstone formation (Berg et al., 2014), the risk of which increases the more rapid the weight loss (Erlinger, 2000; Festi et al., 2000; Johansson et al., 2014). In addition, during energy restriction, several hormonal changes occur, such as a reduction in the concentrations of noradrenaline, triiodothyronine (T3) (but not thyroxine (T4) or thyroid-stimulating hormone (TSH)) and insulin (SCOOP Taskforce, 2002), all of which usually remain within the normal range.

An energy restriction-induced loss of body weight will inevitably also lead to a loss of fat-free mass (FFM). This is undesirable if the loss is excessive. However, the level at which losses of FFM should be considered to be adverse is unclear. A systematic review and meta-analysis of human intervention and observational studies (Chaston et al., 2007), which assessed changes in fat mass and FFM by dual-energy X-ray absorptiometry (DEXA), or underwater weighing after weight loss of more than 10 kg, showed a median loss of FFM of 23.4 % of the body weight loss (interquartile range (IQR): 15.4-31.4 %) with VLCDs (three studies (136 subjects)), of 22.5 % (11.5-33.5 %) with VLCDs plus exercise (two studies (40 subjects)) and 14.0 % (IQR: 4-24 %) with LCDs (eight studies (241 subjects)) with study periods between 6 and 52 weeks. In regression analyses, losses in FFM were explained by the energy content of the diet only. Reported exercise, gender, initial body mass index (BMI) or the magnitude of weight loss was not predictive of FFM loss.

Some studies have looked at the incidence of adverse effects of diets of different energy content. Constipation, diarrhoea, dry skin, dizziness, cold intolerance, hair loss, headache, nausea, fatigue, changes in mood and weakness and difficulty concentrating are side effects which have been associated with very low energy intakes (Foster et al., 1992). Two studies have reported somewhat lower incidence rates of adverse events in subjects consuming diets with around 3 347-3766 kJ (800-900 kcal) per day compared with subjects consuming around 1 883 kJ (450 kcal) per day, but without statistical significance (Rössner and Flaten, 1997; Lin et al., 2009), while in another study (Foster et al., 1992) no such tendency was observed. It has to be noted that none of these studies was powered to detect a difference in adverse events between diet groups and, therefore, they may have been underpowered for this purpose.

A systematic review of the evidence (Rolland et al., 2013) aimed to assess the impact of VLCDs on renal and hepatic outcomes. It included only studies for which the full study report was available and which had assessed liver enzymes, electrolytes, urea, kidney function and non-alcoholic fatty liver disease (n = 8). The results of the included studies were inconsistent as they showed either an improvement in markers of liver or renal function or no change. In one study, markers of liver function deteriorated during the VLCD phase, but subsequently returned to normal levels.

5. Methodological considerations

The guiding principle for providing advice on the essential composition of total diet replacements for weight control should be that products are safe and suitable when consumed as a sole source of nutrition, for several weeks to months, by overweight or obese adults in the context of energy-restricted diets for weight reduction. In order to avoid nutrient deficiencies, these products should, therefore, provide at least the PRI or AI for adults of all indispensable nutrients. As Dietary Reference Values (DRVs) are generally established for healthy normal-weight individuals, specific consideration will be given by the Panel in this opinion to whether there is an increase in nutrient requirements in the overweight or obese or whether (rapid) weight loss leads to an increased nutrient loss and thus a higher requirement. When advising on the macronutrient composition of total diet replacements, the Panel will also consider the extent to which different diet compositions impact on losses in FFM, and on other adverse effects of weight loss diets, such as gallstone formation. The effectiveness of a product in terms of extent of weight loss is not in itself an appropriate determinant for the necessary composition of total diet replacements for weight control.

The classification of total diet replacements for weight control into VLCDs and LCDs depending on their caloric content has originally been established for regulatory purposes and because of safety concerns. There is at present no scientific evidence in terms of energy content below which a diet could be considered to contain a very low amount of calories and thus lead to a substantial energy deficit (or to be of low caloric content and provide a modest energy deficit), the more so as the extent of energy deficit caused by the diet will depend on the energy requirements/expenditure of the individual consuming it. Therefore, the Panel will provide advice on the minimal necessary composition of total diet replacements for weight control to ensure that these products can be safely consumed by overweight or obese adults. The minimal macronutrient composition will therefore

determine the minimum energy content. Products formulated with larger amounts of macronutrients than those proposed by the Panel can thus also be considered safe, provided a certain maximum quantity of protein is not exceeded. Even though the Panel will not distinguish between the two regulatory sub-categories of total diet replacements in the present opinion owing to the lack of basis for such classification in scientific terms, the terms "VLCD" and "LCD" will be used when results of (several) studies are summarised to denominate diets which provided fewer than 3 347 kJ (800 kcal) per day (VLCD) or more than 3 347 kJ (800 kcal) per day, with a maximum of 5 021 kJ (1 200 kcal) per day (LCD).

5.1. Evidence used in the preparation of the opinion

Information on the PRI or AI for adults will be taken from the Panel's previous opinions on DRVs for macro- and micronutrients. To date, the Panel has concluded on DRVs for water, energy, carbohydrates and dietary fibre, fat, protein, molybdenum, fluoride, manganese, chromium, selenium, iodine, zinc, vitamin C, biotin, pantothenic acid, niacin and folate and endorsed opinions on DRVs for vitamin A and calcium for public consultation. For those nutrients for which the Panel has not yet expressed an opinion, the Panel will review reference values set by the Scientific Committee on Food (SCF, 1993) in light of more recent recommendations given by other scientific or authoritative bodies, i.e. the French Food Safety Agency (Afssa), the Health Council of the Netherlands (Gezondheidsraad), the Nordic Council of Ministers, the German-speaking countries (D-A-CH), the US Institute of Medicine (IoM), the National Health and Medical Research Council of the Commonwealth (NHMRC) of Australia and the Ministry of Health of New Zealand and the World Health Organization (WHO). As reference values for adults often differ by gender, the Panel decided to consider only the higher of the two reference values for adult men and women to ensure that products provide sufficient nutrients to all individuals consuming them, unless otherwise noted.

In the framework of a procurement procedure, an extensive literature search was performed to identify peer-reviewed publications on human intervention studies, published in English since 1990, which investigated the effect of differences in composition of total diet replacements for weight control on adverse metabolic effects in otherwise healthy overweight or obese subjects. Owing to the limited number of studies published after 1990 on the subject, an additional literature search was conducted within EFSA to identify studies which were published before 1990 and which would potentially allow the assessment of the impact of different diet compositions on metabolic effects which could be considered adverse and have been discussed to be potentially related to the macro- or micronutrient composition of an energy-restricted diet, such as losses in FFM, changes in nitrogen balance, changes in protein turnover, gallstone formation or changes in mineral balances. The Panel will also consider the implications of diets with low caloric contents on renal and hepatic outcomes and on cognitive function, if available. Studies which investigated metabolic consequences of weight loss in general that are not potentially influenced by the macro- or micronutrient composition of diets but are a result of weight loss *per se*, such as changes in blood pressure, the lipid profile or hormonal status, are not further discussed in this opinion; studies on the rate and amount of weight loss are also excluded, as outlined above.

When evaluating the impact of diets on body composition, studies which used validated methods with sufficient precision to measure changes in body composition during weight loss in the obese (e.g. DEXA, magnetic resonance imaging and computed tomography) will be considered by the Panel. Studies which only used bioelectrical impedance analysis (BIA) will not be considered by the Panel, as BIA is, generally, not appropriate to assess small changes in body fat when used alone, particularly in obese subjects and/or when significant changes in body water compartments occur (EFSA NDA Panel, 2012c).

Several studies have looked at changes in plasma or serum proteins, such as albumin, prealbumin, retinol-binding protein and transferrin, as indirect markers of protein–energy malnutrition (Lewis et al., 1977; Shetty et al., 1979; Bogardus et al., 1981; Hoffer et al., 1984b; Pasquali et al., 1987; Hendler and Bonde, 1988; Ohno et al., 1989; Scalfi et al., 1990; Vazquez and Adibi, 1992; Vazquez et al.,

1995; Moreno et al., 2006). However, plasma/serum proteins are affected by factors other than nutritional status, such as inflammation, infection and liver or kidney disease. Studies have shown poor associations between plasma/serum protein levels in obese but otherwise healthy individuals on VLCDs or LCDs and energy content or macronutrient composition of the diet. Therefore, these outcomes will not be addressed in more detail in the present opinion.

Urinary excretion of 3-methylhistidine has been used in four studies (Garlick et al., 1980; Hoffer et al., 1984b; Pasquali et al., 1987; Vazquez and Adibi, 1992) with the intention of measuring muscle protein breakdown. However, the Panel notes the limitations of this marker for estimating overall muscle protein breakdown and the lack of validation of the marker particularly in the context of weight loss. Therefore, this outcome will not be addressed in more detail in the present opinion.

Diets low in carbohydrates and high in fat are characterised by moderate ketosis. Through the mobilisation of fat, the fatty acid oxidation rate in the liver is increased, leading to an enhanced acetyl coenzyme A (CoA) production, which cannot be oxidised completely via the citrate cycle (because of a lack of oxaloacetate which is used for gluconeogenesis). This will result in an increase in the production of ketone bodies, i.e. acetoacetate (AcAc), 3-hydroxybutyrate (3OHB) and acetone. Ketosis is a normal physiological response during prolonged fasting (Hoffer, 2006). The rise of plasma/serum ketone bodies is usually accompanied by a rise in plasma/serum uric acid concentrations owing to the competition in renal excretion between uric acid and ketone bodies (Lewis et al., 1977). Whether a particular diet induces a higher or lower increase in uric acid levels, in the absence of newly developed clinical symptoms of gout, is thus not an appropriate determinant for the minimal composition of total diet replacements for weight control. Therefore, this outcome will not be addressed in more detail in the present opinion. Whether the absence of carbohydrates from total diet replacements for weight control results in any adverse effects that would warrant recommending a minimum carbohydrate content of such diets is discussed in section 6.2.

Although the present opinion only applies to formulated total diet replacements for weight control, the Panel will also use studies in which well-characterised diets other than formulated diets are administered, as these studies can provide data on important health/metabolic outcomes.

6. Essential composition of total diet replacements for weight control

6.1. Protein

Dietary proteins are the source of nitrogen and indispensable amino acids required for the synthesis of protein and other nitrogenous compounds in the body. In this opinion, "protein" is total nitrogen × 6.25 and protein requirements are based on nitrogen content.

The Panel's opinion on setting DRVs for protein (EFSA NDA Panel, 2012d) concluded that a PRI can be derived from nitrogen balance studies. For healthy adults of both sexes, the AR was established at 0.66 g protein/kg body weight per day based on nitrogen balance data. Based on the 97.5th percentile of the distribution of the requirement, the PRI for adults of all ages was estimated to be 0.83 g protein/kg body weight per day and is applicable to high-quality protein and to protein in mixed diets. The quantity and utilisation of indispensable amino acids is considered to be an indicator of the dietary protein quality, which is usually assessed using the Protein Digestibility-Corrected Amino Acid Score (PD-CAAS). A high-quality protein supply is defined as a protein or a diet with a PD-CAAS value of 1.0, i.e. not limiting in their content of indispensable amino acids. PD-CAAS scores exceeding 1.0 are usually truncated. The PD-CAAS is based on comparison of the concentration of the first limiting indispensable amino acid in the test protein (mg/g protein) with the concentration of that amino acid in a reference (scoring) pattern (mg/g protein). The ratio is corrected for the true faecal nitrogen digestibility, as measured in a rat assay (WHO/FAO/UNU, 2007; Schaafsma, 2012). Estimates for values for the digestibility of protein in humans from selected sources are given in the report by WHO/FAO/UNU (2007). The reference scoring pattern for adults as proposed by WHO/FAO/UNU (2007) is listed in Table 1.

Table 1: Reference scoring pattern for indispensable amino acids for adults as proposed by WHO/FAO/UNU (2007)

Amino acid(s)	mg/g protein
Histidine	15
Isoleucine	30
Leucine	59
Lysine	45
Methionine + cysteine	22
Phenylalanine + tyrosine	38
Threonine	23
Tryptophan	6
Valine	39

Concerns about the potential detrimental effects of very high protein intakes remain controversial. Acute adverse effects have been reported for protein intakes above 3.0 g protein/kg body weight per day (WHO/FAO/UNU, 2007). In its previous opinion on DRVs for protein, the Panel concluded that in adults an intake of twice the PRI (1.66 g/kg body weight per day) is safe. Such intakes from mixed diets are regularly consumed by some physically active and healthy individuals in Europe. Intakes of three to four times the PRI have been observed without apparent adverse effects or benefits (EFSA NDA Panel, 2012d).

The Panel considers that during energy restriction, protein intakes should not be below the PRI for adults (EFSA NDA Panel, 2012d). However, the PRI of 0.83 g/kg body weight per day cannot be directly applied to overweight or obese individuals considering that PRIs are derived for healthy, normal-weight individuals with corresponding body composition. It is established that protein requirements are closely linked to FFM and that in the overweight or obese the percentage of FFM related to whole body weight is lower than in normal-weight persons because of a higher percentage of fat mass in relation to body weight. Accordingly, protein requirement for the overweight or obese should be related to FFM. As both protein requirements and resting energy expenditure (REE) are mainly related to FFM, the Panel proposes to correct the PRI established for a normal-weight person by the quotient of the REE of overweight or obese individuals and the REE of a normal-weight reference subject. This is under the assumption that energy restriction *per se* does not lead to major changes in protein metabolism (as discussed below).

Several equations have been developed to predict REE, mainly based on body mass, height, age and sex. These are discussed in more detail in the Panel's opinion on DRVs for energy (EFSA NDA Panel, 2013c). In that opinion, the Panel concluded that the equations by Harris and Benedict (1919), Schofield et al. (1985), Mifflin et al. (1990), Müller et al. (2004) and Henry (2005) can be considered as equally valid, but the Panel used, for practical reasons and the comprehensiveness of the underlying database, the equations by Henry (2005) to calculate REE for healthy, normal-weight adults.

Two studies investigated the predictive power of different equations to estimate REE in overweight or obese adults (Weijs, 2008; Frankenfield, 2013). Both studies concluded that the Mifflin equation had the highest accuracy rates in predicting REE in overweight or obese US adults. Weijs (2008) also included overweight and obese Dutch subjects in the investigation, but found that there was no single accurate equation for the taller Dutch subjects.

For the present opinion, the Panel decided to use the equation derived by Mifflin et al. (1990) to estimate REE, based on the findings by Frankenfield (2013) and Weijs (2008) in overweight or obese adults. As reference subjects, a 177-cm-tall, 40-year-old male weighing 69 kg and a 163-cm-tall, 40-year-old female weighing 58 kg were chosen. This was based on the average heights of 40- to 49-year-

old males and females measured in nationally representative surveys in 13 EU Member States[15] (EFSA NDA Panel, 2013c) and a calculated body weight based on a BMI of 22 kg/m^2. The same age and height were used for overweight or obese reference subjects with varying BMI, as given in Table 2. The PRI for protein calculated as 0.83 g protein per kilogram reference body weight per day and a protein intake which was previously considered safe by the Panel (EFSA NDA Panel, 2012d) of 1.66 g/kg reference body weight per day (corresponding to twice the PRI) for a normal-weight adult was adjusted, in absolute terms, by a factor which was derived as the quotient of the REE of the overweight or obese subject and the normal-weight reference subject. Thus, protein intakes which could be considered appropriate in terms of minimum and maximum quantities for the overweight or obese were derived.

Table 2: Overview of minimum and maximum recommendable protein intakes in overweight or obese 40-year-old adults based on the PRI of normal-weight subjects and corrected for differences in REE using the equations by Mifflin et al. (1990) [(a)]

	BMI (kg/m^2)	Weight (kg)	REE Mifflin (kcal/day) [(a)]	Factor [(b)]	Min. [(c)] (g/day)	Max. [(d)] (g/day)
Male (age 40, height 177 cm)	22 (reference subject)	69	1 601	1.00	57	115
	25	78	1 694	1.06	61	121
	27.5	86	1 773	1.11	63	127
	30	94	1 851	1.16	66	132
	35	110	2 008	1.25	72	144
	40	125	2 164	1.35	77	155
	45	141	2 321	1.45	83	166
	50	157	2 478	1.55	89	177
Female (age 40, height 163 cm)	22 (reference subject)	58	1 238	1.00	48	96
	25	66	1 322	1.07	51	103
	27.5	73	1 388	1.12	54	108
	30	80	1 455	1.18	57	113
	35	93	1 588	1.28	62	123
	40	106	1 721	1.39	67	134
	45	120	1 853	1.50	72	144
	50	133	1 986	1.60	77	154

(a): Males: REE (kcal/day) = weight × 10 + height (cm) × 6.25 – age × 5 + 5; females: REE (kcal/day) = weight × 10 + height (cm) × 6.25 – age × 5 – 161.
(b): REE BMI overweight or obese/REE BMI normal-weight reference subjects.
(c): 0.83 g/kg reference body weight (BMI 22 kg/m^2) per day × factor.
(d): 1.66 g/kg reference body weight (BMI 22 kg/m^2) per day × factor.

Applying the proposed approach to an obese class II (BMI 35.00-39.99 kg/m^2) 40-year-old male reference subject results in a minimum required daily protein intake of 72-77 g/day, with a midpoint at 74.5 g/day (rounded up to 75 g/day). Such protein intakes ensure, at the same time, that the somewhat lower requirements of women are met and safe levels of protein intakes are not exceeded in any of the overweight and obese reference groups. A safe use level could be derived based on the consideration that none of the overweight or obese reference groups should be exposed to more than twice the PRI for protein. Therefore, a maximum daily protein intake of 103 g/day (rounded up to 105 g/day) could be proposed, corresponding to the recommended maximum intake of an overweight 40-year-old woman with a BMI of 25 kg/m^2.

The Panel acknowledges that the derived values are based on theoretical calculations and that changing the assumption with respect to the reference subjects (i.e. age and height) will lead to

[15] Bulgaria, the Czech Republic, Finland, France, Germany, Ireland, Luxembourg, Poland, Portugal, Slovakia, Spain, the Netherlands, the United Kingdom.

different results. However, the Panel considers them to be the best estimate of what could be judged to be potentially representative of the European target population of overweight or obese adults.

The Panel will, in the following, review the theoretically proposed minimum and maximum daily protein intakes in the overweight or obese in the light of human intervention studies which have investigated the impact of different levels of protein intakes on body composition, protein turnover and nitrogen balance during energy restriction.

Studies on the effect of protein content in energy-restricted diets on body composition in overweight or obese subjects

In a parallel RCT (Soenen et al., 2013), 72 overweight or obese subjects (completers, 48 women, average BMI 32.0 kg/m^2) consumed either a "normal-protein" diet (0.8 g protein per kilogram of actual body weight per day (30 % of total energy (E%)), 35 E% carbohydrates, 35 E% fat) or a "high-protein" diet (1.2 g protein per kilogram of actual body weight per day (60 E%), 35 E% carbohydrates, 5 E% fat) which provided 33 % of each individual's daily energy requirements (around 3 766 kJ (900 kcal) per day). On average, the two diets provided around 72 g ("normal-protein" group) and 108 g ("high-protein" group) of protein per day. The diets were consumed for six weeks. Body composition was calculated from body volume, measured by means of air displacement plethysmography together with total body water measured by the ^2H_2O dilution technique using Siri's three-compartment model. Changes in body weight and fat mass were not significantly different between groups (mean changes for body weight: -5.0 vs. -5.9 kg; mean changes for fat mass: -4.8 vs. -4.6 kg in the "high" and "normal" protein groups, respectively). FFM was significantly decreased in both groups, from (mean ± SD) 54.0 ± 9.8 kg at baseline to 52.7 ± 8.5 kg after caloric restriction for the "normal-protein" group, and from 54.0 ± 9.8 kg at baseline to 53.4 ± 8.1 kg after caloric restriction for the "high-protein" group, with a statistically significant difference between groups.

The Panel notes that although changes in FFM were statistically significantly different between groups, the difference (0.7 kg in six weeks) was modest. The Panel considers that this study does not show a biologically relevant advantage of consuming an energy-restricted diet with around 110 g protein per day compared with a diet that provided around 70 g protein per day at a BMI of 32.0 kg/m^2 with respect to losses in FFM and thus would support that the theoretically calculated minimum daily protein intakes during energy restriction of 75 g/day is sufficient to reduce losses in FFM.

Studies on the effect of protein content in energy-restricted diets on protein turnover in normal-weight or obese subjects

Whether or not energy restriction would result in changes in protein turnover has been addressed by Friedlander et al. (2005) in healthy, normal-weight men by measuring leucine flux before and after caloric restriction. Nine young, normal-weight men were underfed by 40 % of the calories required to maintain body weight for 21 days and lost 3.8 ± 0.3 kg (mean ± SD) body weight (5 % of total body weight). Protein intakes were 1.2 g/kg body weight per day. Leucine kinetics was measured using the α-ketoisocaproic acid reciprocal pool model in the postabsorptive state. At rest, leucine flux and oxidation did not differ before and after caloric restriction. Nitrogen balance was negative throughout the intervention (-3.0 g/day).

In an intervention study (Garlick et al., 1980), nine obese subjects (eight females) received 8.0 MJ (1 912 kcal) per day from a total diet replacement with 70 g protein per day ("normal" diet) for three days and thereafter a diet with 2.1 MJ (502 kcal) per day ("low-energy" diet) for three weeks which provided either 50 g protein per day or no protein. Protein turnover was measured after each period with intravenous infusion of ^{14}C-leucine, or an oral dose of ^{15}N-glycine. When the "low-energy" diet contained 50 g protein per day, the rates of protein synthesis and breakdown were little different from the "normal" diet. When the "low-energy" diet contained no protein there was a 40 % decrease in protein synthesis and a smaller decrease in protein breakdown.

In a parallel RCT (Hoffer et al., 1984a), 17 obese females (130-200 % of the reference body weight) were randomised to consume either only ground beef providing 1.5 g protein per kilogram reference body weight per day (85 ± 6 g/day (mean ± SD)), no carbohydrates, 23 ± 7 g fat per day and 2 339 ± 331 kJ/day (559 ± 79 kcal/day; n = 9) or a diet based on ground beef providing 0.8 g protein per kilogram reference body weight per day (44 ± 2 g/day), 0.7 g carbohydrates per kilogram reference body weight per day (38 ± 2 g/day), 18 ± 4 g/day fat and 2 096 ± 163 kJ/day (501 ± 39 kcal/day; n = 8) for five weeks. Amino acid metabolism was studied by means of tracer infusions of L-[1-^{13}C]leucine and L-[^{15}N]alanine. Postabsorptive plasma leucine and alanine flux decreased similarly from baseline with both diets (by -20 and -40 %, respectively).

In a single-arm intervention study (Gougeon et al., 1992), seven obese female subjects (BMI (mean ± standard error (SE)) 34.4 ± 1.8 kg/m^2) received, for seven days, a control diet with 80 g protein per day (12.8 g nitrogen) and were then placed on an energy-restricted diet with 1.7 MJ (406 kcal) per day consisting only of protein (16.8 g nitrogen; partially hydrolysed collagen supplemented with L-tryptophan and D,L-methionine) for 42 days. At baseline and after four and six weeks of the energy-restricted diet, amino nitrogen flux rate and protein synthesis and breakdown were calculated from ^{15}N abundance in urinary urea using the oral ^{15}N-glycine method. Whole-body nitrogen fluxes did not change between periods. Both protein synthesis and breakdown decreased during energy restriction. Net protein synthesis became negative at week six (-0.9 ± 0.2 g nitrogen per day).

The Panel considers that the studies generally show that protein turnover is either maintained or only slightly decreased during caloric restriction provided a quantity of protein between about 50 g and 100 g/day is supplied in the diet. The Panel considers that these findings are in line with the proposal of a minimum daily protein intake of 75 g/day and a maximum recommended intake of 105 g/day during energy restriction in overweight or obese adults.

Studies on the effect of protein content in energy-restricted diets on nitrogen balance in obese subjects

In a non-randomised, cross-over study (DeHaven et al., 1980), seven obese adults (six females, 120-169 kg) consumed a diet with 1 674 kJ (400 kcal) per day consisting solely of puréed boiled turkey (around 100 g protein/day) and a diet with 1 674 kJ (400 kcal) per day consisting of 50 E% protein (50 g/day) from puréed boiled turkey and 50 E% carbohydrates (50 g/day) from grape juice for 21 days each with a two-week weight maintenance diet in between. There was no significant difference in nitrogen balance between dietary periods ((mean ± SE) -2.1 ± 0.9 vs. -2.6 ± 0.4 g/day in the "turkey only" period and the "turkey and grape juice" period, respectively). Weight loss was 10.2 ± 1.0 kg during the "protein only" period and 8.0 ± 0.8 kg during the "protein and carbohydrate" period ($p < 0.02$).

In the parallel RCT by Hendler and Bonde (1988), 17 obese subjects (sex not reported) were allocated to consume total diet replacements for weight control providing around 1 841 kJ (440 kcal) per day with around 45 g protein per day, 60 g carbohydrates per day and 2 g fat per day (n = 9; BMI (mean ± SE) 46 ±4.0 kg/m^2) or a diet with around 105 g protein per day, 2 g carbohydrates per day and 1.5 g fat per day (n = 8; BMI 45 ±3.1 kg/m^2) for 21 days. A negative nitrogen balance was observed in all subjects in weeks one and two. In week three, one subject in the "low-protein" group and four subjects in the "high-protein" group had a positive nitrogen balance (nitrogen balance at week three: +0.26 ± 0.43 vs. -0.75 ± 0.32 g/week in the "high" and "low-protein" groups, respectively (non-significant). Weight loss was similar in both groups, i.e. 8.74 ± 0.8 kg and 8.88 ± 1.01 kg, respectively.

In the parallel RCT by Hoffer et al. (1984a) described above, 17 obese females were assigned to consume either a diet (around 2 339 kJ (559 kcal/day)) providing 1.5 g protein per kilogram reference body weight per day ((mean ± SD) 85 ± 6 g/day) or an isoenergetic diet providing 0.8 g protein per kilogram reference body weight per day (44 ± 2 g/day) for five weeks. A subset of subjects continued the diet for up to eight weeks. Nitrogen balance was significantly lower in the "low-protein" group at

weeks 2, 3, 4, 6 and 8. While on the 1.5 g of protein per kilogram body weight diet, nitrogen balance returned close to equilibrium during week 2, whereas the subjects on the 0.8 g protein per kilogram body weight diet remained in negative nitrogen balance (around -2 g/day throughout). Weight loss was similar in both groups and amounted, on average, to 200 g/day.

In the non-randomised study by Vazquez et al. (1995), 48 obese women were assigned to consume one of the following four diets for 28 days: (1) 2 510 kJ/day (600 kcal/day, "50P/10C diet"; 52.5 g protein per day, 10 g carbohydrates per day, 38 g fat per day, n = 10, BMI (mean ± SE) 44 ± 2 kg/m^2); (2) 2 510 kJ/day (600 kcal/day, "50P/76C diet"; 50 g protein per day, 76 g carbohydrates per day, 10 g fat per day, n = 11, BMI 46 ± 3 kg/m^2); (3) 2 510 kJ/day (600 kcal/day, "70P/10C diet"; 70.5 g protein per day, 9.3 g carbohydrates per day, 33 g fat per day, n = 14, BMI 38 ± 1 kg/m^2); or (4) 2 510 kJ/day (600 kcal/day, "70P/86C diet"; 70 g protein per day, 86 g carbohydrates per day, 3 g fat per day, n = 13, BMI 36 ± 1 kg/m^2). Cumulative nitrogen losses were somewhat lower in the groups which consumed 70 g protein per day than in the 50 g protein groups, but this difference was not statistically significant. Nitrogen balance improved in all diet groups over time and was close to equilibrium at week four in all groups. Weight loss was similar in all groups and was, on average, 8.4 ± 0.4 kg.

In a parallel RCT (Pasquali et al., 1987), 12 obese subjects (six females) were assigned to diets which provided 2 092 kJ (500 kcal) per day and either 40 g protein per day, 81 g carbohydrates per day and 1.3 g fat per day (n = 6, BMI (mean ± SE) 47.7 ± 7.1 kg/m^2) or 81 g protein per day, 54 g carbohydrates per day and 5.0 g fat per day (n = 6, BMI 46.3 ±5.6 kg/m^2). Nitrogen balance was similar in both groups in the first four weeks combined, while it was significantly less negative in the "high-protein" group in the second four weeks combined. Subjects lost, on average, 21.2 ± 6.3 kg in the "high-protein" group and 18.1 ± 5.0 kg in the "low-protein" group. The difference was not statistically significant.

The Panel notes that there is a wide inter-individual variability in effects on nitrogen balance in response to prolonged energy restriction, as was shown in the studies described above. This makes it difficult to generalise results from these studies with a limited number of subjects to the general overweight or obese population. However, subjects with a BMI of around 40–45 kg/m^2 tended to return closer to nitrogen equilibrium somewhat faster when 70-100 g protein per day was consumed than when 50 g protein per day was consumed as part of energy-restricted diets providing around 1 674-2 510 kJ (400-600 kcal) per day. The Panel considers that these findings are in line with the proposal of a minimum daily protein intake of 75 g/day and a maximum recommended intake of 105 g/day during energy restriction in overweight or obese adults.

6.1.1. Recommendations

A supply of protein in the diet is mandatory to compensate obligatory nitrogen losses and equilibrate nitrogen balance. It is impossible to achieve nitrogen equilibrium without protein (nitrogen) intake with either hypocaloric or normocaloric diets.

The Panel proposes to base the minimum protein content of total diet replacements for weight control on the adjusted PRI for a 40-year-old male subject with class II obesity (BMI 35.00-39.99 kg/m^2) as derived by applying a conversion factor based on differences in REE between a normal-weight reference subject and the obese reference subject as calculated by the equation of Mifflin et al. (1990). This correction translates into a minimum amount of 75 g high-quality protein (i.e. PD-CAAS value of 1.0) per day, which should be provided by total diet replacements for weight control. This value is supported by results from nitrogen balance studies, which have shown that subjects with a BMI of around 40-45 kg/m^2 tended to return closer to nitrogen equilibrium somewhat faster when 70-100 g protein per day was consumed as part of an energy-restricted diet than when lower amounts of protein were consumed. It is also supported by results showing that protein turnover is either maintained or only slightly decreased during caloric restriction provided a quantity of protein of between 50 g and 100 g/day is supplied in the diet. In none of the studies the effects on nitrogen balance or protein turnover were investigated for more than eight weeks.

With respect to the maximum protein content of total diet replacements for weight control, the Panel proposes to derive it from the maximum protein intakes considered as safe (i.e. equal to twice the PRI) of an overweight 40-year-old woman with a BMI of 25 kg/m^2. This derivation results in a maximum quantity of 105 g protein per day in total diet replacements for weight control. This value is similar to the highest protein intakes investigated in the above-described studies with no apparent adverse effects.

6.2. Glycaemic carbohydrates

In healthy people, the brain, the medulla of the kidney and red and white blood cells are dependent on carbohydrates, namely glucose**,** for energy production, either by glucose oxidation (brain) or by aerobic glycolysis (kidney medulla and blood cells with a total daily requirement of about 32 g/day) (Cahill, 1970). The glucose requirement of the brain has been estimated to be 110-140 g/day (Scheinberg and Stead, 1949; Reinmuth et al., 1965; Cahill et al., 1968; Sokoloff et al., 1977; Gottstein and Held, 1979), to be proportional to the size of the brain and to be constant until the age of 73 years (Reinmuth et al., 1965). Sokoloff et al. (1977) determined glucose utilisation by measuring brain oxygen consumption from the arteriovenous difference in 12 adults with brain weights of about 1 450 g and arrived at a daily glucose consumption of the brain of 101 g/day.

The overall daily dietary requirement for glucose is, in the presence of an energy-adequate diet, 117 to 142 g minus 30 g glucose produced in gluconeogenesis from amino acids and glycerol, and amounts to 87-112 g/day. A similar amount (50-100 g/day) of glucose is sufficient to prevent ketosis (Bell et al., 1969; Calloway, 1972; Sapir et al., 1972). The US Institute of Medicine (IoM, 2005a) has set a reference value for glycaemic carbohydrates of 130 g/day based on these considerations.

6.2.1. Gluconeogenesis

Gluconeogenesis from glucogenic amino acids and from the glycerol of triacylglycerols (TAGs) can provide the glucose needed by glucose-dependent organs/cells, at the expense of increased ketogenesis (Hultman et al., 1999). Total endogenous glucose production in healthy adults is about 2.2 mg/kg body weight per minute after overnight fasting, with liver gluconeogenesis contributing about 1.0 mg/kg per minute, i.e. about half of total glucose production and glycogenolysis contributing the other half, whereas the total endogenous glucose production upon prolonged fasting is about 1.5 mg/kg per minute, with liver gluconeogenesis contributing almost all of glucose production (Landau et al., 1996; Chandramouli et al., 1997; Hellerstein et al., 1997), which is also in agreement with the model proposed by König et al. (2012). Considering that about 45 % of endogenous amino acids are glucogenic, it has been proposed that during starvation oxidation of 1 g of endogenous protein produces about 0.5-0.6 g of glucose (e.g. Janney, 1915). If it is assumed that 10 % of a TAG is glycerol, which can be converted into glucose, glucose production from protein and glycerol amounts to about 30-40 g/day. If the brain had to cover a glucose requirement of 120 g by gluconeogenesis from amino acids in the absence of exogenous carbohydrates and in the absence of ketone bodies, it would use about 200 g protein per day. This means that about 1 kg of FFM (with a water content of 80 %) would have to be broken down per day (Halperin and Cheema-Dhadli, 1989).

6.2.2. Ketones as alternative fuel

During starvation or significant energy/carbohydrate restriction, the glycogen reserves (approximately 7 500 kJ or 1 880 kcal for a well-fed 70 kg man), i.e. 150 g in liver plus about 300 g in muscle (Schaub et al., 1987), are exhausted after about 24 hours. Gluconeogenesis prevents hypoglycaemia and provides glucose for glucose-dependent blood cells. To save the glucogenic amino acids that could be released from body protein degradation, there is a switch from glucose to fatty acid oxidation in the liver and muscle. The resulting acetyl-CoA is converted to great amounts of ketone bodies. Both brain and heart increasingly oxidise AcAc and 3OHB. After three days of starvation, about 30 % of the energy requirement of the brain is covered by ketone bodies, which increases up to 80 % with prolonged starvation/carbohydrate restriction (Cahill et al., 1973), leaving an absolute requirement for 22-28 g glucose per day (Carlson et al., 1994; Owen et al., 1998). Total diet replacements for weight

control that provide small amounts of carbohydrates force the body to rely on energy production from fat stores and potentially spare body protein from degradation for gluconeogenesis, particularly when combined with an ample protein intake (Flatt and Blackburn, 1974).

Lobley et al. (2014) have shown that hunger is lower in individuals on high-protein diets when combined with a low carbohydrate intake rather than with a moderate carbohydrate intake. They investigated in a cross-over RCT on 12 men with a mean BMI of 34.9 kg/m² the effects of two isoenergetic diets, each given for four weeks, with 7 950 kJ (1 900 kcal) per day and 30 E% of protein (149 g protein/day) that contained either 22 g ("low") or 182 g ("moderate") carbohydrates. At the end of each dietary intervention period, following an overnight fast (n = 4), or four hours after consumption of a test meal (n = 8), a ^{18}F-fluoro-deoxyglucose positron emission tomography scan of the brain was conducted, followed on the next day by a quantification of whole-body ketone and glucose metabolism using [1,2,3,4-^{13}C]AcAc, [2,4-^{13}C]3-OHB and [6,6-$^{2}H_2$]glucose. Whole-body ketone flux was approximately four-fold greater for the "low-carbohydrate" dietary intervention than for the "moderate-carbohydrate" diet ($p < 0.001$). The nine-fold difference in carbohydrate intake between the dietary interventions led to a 5 % lower supply of glucose to the brain. Despite this, the uptake of glucose by the analysed 54 regions of the brain remained similar for the two dietary interventions. The composite hunger score was 14 % lower with the "low-carbohydrate" diet than with the "moderate-carbohydrate" diet.

The Panel considers that this study shows that glucose uptake in the brain was similar on isoenergetic high-protein diets with "low" and "moderate" carbohydrate intakes and independent of the presence of ketosis. The Panel notes that a higher level of ketosis was associated with reduced hunger. The Panel also notes that similar studies on subjects on energy-restricted diets are not available.

6.2.3. Adverse effects of low-carbohydrate ketogenic diets

Severe metabolic acidosis is one of the reported adverse effects of diets very low in carbohydrates (< 40 g/day) consumed by adults who wanted to lose weight (IoM, 2005a; Chen et al., 2006; Shah and Isley, 2006). This is a rare occurrence and may have been caused by unrecognised predisposing metabolic abnormalities or diseases, whilst a mild metabolic acidosis characterised by low bicarbonate levels (< 22 mmol/L) with an increased anion gap is a common physiological occurrence. Because of the metabolic acidosis induced by LCDs, and particularly by VLCDs, a risk of adverse effects on body mineral balance and on bone mineral content (BMC) has been suggested and is addressed in section 6.6. Despite the negative influence of ketone bodies on uric acid clearance, hyperuricaemia is usually transient and gout, as a consequence of hyperuricaemia, has not been reported in subjects consuming total diet replacements for weight control. Other potential adverse effects include the lack of glycogen stores to counteract hypoglycaemic episodes and short-term intense power production by muscles. Other reported untoward effects are a decrease in well-being, i.e. dizziness, light-headedness, halitosis, concentration difficulties, cold intolerance, constipation, postural hypotension, headache, dry skin and alopecia (Foster et al., 1992; Rössner and Flaten, 1997). In most instances these symptoms will be mild and transient, but they may interfere with adherence to the dietary regimen. The Panel notes that these adverse effects may be related not specifically to the macronutrient composition of the energy-restricted diet, but rather to their low energy content *per se*.

Studies on the effect of energy-restricted diets with a low carbohydrate content on ketosis

In a single-arm study in seven obese female subjects (BMI (mean ± SE) 34.4 ± 1.8 kg/m^2), 3OHB in serum rose from 13 ± 7 to 1 115 ± 321 µmol/L after six weeks of consuming a 100 % protein 1 674 kJ (400 kcal) per day diet (partially hydrolysed collagen supplemented with L-tryptophan and D,L-methionine) and with 16 mmol potassium (Gougeon et al., 1992). Weight loss was 12.8 ± 0.9 kg. There was no acidosis and only an insignificant decrease in venous blood bicarbonate.

DeHaven et al. (1980) described seven obese adults (six females, 120-169 kg) each consuming two diets with 1 674 kJ (400 kcal) per day for 21 days that consisted either of solely boiled turkey or provided 50 E% from turkey protein and 50 E% from grape juice carbohydrates. In between the two

diets, the subjects received for two weeks a maintenance diet (8 452 kJ (2 020 kcal) per day). The concentrations of the sum of 3OHB and AcAc were significantly higher after the "turkey only" period than after the "turkey and grape juice" period (mean ± SE: 1.94 ± 0.23 vs. 1.08 ± 0.12 mmol/L; $p < 0.001$), as was 24-hour urinary excretion of ketone bodies (50.9 ± 12.5 vs. 10.2 ± 2.9 mmol; $p < 0.02$). The Panel notes that in this study, with a small sample size, the substitution of 50 % of the protein content with carbohydrates of a 1 674 kJ (400 kcal) diet reduced but did not abolish ketosis.

Studies on the effect of energy-restricted diets with a low carbohydrate content on nitrogen balance

Prolonged fasting to reduce excess body weight leads to a negative nitrogen balance because weight loss is always composed of both fat mass and smaller quantities of FFM. Through adaptation of the body protein breakdown, the highly negative nitrogen balance of the first days of total fasting (12–15 g nitrogen per day, including skin and faecal losses), decreases to a stable loss of 5 g nitrogen per day (4-6 g/day) (Marliss et al., 1978; Hannaford et al., 1982) after two to three weeks. The urine nitrogen is composed of 50 % urea and 50 % ammonia. Whilst the quantity of urinary urea represents the quantity of protein broken down to produce substrates for gluconeogenesis and so maintain blood glucose concentrations and provide the minimum of glucose for glucose-consuming tissues, the increase in urinary ammonia during fasting is secondary to the metabolic acidosis and is essential for preserving acid–base balance in the face of an increasing acid load. A loss of 4-6 g nitrogen corresponds to the catabolism of 25-37.5 g protein assuming a conversion factor of 6.25 (Hannaford et al., 1982).

Protein breakdown in fasting can be decreased by the addition of carbohydrates, because it reduces the need for protein breakdown for gluconeogenesis (Blackburn et al., 1973; Flatt and Blackburn, 1974). Addition of small amounts of carbohydrates (20 g/day) to a diet with about 1 g of protein per kilogram body weight per day resulted in similar neutral or positive nitrogen balance in adolescents on a normocaloric diet (Pencharz et al., 1980) and in obese adults on VLCDs providing 1 644 kJ (393 kcal) per day consisting of 82.5 g protein (81 E%), 6.9 g fat (16 E%) and 3.2 g carbohydrates (3 E%) (Marliss et al., 1978). With the development of ketoacidosis, renal ammonia excretion rises because excess ketones are excreted in the urine as ammonium salts until they make up approximately 50 % of urinary nitrogen (Marliss et al., 1978; Halperin and Cheema-Dhadli, 1989). Ammonia excretion in acidosis as a result of energy-restricted low-carbohydrate diets contributes to the negative nitrogen balance, if dietary protein intake is insufficient.

Two studies from the same research group assessed the impact of a difference in carbohydrate content in isoenergetic diets at the same levels of protein intakes on nitrogen balance. In the non-randomised parallel study by Vazquez and Adibi (1992), 16 obese women were assigned to consume either a VLCD with 2 469 kJ/day (590 kcal/day; "non-ketogenic diet", 50 g protein per day, 76 g carbohydrates per day, 10 g fat per day, n = 8, BMI (mean ± SE) 47 ± 2 kg/m^2) or a VLCD with 2 485 kJ/day (594 kcal/day "ketogenic diet" 52 g protein per day, 10 g carbohydrates per day, 38 g fat per day, n = 8, BMI 49 ± 4 kg/m^2) for 28 days. The diets provided similar amounts of vitamins and minerals. Cumulative nitrogen balance was -18.8 ± 5.7 vs. -50.4 ± 4.4 g in 28 days for the "non-ketogenic diet" and the "ketogenic diet" group, respectively ($p < 0.02$). Nitrogen balance became less negative over time in both groups. Subjects on the "non-ketogenic diet" were close to nitrogen equilibrium on day 14 and subjects on the "ketogenic diet" on day 21. Weight loss was similar in both groups (8.5 ± 0.3 kg vs. 8.3 ± 0.5 kg on the "ketogenic" and "non-ketogenic" diet, respectively). The Panel notes that in this study with VLCDs differing in the carbohydrate content, the cumulative nitrogen balance over four weeks was less negative with a carbohydrate intake of 76 g than with 10 g at a protein intake of 50 g/day. The nitrogen saving effect was significantly greater with the "non-ketogenic" diet (cumulative loss of 117.5 vs. 315 g protein).

In the non-randomised study by Vazquez et al. (1995), 48 obese women were assigned to consume one of the following four diets for 28 days: (1) 2 510 kJ/day (600 kcal/day, "50P/10C diet"; 52.5 g protein per day, 10 g carbohydrates per day, 38 g fat per day, n = 10, BMI (mean ± SE) 44 ± 2 kg/m^2); (2) 2 510 kJ/day (600 kcal/day, "50P/76C diet"; 50 g protein per day, 76 g carbohydrates per day, 10 g fat

per day, n = 11, BMI 46 ± 3 kg/m^2); (3) 2 510 kJ/day (600 kcal/day, "70P/10C diet"; 70.5 g protein per day, 9.3 g carbohydrates per day, 33 g fat per day, n = 14, BMI 38 ± 1 kg/m^2); or (4) 2 510 kJ/day (600 kcal/day, "70P/86C diet"; 70 g protein per day, 86 g carbohydrates per day, 3 g fat per day, n = 13, BMI 36 ± 1 kg/m^2). Cumulative nitrogen losses were significantly lower in the ≥ 76C groups than in the 10C groups (1 869 ± 392 vs. 3 611 ± 328 mmol per 28 days, (26.2 ± 5.5 g vs. 50.6 ± 4.6 g nitrogen) p = 0.003). Nitrogen balance improved in all diet groups over time and was close to equilibrium at week four in all groups. Weight loss was similar in all diet groups, with mean weight losses ranging from 7.6 to 8.9 kg. The Panel notes that in this study VLCDs with a protein content of 50-70 g/day and around 70 g carbohydrates per day had a greater nitrogen-saving effect than their counterparts providing around 10 g carbohydrates per day.

6.2.4. Recommendations

The Panel notes that some studies seem to indicate that with a high protein supply of 100 g/day carbohydrates are not needed to achieve the desired effect of near-neutral nitrogen balance. However, such products may carry a higher risk of severe ketoacidosis. Other studies on VLCDs with a lower protein intake of between 50 and 70 g/day and supplying around 70 g carbohydrates per day indicated that these are of advantage with respect to nitrogen loss compared with a carbohydrate supply of around 10 g/day. Considering that up to 80 % of the energy requirement of the brain (around 2 092 kJ (500 kcal) per day) can be supplied by ketone bodies, there remains a demand for, about, 25-30 g of glucose that can be produced via gluconeogenesis from glycerol and amino acids or be supplied by the diet. In order to keep the need for gluconeogenesis low, the Panel proposes a minimum content of digestible carbohydrates in total diet replacements for weight control of 30 g/day.

6.3. Dietary fibre

Dietary fibre is not an indispensable component of the diet. However, dietary fibre has a major role in bowel function. The role of dietary fibre in bowel function was considered the most suitable criterion for establishing an AI. Based on available evidence on bowel function, the Panel considered dietary fibre intakes of 25 g/day to be adequate for normal laxation in adults on an habitual diet (EFSA NDA Panel, 2010a). Dietary fibre doses of around 7-30 g/day with total diet replacements for weight control have been reported (Astrup et al., 1990; Quaade et al., 1990; Kovacs et al., 2001; Kovacs et al., 2002). Often the amount is individually determined.

No effects of dietary fibre addition to diet replacements for weight control on satiety ratings were observed either with 7.5 g guar gum per day (energy content 1 623-1 950 kJ/day or 388-466 kcal/day) (Kovacs et al., 2001; Kovacs et al., 2002) or 30 g birch fibre (98.5 % cellulose) per day (energy content 5 648 kJ/day or 1 350 kcal/day) (Astrup et al., 1990; Quaade et al., 1990). Astrup et al. (1990) and Quaade et al. (1990) reported lower hunger scores when the energy-restricted diet was supplemented with 30 g of fibre per day, whereas Kovacs et al. (2001) and Kovacs et al. (2002) observed no such effect.

6.3.1. Recommendations

Owing to the lack of scientific evidence, the Panel considers that an absolute minimum requirement for fibre in overweight and obese subjects during weight loss cannot be established, the more so as both constipation and diarrhoea have been reported during the use of total diet replacements. Therefore, the Panel cannot propose a minimum content of dietary fibre in total diet replacements for weight control.

6.4. Fat

Dietary fat is a major source of energy because of its high energy density and is often limited in weight reduction diets. However, some dietary fat is needed to provide the essential fatty acids (EFA), linoleic acid (LA) and α-linolenic acid (ALA), and to ensure adequate absorption of fat-soluble vitamins. The relevant endpoints to consider in relation to the composition of total diet replacements with respect to their fat content would be nutritional status with respect to EFA and fat-soluble

vitamins as well as gallstone formation. As there are no studies that examined the effect of total diet replacements on status of EFA and fat-soluble vitamins, the Panel will in the following address only the effects of total diet replacements for weight control with varying fat content on gallstone formation.

The Panel has set a Reference Intake range for fat of 20-35 E% for healthy normal-weight adults on energy-adequate diets, which was based on practical considerations (e.g. current levels of intake, achievable dietary patterns). For LA and ALA, the Panel proposed to set AIs of 4 E% and 0.5 E%, respectively, based on the lowest estimated mean intakes of various population groups from a number of European countries where overt LA and ALA deficiency is not present. For a diet with around 10.7 MJ/day (2 500 kcal/day, i.e. the AR of a 40-year-old male with a physical activity level of 1.6 (moderately active)), this would amount to a daily intake of LA of around 11 g and of ALA of around 1.4 g. For eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) the Panel established an AI of 250 mg/day based on the primary prevention of cardiovascular disease (EFSA NDA Panel, 2010c).

Adipose tissue acts as an EFA reserve, especially with respect to LA (typically around 100-150 g per kilogram adipose tissue in Western populations). However, there are wide variations, especially in LA content, which has been shown to be between 25 and 250 g/kg adipose tissue. There are lower quantities of n-3 polyunsaturated fatty acids (PUFAs) in the adipose tissue stores, which have ALA concentrations ranging from around 6 to 32 g/kg, (typically in the range of 10–20 g/kg). DHA is found in adipose tissue of Western populations in concentrations of about 1-3 g/kg. EPA has only been detected in trace amounts (Seidelin, 1995). During weight loss, the fatty acid reserve in adipose tissue becomes available. At a rate of weight loss of 1 kg per week (corresponding to 0.8 kg estimated loss of adipose tissue), this would theoretically result in a release of around 11 g LA, 1 g ALA and 114 mg DHA per day (taking the LA, ALA and DHA content in adipose tissue to be 100, 10 and 1 g/kg, respectively).

6.4.1. Gallstone formation

It has been suggested that the increased risk of gallstone formation during rapid weight loss could be partly explained by a low fat content of the diet, in particular in VLCDs, and that a certain minimum amount of fat is needed in a diet to prevent or reduce the incidence of gallstone formation. The most commonly proposed mechanisms for gallstone formation during rapid weight loss are supersaturation of bile with cholesterol in combination with an impaired gallbladder emptying as a result of the reduced gallbladder stimulation because of the low fat content of weight loss diets (Johansson et al., 2014). It has been proposed that 5-10 g/day of fat in VLCDs would be sufficient to attenuate the higher risk for gallstone formation associated with rapid weight loss (Festi et al., 2000; SCOOP Taskforce, 2002).

Studies on gallbladder emptying and/or gallstone formation on isocaloric low-calorie diets with varying fat content

In a parallel RCT, Festi et al. (1998) compared gallbladder emptying in response to two VLCDs providing 2 238-2 414 kJ (535-577 kcal) per day and 3.0 and 12.2 g fat per day in 32 obese subjects (20 females). There was no diet-specific effect on cholesterol saturation index of the bile. Weight loss was similar in both groups. Gallbladder emptying was higher in response to the "high-fat" VLCD than to the "low-fat" VLCD. The effect of the "high-fat" VLCD was similar to a standard liquid test meal administered to induce maximal gallbladder emptying. Six of the 11 subjects who followed the "low-fat" VLCD for 90 days developed gallstones (asymptomatic), while none did on the "high-fat" VLCD.

In a non-randomised manner, Vezina et al. (1998) studied 272 obese subjects (209 females) who were on a LCD providing 3 766 kJ (900 kcal) per day and containing either 16 or 30 g fat per day (4 and 10 g/meal) for 13 weeks. The diets also differed in the content of dietary fibre (11 vs. 15 g/day). Weight loss was similar in both groups. Sixteen of 94 subjects (17.0 %) in the "low-fat" LCD group and 20 of 178 (11.2 %) in the "high-fat" LCD group ($p = 0.18$) developed gallstones.

Studies on gallbladder emptying and/or gallstone formation on diets with different fat and energy contents

In a non-randomised study, Stone et al. (1992) investigated gallbladder emptying in seven normal-weight (BMI (mean ± SE) 22 ± 1 kg/m^2) and seven obese subjects (BMI 36 ± 1 kg/m^2) in response to four different test meals with varying fat content (i.e. 0, 4, 10 and 20 g per meal). The percentage of gallbladder emptying after the test meals containing 10 and 20 g of fat were similar to the maximal gallbladder emptying levels under maximal stimulating conditions of each individual while fat doses ≤ 4 g induced significantly lower degrees of emptying than the 10 g dose. This study also showed that there was no difference in gallbladder emptying between normal-weight and obese subjects.

Gebhard et al. (1996) investigated gallbladder emptying in 13 obese subjects (10 females) who were randomised to consume either a VLCD containing 2 176 kJ/day (520 kcal/day; < 2 g fat per day; n = 6) or a LCD containing 3 766 kJ/day (900 kcal/day; 30 g fat per day n = 7) for 12 weeks. There was no diet-specific effect on the cholesterol saturation index of the bile. Weight loss was similar in both groups. Gallbladder emptying in response to the consumption of a meal < 1 g fat vs. a meal containing 10 g fat was tested at the beginning of the intervention and at weeks 2, 4 and 8. Maximal stimulation under maximal stimulating conditions was found to amount to a 66 % gallbladder emptying. This was also achieved by the "high-fat" meal whereas the "low-fat" meal resulted in only 35 % emptying. Four subjects in the VLCD group developed gallstones (asymptomatic) in the course of the study, but none in the LCD group (p = 0.02). Owing to the pronounced effect on incidence of gallstones, the study was stopped early for ethical reasons.

The Panel notes that the incidence of gallstones is reduced with increasing fat and energy content of the diet. However, the available evidence does not allow a precise cut-off value to be defined above which the risk for gallstone formation would be reduced.

6.4.2. Recommendations

Although the addition of EFA to total diet replacements for weight control may not be needed owing to their release from tissue stores during weight loss, the Panel considers that total diet replacements for weight control should provide at least the AI for LA and ALA established for energy-adequate diets. This recommendation is based on the consideration that the fatty acid content of adipose tissue and the rate of adipose tissue loss may vary between individuals; thus, there is considerable uncertainty as to whether body stores can completely cover requirements. Therefore, the Panel proposes that total diet replacements for weight control should provide at least 11 g LA per day and 1.4 g ALA per day.

The Panel notes that although an AI for DHA and EPA has been set, this AI does not indicate a necessity to supply DHA and EPA continuously on a daily basis. As total diet replacements for weight control are indicated for use over a restricted period of time and there is no evidence that the absence of DHA and EPA from the diet of an adult over a short period of time would result in any adverse effects, the Panel does not propose a minimum content of DHA and EPA in total diet replacements for weight control.

The available evidence is insufficient to establish a minimum fat content in total diet replacements for weight control beyond their content of EFA. The above-proposed minimum content of LA and ALA leads to a minimum amount of total fat provided by total diet replacements for weight control of around 20 g/day, as oils used to supply these fatty acids have a maximum EFA content of 55-75 % of total fatty acids.

There is no evidence to support proposing a maximum fat content in total diet replacements for weight control.

6.5. Energy

The Panel considers that the minimum energy content of total diet replacements for weight control can be derived from the minimum macronutrient content of such diets. Considering that the Panel proposed that total diet replacements should provide at least 75 g protein per day, 30 g carbohydrates per day and LA and ALA in amounts which sum up to around 20 g fat per day a minimum energy content of 2 510 kJ (600 kcal) per day could be derived.

In terms of weight loss, studies have not shown additional benefits of diets which provided fewer than 3 347 kJ (800 kcal) per day as compared with diets with 3 347 kJ (800 kcal) per day (Davies et al., 1989; Foster et al., 1992; Rössner and Flaten, 1997; Moreno et al., 2006; Lin et al., 2009). Somewhat lower losses in FFM (expressed in per cent of weight lost) have been observed with diets providing more than 3 347 kJ (800 kcal) per day (14.0 % (IQR: 4-24 %)) than with diets providing fewer than that (23.4 % (IQR: 15.4-31.4 %)) (Chaston et al., 2007).

Directive 96/8/EC specifies a maximum energy content of total diet replacements for weight control of 5 040 kJ (1 200 kcal) per daily ration. The Panel notes that diets with 5 040 kJ (1 200 kcal) per day result in a meaningful energy restriction with the objective of weight loss for overweight or obese adults. There is no further scientific evidence justifying this cut-off.

6.5.1. Recommendations

The Panel proposes that total diet replacements for weight control should provide at least 2 510 kJ (600 kcal) per day. From a scientific point of view, there is no evidence to establish a threshold below which a diet could be considered to be very low in energy content.

6.6. Calcium

In an opinion endorsed for public consultation (EFSA NDA Panel, 2014h), the Panel proposed a PRI for calcium for adults ≥ 25 years of 950 mg/day, which was derived from calcium balance data.

A UL of 2 500 mg/day has been established by the Panel (EFSA NDA Panel, 2012a) based on evidence from placebo-controlled human intervention studies in adults in which total daily calcium intakes of 2 500 mg from both diet and supplements were tolerated without adverse effects.

Chronic metabolic acidosis increases urine calcium without increasing intestinal calcium absorption resulting in bone calcium loss, acute by physicochemical dissolution, chronically by cell-mediated bone resorption (Frick and Bushinsky, 2010). This effect is independent of the nature of the metabolic acidosis. Ketogenic diets leading to metabolic acidosis, therefore, may have an adverse effect on BMC.

This has been investigated in children and adults with inborn errors of glucose transport, carbohydrate metabolism and intractable epilepsy treated with normocaloric ketogenic diets. Bertoli et al. (2014) treated three adults with glucose transporter 1 deficiency for five years with a normocaloric diet that provided, besides normal amounts of protein, 87 E% as fat and 2.2 E% as carbohydrates, supplemented daily with 1 000-1 320 mg calcium, 790-900 mg phosphorus, 2.7-2.9 g potassium and vitamins and minerals. BMC and bone mineral density were normal at baseline. BMC decreased in all patients after three years but returned to normal values after five years. No nephrolithiasis or other adverse effects occurred. Twenty-five children (1-14 years of age) with intractable epilepsy, who consumed, for 15 months, a 4:1 ketogenic diet (fat:carbohydrate plus protein by weight) supplemented with vitamin D, calcium, phosphorus and other vitamins and minerals at recommended intakes, showed progressive slowing of growth during treatment and a further decrease of low z-scores for whole-body BMC and lumbar spine BMC at baseline by 0.6 z-score units per year. Dietary intakes of vitamin D and calcium had been low at baseline and serum 25OH-vitamin D was below 32 ng/mL in 73 % of the children (Bergqvist et al., 2008). The Panel notes that ketoacidosis resulting from long-term dietary manipulation without energy restriction may lead to urinary and bone calcium losses and growth retardation in children.

Only few studies with total diet replacements for weight control have reported the intake of calcium or assessed the effect on calcium metabolism.

Nishizawa et al. (1992) reported the effect of a VLCD on calcium homeostasis and BMC in eight obese women (BMI (mean ± SE) 42.7 ± 1.1 kg/m^2), who consumed diets with stepwise decreasing energy content: starting with 6 025 kJ (1 440 kcal) per day and reducing, each week, to 5 021 kJ (1 200 kcal), then 3 682 kJ (880 kcal) and, finally, 1 757 kJ (420 kcal) per day. The final diet (1 757 kJ (420 kcal) per day) was continued for four weeks, after which the subjects returned to the diet providing 3 682 kJ (880 kcal) per day. The initial three diets provided 600 mg calcium and 900 mg phosphorus per day and the 1 757 kJ (420 kcal)-diet 800 mg calcium and 800 mg phosphorus per day. Total and regional BMC before and after the 1 757 kJ (420 kcal) period were measured by dual-photon absorptiometry. There were no untoward effects on BMC observed in this study. However, the Panel notes that the intervention period of four weeks was too short to result in significant changes in BMC.

DeHaven et al. (1980) found no difference in the calcium or phosphorus balance of seven obese adults (six females, 120-169 kg) consuming two diets with 1 674 kJ (400 kcal) per day for 21 days each that provided either 100 E% as protein or 50 E% each as protein and carbohydrates. This study is described in more detail in section 6.1. The weight-loss diets were supplemented with calcium and phosphorus in similar amounts. Cumulative calcium balance and cumulative phosphorus balance were negative in both diet periods without statistically significant differences between them, i.e. -6.4 ± 0.4 and -4.5 ± 1.5 g in the 100 % protein diet vs. -5.5 ± 0.4 and -3.9 ± 0.8 g over 21 days in the 50 % protein–50 % carbohydrate diet, respectively. This corresponds to a daily calcium loss of about one-third of the PRI.

The consumption of a VLCD (2 720-3 033 kJ/day or 650-725 kcal/day) high in protein (80-100 g/day), low in carbohydrate (25 g/day) and low in fat (25 g/day) with 1 250 mg calcium and 20 µg vitamin D per day by six adolescents (12-15 years of age) over eight weeks, followed by 12 weeks of the same diet enriched with 90 g carbohydrates per day (+1 506 kJ/day or + 360 kcal/day) resulted in a significant weight loss (15.4 ± 1.4 kg) during phase 1 and an additional loss of 2.3 ± 2.9 kg during phase 2. Ketosis developed within three days after starting the low-carbohydrate diet and disappeared quickly when carbohydrates were added after eight weeks. Urinary calcium excretion increased significantly shortly after the introduction of the diet but returned to normal when carbohydrates were added. The rise in calcium excretion was accompanied by a statistically significant decrease in total body BMC (-0.15 ± 0.04 kg), which returned close to baseline when carbohydrates were reintroduced in the diet (Willi et al., 1998). The Panel considers that this small study shows that ketoacidosis is associated with increased calcium excretion and changes in BMC during an eight-week observation period, both of which seem to be reversible with the reintroduction of carbohydrates into the diet.

The Panel notes that the calcium content of total diet replacements for weight control is dependent on the protein source, with higher contents when milk proteins are used, reaching up to 1 900 mg/day (Vazquez et al., 1995). The Panel also notes that an increased urinary calcium loss related to a high-protein diet (0.5 mg for each gram of dietary protein, when intake is > 47 g/day (Walker and Linkswiler, 1972; Whiting et al., 1998) is quantitatively of little importance.

The Panel considers that there is an increased risk of loss of calcium, and potentially BMC, after the initiation of ketoacidosis by a low-carbohydrate, energy-restricted diet. It is not clear if this can be avoided by adjustment of calcium and vitamin D intake.

The Panel notes that available data do not give rise to concerns with respect to calcium loss and bone health in adults when VLCDs are used for a single short period of time (up to eight weeks). The consequences of the increased calcium loss in urine on bone health may be of concern when VLCDs are used repeatedly or over prolonged periods of time without medical supervision.

The Panel considers that total diet replacements for weight control should provide calcium corresponding to the PRI for adults. Therefore, the Panel proposes that total diet replacements for weight control should provide at least 950 mg calcium per day.

6.7. Phosphorus

The SCF (1993) suggested that phosphorus intakes should relate on a molar basis to those of calcium and set a PRI of 500 mg/day for women and 550 mg/day for men of all adult age groups. More recent reference values for phosphorus from other authoritative bodies for both adult men and women are in the range of 600-1 000 mg/day (i.e. 600 mg/day (Nordic Council of Ministers, 2014), 700 mg/day (IoM, 1997; D-A-CH, 2013), 750-800 mg/day (Afssa, 2001) and 1 000 mg/day (NHMRC, 2006)).

No UL for phosphorus could be derived by the Panel owing to insufficient data (EFSA, 2005a), but the Panel considered that normal healthy individuals can tolerate phosphorus intakes up to at least 3 000 mg/day without adverse systemic effects.

Very limited data are available on the effects of total diet replacements for weight control on phosphorus metabolism. The study by DeHaven et al. (1980), described above, did not find any differences in phosphorus balance between diet periods (total phosphorus intake not reported, but was similar in both diets) in which 100 % protein, and 50 % protein and 50 % carbohydrates were consumed, although cumulative phosphorus balance was negative during both diet periods (-4.5 ± 1.5 g vs. -3.9 ± 0.8 g over 21 days).

The Panel considers that total diet replacements for weight control should provide phosphorus in equimolar amounts to calcium, as proposed by the SCF (1993), and thus proposes that total diet replacements for weight control should provide at least 730 mg phosphorus per day (734 mg/day rounded down).

6.8. Magnesium

The SCF (1993) did not set a PRI for magnesium, but concluded on an acceptable range of intake of 150-500 mg/day based on observed magnesium intakes in the USA and the UK, as it considered that results from balance studies were difficult to interpret owing to methodological considerations. More recent reference values for magnesium from other authoritative bodies for adult women are in the range of 220-360 mg/day (i.e. 220 mg/day (WHO/FAO, 2004), 280 mg/day (Nordic Council of Ministers, 2014), 300-310 mg/day (D-A-CH, 2013), 310-320 mg/day (IoM, 1997; NHMRC, 2006) and 360 mg/day (Afssa, 2001)). For adult men, reference values range from 260-420 mg/day (i.e. 260 mg/day (WHO/FAO, 2004), 350 mg/day (Nordic Council of Ministers, 2014), 350-400 mg/day (D-A-CH, 2013), 400-420 mg/day (IoM, 1997; NHMRC, 2006) and 420 mg/day (Afssa, 2001)).

Magnesium naturally present in food has not been shown to have any adverse effects. Easily dissociable magnesium salts, however, exert dose-dependent laxative effects. The UL for magnesium for readily dissociable magnesium salts of 250 mg/day was based on studies in which daily supplemental magnesium doses of up to 250 mg were tolerated without adverse effects (SCF, 2001b).

Very limited data are available on the effect of total diet replacements for weight control on magnesium metabolism. The study by DeHaven et al. (1980), described above, did not find any differences in magnesium balance between diet periods (magnesium intake: 81 mg/day) in which 100 % protein, and 50 % protein and 50 % carbohydrates were consumed, although cumulative magnesium balance was negative during both diet periods (-340 ± 85 mg vs. -170 ± 61 mg over 21 days).

The Panel considers that the minimum content of magnesium in total diet replacements for weight control should be within the acceptable range of intakes for adults proposed by the SCF in 1993 of (150-500 mg/day). However, as most of the magnesium in total diet replacements for weight control would be easily dissociable magnesium salts, the UL of 250 mg/day applies. Therefore, the Panel

proposes that total diet replacements for weight control should provide magnesium in the range of 150 to 250 mg/day.

6.9. Sodium and chloride

The SCF (1993) did not set a PRI for sodium but an acceptable range of intake of 575-3 500 mg/day. The lower bound was derived based on sodium intakes which would allow the maintenance of sodium balance when also considering changes in physical activity and climate. The SCF (1993) also did not derive a PRI for chloride but indicated that chloride intakes should match with the acceptable range of intake of sodium. More recent reference values for sodium from other authoritative bodies for both adult men and women are in the range of 460-1 500 mg/day (i.e. 460-920 mg/day (NHMRC, 2006), 550 mg/day (D-A-CH, 2013) and 1 500 mg/day (IoM, 2005b)). More recent reference values for chloride from other authoritative bodies for both men and women are in the range of 830-2 300 mg/day (i.e. 830 mg/day (D-A-CH, 2013) and 2 300 mg/day (IoM, 2005b)).

Available data were insufficient for the Panel to establish a UL for sodium or chloride (EFSA, 2005d, 2005c).

Only limited data are available on the effect of total diet replacements for weight control on sodium and chloride metabolism. In a small study carried out within a metabolic ward, moderate energy restriction (3 556 to 5 858 kJ/day or 850 to 1 400 kcal/day) with similar intake of protein and either high or low in carbohydrates (70 vs. 10 weight%) did not lead to a significant increase in 24-hour urinary sodium excretion (Lewis et al., 1977). The study by DeHaven et al. (1980), described above, showed significant differences in sodium balance between diet periods (sodium intake: 1.2 g/day) in which 100 % protein, and 50 % protein and 50 % carbohydrates were consumed. Cumulative sodium balance was -8.8 ±2.7 g in 21 days during the 100 % protein diet and -0.57 ± 2.4 g during the 50 % protein and 50 % carbohydrate period ($p < 0.02$). The higher loss of sodium during the protein-only diet period might have contributed to a greater maximal orthostatic decrease in systolic blood pressure with the protein diet (-28 ± 3 mmHg) than with the mixed diet (-18 ± 3 mmHg, $p < 0.02$) and the higher incidence of symptoms of orthostatic hypotension observed during the protein-only diet. The Panel notes that the sodium intake in this study was low (3.1 g of salt) and that the pathophysiology of the increased sodium losses during the protein only diet is unclear. The Panel considers that protein-only diets may give rise to a concern with respect to sodium metabolism.

The Panel considers that total diet replacements for weight control should provide sodium and chloride corresponding to the acceptable range of intake for adults. Based on the recommendations by the SCF (1993), the Panel proposes that total diet replacements for weight control should provide at least 575 mg sodium and 830 mg chloride per day.

6.10. Potassium

The SCF (1993) derived a PRI for potassium for both men and women of 3 100 mg/day using evidence from studies which investigated the relationship between potassium intake and blood pressure. More recent reference values for potassium from other authoritative bodies for adult men are in the range of 2 000-4 700 mg/day (i.e. 2 000 mg/day (D-A-CH, 2013), 3 500 mg/day (WHO/FAO, 2004; Nordic Council of Ministers, 2014), 3 800 mg/day (NHMRC, 2006) and 4 700 mg/day (IoM, 2005b)). Lower reference values for adult women were recommended by the Nordic Council of Ministers (2014) (i.e. 3 100 mg/day) and in the recommendations of Australia and New Zealand (NHMRC, 2006) (i.e. 2 800 mg/day).

A UL for potassium could not be derived by the Panel owing to insufficient data (EFSA, 2005b).

The limited information available on potassium in total diet replacements for weight control indicates that energy-restricted diets are not associated with decreases in plasma potassium concentrations (Wing et al., 1995). However, they can be associated with significant decreases of total body potassium (around 10-20 %) irrespective of the energy content of the VLCDs studied (Archibald et al.,

1983; Davies et al., 1989; Krotkiewski et al., 2000), which probably result from reductions in body cell mass and glycogen stores (Patrick, 1977).

The Panel considers that total diet replacements for weight control should provide potassium corresponding to the reference values for adults. Based on the PRI established by the SCF (1993), the Panel proposes that total diet replacements for weight control should provide at least 3.1 g potassium per day.

6.11. Iron

The SCF (1993) derived a PRI for iron for adult men of 9 mg/day and for adult women of 16 mg/day at the 90th percentile (P90), and 20 mg/day at the P95 assuming a bioavailability of 15 % based on a factorial approach. The decision to provide a separate value for women at the P90 originated from the consideration that a PRI based on the P95 would be unrealistically high for the majority of women. More recent reference values for iron from other authoritative bodies for adult men are in the range of 8-10 mg/day (i.e. 8 mg/day (IoM, 2001; NHMRC, 2006), 9.0-9.1 mg/day (Afssa, 2001; WHO/FAO, 2004; Nordic Council of Ministers, 2014) and 10 mg/day (D-A-CH, 2013)). For pre-menopausal adult women these values range from 15 to 19.6 mg/day (i.e. 15 mg/day (D-A-CH, 2013; Nordic Council of Ministers, 2014), 16 mg/day (Afssa, 2001), 18 mg/day (IoM, 2001; NHMRC, 2006) and 19.6 mg/day (WHO/FAO, 2004)). For post-menopausal women reference values are generally lower (7.5-10 mg/day) (SCF, 1993; IoM, 2001; WHO/FAO, 2004; NHMRC, 2006; D-A-CH, 2013; Nordic Council of Ministers, 2014).

The Panel considers that basing the minimum iron content of total diet replacements for weight control on the PRI for women (i.e. 20 mg/day) following the general principles which had a priori been established by the Panel may not be justified in the case of iron owing to the uncertainties related to what could constitute the lowest dose of supplemental or fortification iron not associated with any untoward gastrointestinal effects when the food volume consumed is very low. Doses of around 50-60 mg of supplemental iron per day have been associated with nausea, vomiting, heartburn, epigastric discomfort, constipation and occasional diarrhoea (Nordic Council of Ministers, 2014), though data were insufficient to derive a UL (EFSA, 2004b). During consumption of total diet replacements for weight control luminal concentrations of iron may be higher than during habitual diets owing to the low food volume and the resulting low luminal content of the gut. This may render individuals consuming total diet replacements for weight control more prone to developing adverse gastrointestinal symptoms in response to high iron intakes, although this assumption has not been investigated in any of the clinical studies available.

Therefore, the Panel proposes to base the minimum iron content in total diet replacements for weight control on the PRI established by the SCF (1993) for adult men and covering postmenopausal women, i.e. 9 mg/day. The Panel notes that this amount may not cover the iron requirement of some pre-menopausal women with high menstrual blood losses but considers that this is acceptable over a restricted period of time and thus over very few menstruation cycles.

6.12. Zinc

In a previous opinion (EFSA NDA Panel, 2014f), the Panel derived a PRI for zinc for normal-weight adult men of 9.4 mg/day and for normal-weight adult women of 7.5 mg/day when a phytate intake of 300 mg/day is assumed. The PRI was based on saturation response modelling to estimate physiological requirements.

The UL for zinc has been set by the SCF (2002e) at 25 mg/day.

The Panel notes that zinc metabolism during the consumption of total diet replacements for weight control has not been investigated.

As total diet replacements for weight control are assumed to contain little phytates, the Panel considers that total diet replacements for weight control should provide zinc corresponding to the PRI for adult men consuming small amounts of phytates. Therefore, the Panel proposes that total diet replacements for weight control should provide at least 9.4 mg zinc per day.

6.13. Copper

The SCF (1993) set a PRI for copper for both adult men and women of 1.1 mg/day based on the maintenance of copper status. More recent reference values for copper from other authoritative bodies for adult men are in the range of 0.9-2.0 mg/day (i.e. 0.9 mg/day (IoM, 2001; Nordic Council of Ministers, 2014), 1-1.5 mg/day (D-A-CH, 2013), 1.7 mg/day (NHMRC, 2006) and 2.0 mg/day (Afssa, 2001)). For adult women, Afssa (2001) and NHMRC (2006) derived separate reference values set at 1.5 mg/day and 1.2 mg/day, respectively.

A UL for copper of 5 mg/day has been derived (SCF, 2003b) based on the absence of adverse effects on liver function at a dose of 10 mg/day, which was taken as the No Observed Adverse Effect Level (NOAEL).

The Panel notes that copper metabolism during the consumption of total diet replacements for weight control has not been investigated.

The Panel considers that total diet replacements for weight control should provide copper corresponding to the reference values for adults. Based on the PRI established by the SCF (1993), the Panel proposes that total diet replacements for weight control should provide at least 1.1 mg copper per day.

6.14. Selenium

The Panel has proposed an AI for selenium for adults of 70 µg/day (EFSA NDA Panel, 2014e) based on the levelling off of plasma selenoprotein P (SEPP1) concentrations.

The UL for selenium for adults has been set at 300 µg/day. The UL was based on the absence of clinical selenosis at selenium intakes of 850 µg/day which was taken as the NOAEL (SCF, 2000e).

The Panel notes that selenium metabolism during the consumption of total diet replacements for weight control has not been investigated.

The Panel considers that total diet replacements for weight control should provide selenium corresponding to the AI for adults. Therefore, the Panel proposes that total diet replacements for weight control should provide at least 70 µg selenium per day.

6.15. Iodine

The Panel has proposed an AI for iodine for adults of 150 µg/day (EFSA NDA Panel, 2014d). The AI was derived assuming that a urinary iodine concentration of ≥ 100 µg/L is associated with the lowest goitre prevalence and thus indicates sufficient iodine intake both in children and adults, and taking into account urinary volume and an absorption efficiency of 92 %.

A UL for iodine for adults was set at 600 µg/day on the basis of an elevation of serum TSH concentrations in response to iodine intakes, and an increased response of TSH concentrations to thyrotropin-releasing hormone stimulation (SCF, 2002a).

The Panel notes that iodine metabolism during the consumption of total diet replacements for weight control has not been investigated.

The Panel considers that total diet replacements for weight control should provide iodine corresponding to the AI for adults. Therefore, the Panel proposes that total diet replacements for weight control should provide at least 150 µg iodine per day.

6.16. Chromium

In a previous opinion, the Panel concluded that no AR and no PRI for chromium for the performance of physiological functions can be defined (EFSA NDA Panel, 2014c). The Panel also considered that there is no evidence of beneficial effects associated with chromium intake in healthy subjects and that the setting of an AI for chromium was also not appropriate.

Owing to limited data, the SCF (2003d) was unable to set a UL.

Because of the unproven essentiality of chromium together with the fact that no specific physiological function can be ascribed to chromium, the Panel considers that the addition of chromium to total diet replacements for weight control is not necessary.

6.17. Molybdenum

The Panel has set an AI for molybdenum for adults of 65 µg/day, which was based on molybdenum intakes from mixed diets in Europe (EFSA NDA Panel, 2013b).

Adverse effects of molybdenum on reproduction in rats have been used to set the UL for molybdenum for adults of 600 µg/day (SCF, 2000d).

The Panel notes that molybdenum metabolism during the consumption of total diet replacements for weight control has not been investigated.

The Panel considers that total diet replacements for weight control should provide molybdenum corresponding to the AI for adults. Therefore, the Panel proposes that total diet replacements for weight control should provide at least 65 µg molybdenum per day.

6.18. Manganese

The Panel has set an AI for manganese for adults of 3 mg/day, which was based on manganese intakes in adults in the EU and evidence that null or positive manganese balances have consistently been observed with manganese intakes above 2.5 mg/day (EFSA NDA Panel, 2013a).

Owing to the limitations in available data from humans and the non-availability of a NOAEL from animal studies, a UL for manganese could not be set (SCF, 2000g).

The Panel notes that manganese metabolism during the consumption of total diet replacements for weight control has not been investigated.

The Panel considers that total diet replacements for weight control should provide manganese corresponding to the AI for adults. Therefore, the Panel proposes that total diet replacements for weight control should provide at least 3 mg manganese per day.

6.19. Vitamin A

In a recent draft opinion on DRVs for vitamin A released for public consultation (EFSA NDA Panel, 2014b), the Panel has proposed a PRI of 700 µg retinol equivalents (RE)/day for adult men and 600 µg RE/day for adult women, based on a target value for liver concentration of 20 µg retinol per gram of liver tissue.

In tissues, blood, milk and food, vitamin A contents are conventionally expressed as RE, with 1 RE equal to 1 µg all-*trans*-retinol. The Panel uses conversion factors proposed by the SCF (1993) for the

European populations, namely 1 µg RE equals 1 µg of all-*trans*-retinol, 6 µg of all-*trans*-β-carotene, and 12 µg of other carotenoids with provitamin A activity.

The UL for women of childbearing age and men was set at 3 000 µg RE/day based on the lowest dose shown to be teratogenic. Even though an increased risk of bone fractures was reported at lower intakes, available data were not sufficient to establish causality and to derive a UL (SCF, 2002d).

The Panel notes that vitamin A metabolism during the consumption of total diet replacements for weight control has not been investigated.

The Panel considers that total diet replacements for weight control should provide vitamin A corresponding to the PRI for adult men. Therefore, the Panel proposes that total diet replacements for weight control should provide vitamin A in amounts of at least 700 µg RE per day.

6.20. Vitamin D

The SCF (1993) derived a PRI for vitamin D for adults up to 64 years of age of 0-10 µg/day and for adults ≥ 65 years of 10 µg/day based on the intake needed to maintain serum 25OH vitamin D concentrations in the range of 25-100 nmol/L. Dietary vitamin D intakes were not considered to be essential for healthy adults with adequate calcium and phosphorus intakes, unless confined indoors. More recent reference values for vitamin D from other authoritative bodies for adults up to around 50-74 years of age ranged from 5 to 20 µg/day (i.e. 5 µg/day (Afssa, 2001; WHO/FAO, 2004; NHMRC, 2006), 10 µg/day (Gezondheidsraad, 2012; Nordic Council of Ministers, 2014), 15 µg/day (IoM, 2011) and 20 µg/day (D-A-CH, 2013)). For older adults, reference values ranged from 10-20 µg/day (i.e. 10-15 µg/day (Afssa, 2001; WHO/FAO, 2004) and 20 µg/day (IoM, 2011; Nordic Council of Ministers, 2014)).

A UL for vitamin D for adults was set at 100 µg/day based on the risk of hypercalciuria and hypercalcaemia (EFSA NDA Panel, 2012b).

The Panel notes that vitamin D metabolism during the consumption of total diet replacements for weight control has not been investigated.

The Panel considers that total diet replacements for weight control should provide vitamin D corresponding to the reference values for adults. Based on the upper bound of the PRI established by the SCF (1993), the Panel proposes that total diet replacements for weight control should provide at least 10 µg vitamin D per day.

6.21. Vitamin E

The SCF (1993) defined the vitamin E requirements for adults as 0.4 mg α-tocopherol equivalents (α-TE)/g PUFA. It considered that vitamin E intakes should be above 4 mg α-TE/day for adult men and 3 mg α-TE/day for adult women. Total α-TE are determined from α-, β-, γ-, and δ-tocopherols and was traditionally used as the measure of vitamin E activity. Currently only α-tocopherol is recognised as contributing to vitamin E activity, because the other naturally occurring tocopherols are not converted to α-tocopherol in humans.

More recent reference values for vitamin E from other authoritative bodies for adult men range from 10 to 15 mg α-tocopherol (equivalents)/day (i.e. 10 mg/day (WHO/FAO, 2004; NHMRC, 2006; Nordic Council of Ministers, 2014), 12 mg/day (Afssa, 2001) and 15 mg/day (IoM, 2000; D-A-CH, 2013)). For adult women, reference values were set in the range of 7-15 mg α-tocopherol (equivalents)/day (i.e. 7 mg/day (NHMRC, 2006), 7.5 mg/day (WHO/FAO, 2004), 8 mg/day (Nordic Council of Ministers, 2014), 12 mg/day (Afssa, 2001; D-A-CH, 2013) and 15 mg/day (IoM, 2000)).

A UL for vitamin E for adults of 300 mg/day was derived based on the effect of vitamin E on blood clotting (SCF, 2003c).

The Panel notes that vitamin E metabolism during the consumption of total diet replacements for weight control has not been investigated.

The Panel considers that total diet replacements for weight control should provide vitamin E corresponding to the reference values for adult men. Based on the lower bound of recommended vitamin E intakes for adult men from the most recent evaluations of scientific or authoritative bodies (based on the required vitamin E intake per gram PUFA and observed intakes), the Panel proposes that total diet replacements for weight control should provide at least 10 mg α-tocopherol per day.

6.22. Vitamin K

The SCF (1993) indicated that an intake of vitamin K of about 1 µg/kg body weight per day appeared adequate but decided not to make any recommendation. More recent reference values for vitamin K from other authoritative bodies for adult men range from 45 to 120 µg/day (i.e. 45 µg/day (Afssa, 2001), 65 µg/day (WHO/FAO, 2004), 70 µg/day (NHMRC, 2006; D-A-CH, 2013) and 120 µg/day (IoM, 2001)). For adult women, reference values were proposed in the range of 45-90 µg/day (i.e. 45 µg/day (Afssa, 2001), 60 µg/day (NHMRC, 2006; D-A-CH, 2013), 55 µg/day (WHO/FAO, 2004) and 90 µg/day (IoM, 2001)).

There were no appropriate data to set a UL for vitamin K (SCF, 2003a).

The Panel notes that vitamin K metabolism during the consumption of total diet replacements for weight control has not been investigated. In addition, there is still a lack of suitable biomarkers or clinical endpoints that can be used to determine vitamin K requirements among adults (Shearer et al., 2012).

The Panel considers that total diet replacements for weight control should provide vitamin K corresponding to the reference values for adult men. Based on the recommendations by the SCF (1993) and a reference body weight of 69 kg of a normal-weight male, the Panel proposes that total diet replacements for weight control should provide at least 70 µg vitamin K per day (69 µg/day rounded up). Even though the proposed value was derived from a reference body weight of a normal-weight adult, the Panel considers that the proposed amount will be sufficient to prevent deficiencies in overweight or obese subjects consuming total diet replacements for weight control for a restricted period of time.

6.23. Thiamin (vitamin B1)

The SCF (1993) set the PRI for thiamin at 100 µg/MJ, resulting in a total daily intake of 1.1 mg for adult men and 0.9 mg for adult women. The PRI was based on the maintenance of a normal erythrocyte transketolase activity coefficient. For diets with an energy content of less than 8 MJ (1 912 kcal) per day, a PRI of 0.8 mg/day was suggested irrespective of the energy intake. More recent reference values for thiamin from other authoritative bodies for adult men range from 1.1-1.4 mg/day (i.e. 1.1 mg/day (Gezondheidsraad, 2000), 1.2 mg/day (IoM, 1998; WHO/FAO, 2004), 1.3 mg/day (Afssa, 2001; D-A-CH, 2013) and 1.4 mg/day (Nordic Council of Ministers, 2014)). For adult women, all bodies except D-A-CH (2013) proposed a reference value of 1.1 mg/day, while D-A-CH (2013) set a value of 1.0 mg/day. The Nordic Council of Ministers (2014) also recommended that when planning diets with energy levels below 8 MJ (1 912 kcal) per day, the thiamin content of these diets should be at least 0.8 mg/day

Owing to the low toxicity and the lack of systematic dose–response studies no UL for thiamin could be derived (SCF, 2001a).

The Panel notes that thiamin metabolism during the consumption of total diet replacements for weight control has not been investigated.

The Panel considers that total diet replacements for weight control should provide thiamin corresponding to the minimum thiamin intakes during energy-restricted diets as established by the SCF (1993). Therefore, the Panel proposes that total diet replacements for weight control should provide at least 0.8 mg thiamin per day.

6.24. Riboflavin (vitamin B2)

The SCF (1993) set the PRI for riboflavin at 1.6 mg/day for adult men and 1.3 mg/day for adult women based on studies reporting on riboflavin deficiency and data on urinary riboflavin excretion. More recent reference values for riboflavin from other authoritative bodies for adult men up to 65-75 years of age range from 1.3 to 1.6 mg/day (i.e. 1.3 mg/day (IoM, 1998; WHO/FAO, 2004; NHMRC, 2006), 1.4 mg/day (D-A-CH, 2013), 1.5 mg/day (Gezondheidsraad, 2000; Nordic Council of Ministers, 2014) and 1.6 mg/day (Afssa, 2001)). For adult women up to 65-75 years of age, reference values were derived in the range of 1.1-1.5 mg/day (i.e. 1.1 mg/day (IoM, 1998; Gezondheidsraad, 2000; WHO/FAO, 2004; NHMRC, 2006), 1.2 mg/day (D-A-CH, 2013; Nordic Council of Ministers, 2014) and 1.5 mg/day (Afssa, 2001)). It was noted by D-A-CH (2013) and the Nordic Council of Ministers (2014) that, for planning diets with an energy intake below 8 MJ (1 912 kcal) per day, the riboflavin content should not be less than 1.2 mg/day.

Human studies have not shown riboflavin to be toxic when administered orally in high doses. A UL for riboflavin could not be derived (SCF, 2000c).

The Panel notes that riboflavin metabolism during the consumption of total diet replacements for weight control has not been investigated.

The Panel considers that total diet replacements for weight control should provide riboflavin corresponding to the reference values for adult men. Based on the PRI set by the SCF (1993), the Panel proposes that total diet replacements for weight control should provide at least 1.6 mg riboflavin per day.

6.25. Niacin

In a previous opinion (EFSA NDA Panel, 2014a), the Panel endorsed the PRI derived by the SCF (1993) which was based on data on urinary niacin metabolite excretion and proposed a PRI of 1.6 mg niacin equivalents (NE)/MJ. For moderately active 40-year-old normal-weight male and female adults, this translates into niacin intakes of 16.7 mg and 13.4 mg NE/day. Tryptophan can be converted to niacin. Approximately 60 mg of tryptophan yields 1 mg niacin and is considered to be equivalent to 1 mg NE. Inadequate iron, riboflavin or vitamin B6 status decreases the conversion of tryptophan to niacin.

The UL for nicotinic acid of 10 mg/day is based on flushing as an endpoint. The UL for nicotinamide of 900 mg/day was based on the NOAEL derived from studies in humans in which no significant adverse effects have been reported (SCF, 2002b).

The Panel notes that niacin metabolism during the consumption of total diet replacements for weight control has not been investigated.

The Panel considers that total diet replacements for weight control should provide niacin corresponding to the PRI for a moderately active 40-year-old adult male on an energy-adequate diet. Therefore, the Panel proposes that total diet replacements for weight control should provide niacin in amounts of at least 17 mg NE/day. This amount will safely cover requirements of overweight and obese adults on an energy-restricted diet.

6.26. Pantothenic acid

In a previous opinion (EFSA NDA Panel, 2014g), the Panel has set an AI for pantothenic acid for adults of 5 mg/day based on observed pantothenic acid intakes and the absence of signs of deficiency in the EU.

Owing to the lack of systematic oral dose–response studies and the low toxicity of pantothenic acid no UL could be derived (SCF, 2002c).

The Panel notes that pantothenic acid metabolism during the consumption of total diet replacements for weight control has not been investigated.

The Panel considers that total diet replacements for weight control should provide pantothenic acid corresponding to the AI for adults. Therefore, the Panel proposes that total diet replacements for weight control should provide at least 5 mg pantothenic acid per day.

6.27. Vitamin B6

The SCF (1993) established a PRI for vitamin B6 for adults of 15 µg/g dietary protein, translating into a PRI of 1.5 mg/day for adult men and 1.1 mg/day for adult women. The PRI was based on data on changes in tryptophan and methionine metabolism and on the decline in blood concentrations of vitamin B6 during depletion–repletion studies. More recent reference values for vitamin B6 from other authoritative bodies for younger adult men (up to 50–64 years of age) range from 1.3 to 1.8 mg/day (i.e. 1.3 mg/day (IoM, 1998; WHO/FAO, 2004; NHMRC, 2006), 1.5 mg/day (Gezondheidsraad, 2000, 2003), 1.6 mg/day (Nordic Council of Ministers, 2014) and 1.8 mg/day (Afssa, 2001)). For younger women, reference values were set in the range of 1.2-1.5 mg/day (i.e. 1.2 mg/day (D-A-CH, 2013), 1.3 mg/day (IoM, 1998; WHO/FAO, 2004; NHMRC, 2006; Nordic Council of Ministers, 2014) and 1.5 mg/day (Afssa, 2001; Gezondheidsraad, 2003)).

The UL for vitamin B6 for adults has been set at 25 mg/day (SCF, 2000b).

The Panel notes that vitamin B6 metabolism during the consumption of total diet replacements for weight control has not been investigated.

The Panel considers that total diet replacements for weight control should provide vitamin B6 corresponding to the reference values for adult men. Based on the PRI derived by the SCF (1993) on a microgram per gram of protein basis and taking the proposed maximum protein content in total diet replacement for weight control (i.e. 105 g/day) as reference point, the Panel proposes that total diet replacements for weight control should provide at least 1.6 mg vitamin B6 per day.

6.28. Biotin

In a previous opinion (EFSA NDA Panel, 2014j), the Panel has set an AI for biotin for adults of 40 µg/day based on observed biotin intakes and the absence of signs of deficiency in the EU.

Owing to the lack of systematic studies on adverse effects of excess biotin intakes in healthy humans, the SCF (2001c) could not derive a UL for biotin.

The Panel notes that biotin metabolism during the consumption of total diet replacements for weight control has not been investigated.

The Panel considers that total diet replacements for weight control should provide biotin corresponding to the AI for adults. Therefore, the Panel proposes that total diet replacements for weight control should provide at least 40 µg biotin per day.

6.29. Folate

In a previous opinion (EFSA NDA Panel, 2014i), the Panel proposed a PRI for folate for adults of 330 µg dietary folate equivalents (DFE) per day. As there is evidence that natural food folates have a lower bioavailability than folic acid, DFE have been introduced in order to account for these differences and were defined as 1 µg DFE = 1 µg food folate = 0.6 µg folic acid from fortified food or as a supplement consumed with food = 0.5 µg of a folic acid supplement taken on an empty stomach.

The UL for (synthetic) folic acid for adults was set at 1 mg/day as it was considered that it is unlikely such a dose would mask the haematological signs of cobalamin deficiency (SCF, 2000a).

The Panel notes that folate metabolism during the consumption of total diet replacements for weight control has not been investigated.

The Panel considers that total diet replacements for weight control should provide folate corresponding to the PRI for adults. Therefore, the Panel proposes that total diet replacements for weight control should provide folate in amounts of at least 330 µg DFE per day.

6.30. Cobalamin (vitamin B12)

The SCF (1993) derived a PRI for cobalamin for adults of 1.4 µg/day based on studies on vitamin turnover and on biochemical deficiencies. More recent reference values for cobalamin from other authoritative bodies for adults range from 2.0-3.0 µg/day (i.e. 2.0 µg/day (Nordic Council of Ministers, 2014), 2.4 µg/day (IoM, 1998; Afssa, 2001; WHO/FAO, 2004; NHMRC, 2006) and 3.0 µg/day (D-A-CH, 2013)).

In the absence of any clearly defined adverse effects, no UL could be derived for cobalamin (SCF, 2000f).

The Panel notes that cobalamin metabolism during the consumption of total diet replacements for weight control has not been investigated.

The Panel considers that total diet replacements for weight control should provide cobalamin corresponding to the reference values for adults. Based on the upper bound of recommended cobalamin intakes in adults from the most recent evaluations of scientific or authoritative bodies (based on the amount of cobalamin needed to maintain plasma concentrations of cobalamin and haematological parameters within the normal range), the Panel proposes that total diet replacements for weight control should provide at least 3 µg cobalamin per day.

6.31. Vitamin C

In a previous opinion (EFSA NDA Panel, 2013d), the Panel has set a PRI for vitamin C for adult men of 110 mg/day and for adult women of 95 mg/day. This was based on the quantity of vitamin C that balances metabolic vitamin C losses and allows the maintenance of an adequate body pool.

There were insufficient data to establish a UL for vitamin C (EFSA, 2004a).

Caloric restriction was shown to reduce the rate of mitochondrial reactive oxygen species production and the rate of oxidative attack to biological macromolecules such as mitochondrial deoxyribonucleic acid (DNA) in rodents (Kim et al., 1996; Ikeno et al., 1997; Masoro, 1998; Lindsay, 1999; Lal et al., 2001; López-Torres et al., 2002). The use of total diet replacements for weight control in obese subjects resulted in a decline in oxidative stress markers, especially in patients with metabolic syndrome (Tzotzas et al., 2008; Tumova et al., 2013). As a consequence, it can be expected that caloric restriction does not increase vitamin C metabolic losses and requirement.

The Panel considers that total diet replacements for weight control should provide vitamin C corresponding to the PRI for adult men. Therefore, the Panel proposes that total diet replacements for weight control should provide at least 110 mg vitamin C per day.

6.32. Choline

The SCF (1993) has not considered choline when deriving an AI or PRI, or a UL. Among the other authoritative bodies only IoM (1998) and NHMRC (2006) suggested an AI for choline. The AI was set by both bodies at 550 mg/day for adult men and at 425 mg/day for adult women. This AI was based on data on the prevention of liver damage as assessed by measuring alanine aminotransferase concentrations.

A UL for choline for adults of 3.5 g/day was derived on the basis of the effects of choline on hypotension and fishy body odour as endpoints (IoM, 1998).

Most studies reporting on the effects of total diet replacements for weight control do not mention if and how much choline was provided by the diets. Taking into account that the choline content of both diets varies according to the protein source and also depends on the fat source (vegetable oil without choline vs. animal derived fats potentially containing variable amounts of phospholipids, i.e. choline), and that dietary choline deficiency over prolonged periods of time may lead to liver and muscle damage, the Panel considers that choline should be supplied by total diet replacements for weight control in amounts corresponding to the AI derived by IoM (1998) and NHMRC (2006) for adults. Therefore, the Panel proposes that total diet replacements for weight control should provide at least 550 mg choline per day.

7. Conditions and possible restrictions of use

Available data do not support a precise cut-off between VLCDs and LCDs. Therefore, the Panel proposes a single minimum energy content for all total diet replacements for weight control of 2 510 kJ (600 kcal) per day.

From a regulatory point of view, VLCDs have been defined as formulated foods which provide between 1 880 kJ (450 kcal) and 3 350 kJ (800 kcal) per day in Codex-Stan 203-1995. LCDs defined by Directive 96/8/EC and Codex-Stan 181-1991 should provide between 3 350 kJ (800 kcal) and 5 020 kJ (1 200 kcal) per day. Directive 96/8/EC also stipulates, based on the advice by the SCF (1990), that the labelling of LCDs should inform consumers that LCDs should not be used for more than three weeks without medical supervision.

Available European clinical guidelines for the management of overweight and obesity in adults (Tsigos et al., 2008), state that "the use of VLCDs may form part of a comprehensive programme undertaken by an obesity specialist or other physician trained in nutrition and dietetics; however their administration should be limited for specific patients and for short periods of time; VLCDs are unsuitable as a sole source of nutrition for infants and children, adolescents, pregnant or lactating women and the elderly".

The Panel emphasises that the compositional advice given in the present opinion solely applies to total diet replacements for weight control which are to be used by otherwise healthy overweight or obese adults with the intention of weight loss. They are not intended for use in normal-weight adults, infants, children, adolescents, pregnant or lactating women and the elderly. They may also not be appropriate for overweight or obese populations with one or more medical conditions, such as, but not limited to, diabetes, gout, thyroid disease, kidney disease, liver disease, cardiovascular disease and gallstones. The appropriateness of the use of total diet replacements for weight control by individuals other than overweight or obese adults, such as obese adolescents or obese pregnant women, or by individuals with a medical condition, should be established on a case-by-case basis by a physician and may require continued medical and dietetic supervision.

The Panel notes that there is no scientific evidence which supports the current provisions that labelling of LCDs should inform consumers that LCDs should not be used for more than three weeks without medical supervision. However, none of the studies which investigated adverse metabolic consequences of total diet replacements had a duration of more than three months. In particular, studies which investigated critical endpoints, such as the effect of total diet replacements for weight control on calcium loss and bone health, have not been conducted for periods longer than eight weeks. While the available evidence does not raise any concern with respect to bone health in adults when total diet replacements for weight control are consumed for a single period of up to eight weeks, there are no data on the impact of the increased calcium losses on bone health when these products are used over prolonged periods of time or repeatedly for short periods. In addition, the compositional advice given by the Panel is based on the assumption that total diet replacements for weight control are used for a single short period of time and the nutrient content may not necessarily be appropriate when these products are consumed for prolonged or repeated short periods of time.

Finally, the Panel also notes the importance of an adequate fluid intake during energy restriction in line with the AIs for adult men and women, i.e. 2.5 L/day and 2.0 L/day, respectively (EFSA NDA Panel, 2010b). The reference value for total water intake includes water from drinking water, beverages of all kind and from food moisture.

CONCLUSIONS

The Panel proposes that total diet replacements for weight control should provide energy and nutrient at least in the following amounts:

	Unit	Amount
Energy	kJ/day	2 510
Energy	kcal/day	600
Protein	g/day	Min.: 75 Max.: 105
LA [(a)]	g/day	11
ALA [(b)]	g/day	1.4
Carbohydrates	g/day	30
Calcium	mg/day	950
Phosphorus	mg/day	730
Magnesium	mg/day	Min.: 150 Max.: 250
Sodium	mg/day	575
Chloride	mg/day	830
Potassium	g/day	3.1
Iron	mg/day	9
Zinc	mg/day	9.4
Copper	mg/day	1.1
Selenium	µg/day	70
Iodine	µg/day	150
Molybdenum	µg/day	65
Manganese	mg/day	3
Vitamin A	µg RE [(c)]/day	700
Vitamin D	µg/day	10
Vitamin E [(d)]	mg/day	10
Vitamin K	µg/day	70
Thiamin	mg/day	0.8
Riboflavin	mg/day	1.6
Niacin	mg NE [(e)]/day	17
Pantothenic acid	mg/day	5
Vitamin B6	mg/day	1.6
Biotin	µg/day	40
Folate	µg DFE [(f)]/day	330
Cobalamin	µg/day	3
Vitamin C	mg/day	110
Choline	mg/day	550

(a): linoleic acid.
(b): alpha-linolenic acid.
(c): retinol equivalents.
(d): Vitamin E activity of RRR α-tocopherol.
(e): niacin equivalents.
(f): dietary folate equivalents.

- The compositional advice given in the present opinion solely applies to total diet replacements for weight control which are to be used by otherwise healthy overweight or obese adults with the intention of weight loss. They are not intended for use in normal-weight adults, infants, children, adolescents, pregnant or lactating women and the elderly. They may also not be appropriate for overweight or obese populations with one or more medical conditions, such as, but not limited to diabetes, gout, thyroid diseases, kidney diseases, liver diseases, cardiovascular diseases and gallstones. The appropriateness of the use of total diet

replacements for weight control by individuals other than overweight or obese adults, such as obese adolescents or obese pregnant women, or by individuals with a medical condition, should be established on a case-by-case basis by a physician and may require continued medical and dietetic supervision.

- None of the studies which investigated adverse metabolic consequences of total diet replacements had a duration of more than three months. In particular, studies which investigated critical endpoints, such as the effect of total diet replacements for weight control on calcium loss and bone health, have not been conducted for periods longer than eight weeks. While the available evidence does not raise any concern with respect to bone health in adults when total diet replacements for weight control are consumed for a single period of up to eight weeks, there are no data on the impact of the increased calcium losses on bone health when these products are used over prolonged periods of time or repeatedly for short periods. In addition, the compositional advice given by the Panel is based on the assumption that total diet replacements for weight control are used for a single short period of time and the nutrient content may not necessarily be appropriate when these products are consumed for prolonged or repeated short periods of time.

- The importance of an adequate fluid intake during energy restriction in line with the AIs for adult men and women, i.e. 2.5 L/day and 2.0 L/day, respectively is noted. The reference value for total water intake includes water from drinking water, beverages of all kind and from food moisture.

DOCUMENTATION PROVIDED TO EFSA

Evidence report related to an extensive literature search and review as preparatory work for the evaluation of the essential composition of total diet replacement products for weight control provided by Pallas Health Research and Consultancy following a procurement procedure.

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GLOSSARY AND ABBREVIATIONS

3OHB	3-hydroxybutyrate
α-TE	α-tocopherol equivalents
AcAc	acetoacetate
Afssa	Agence française de sécurité sanitaire des aliments
AI	Adequate Intake
ALA	α-linolenic acid
AR	Average Requirement
BIA	bioelectrical impedance analysis
BMC	bone mineral content
BMI	body mass index
CoA	coenzyme A
D-A-CH	German-speaking countries (Germany, Austria and Switzerland)
DEXA	dual-energy X-ray absorptiometry
DFE	dietary folate equivalents
DHA	docosahexaenoic acid
DNA	deoxyribonucleic acid
DRV	Dietary Reference Value
E%	per cent of total energy
EFA	essential fatty acids
EPA	eicosapentaenoic acid
EU	European Union
FFM	fat-free mass
indispensable nutrients	Nutrients which cannot be synthesised by the human body in sufficient quantities to meet the physiological needs and which must be supplied by the diet
IQR	interquartile range
IoM	Institute of Medicine
LA	linoleic acid
LCD	low-calorie diet
NE	niacin equivalents
NHMRC	National Health and Medical Research Council of the Commonwealth
NOAEL	No Observed Adverse Effect Level
P	percentile
PD-CAAS	Protein Digestibility-Corrected Amino Acid Score
PRI	Population Reference Intake
PUFA	polyunsaturated fatty acid

RCT	randomised controlled trial
RE	retinol equivalents
REE	resting energy expenditure
SCF	Scientific Committee on Food
SD	standard deviation
SE	standard error
SEPP1	plasma selenoprotein P
T3	triiodothyronine
T4	thyroxine
TAG	triacylglycerol
TSH	thyroid-stimulating hormone
UL	Tolerable Upper Intake Level
USA	United States of America
VLCD	very low-calorie diet
WHO	World Health Organization