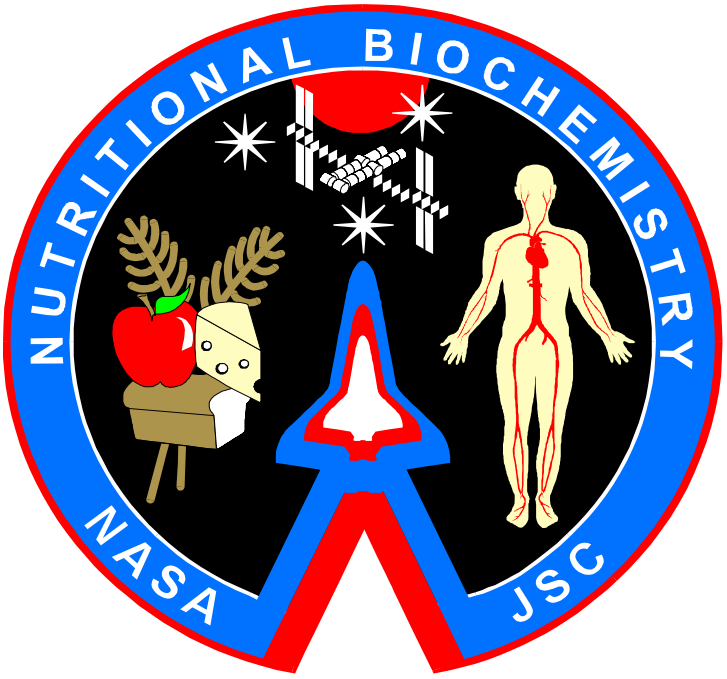
Nutrition Requirements, Standards, and Operating Bands for Exploration Missions



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Executive Summary

The challenge was brought forward in early 2005 to define the nutritional requirements for Exploration missions, and to define the relevant standards and associated operating bands related to nutrition. This document is the result of this charge. An extensive review of existing knowledge was conducted with participation of intramural and extramural experts, and the findings are summarized herein. In short, the approach taken was to define the nutrient intake requirements, that is, the amount of each nutrient expected to be available in the food system. The standards are defined as markers of nutritional status, with optimal (green), sub-optimal (yellow), and critical (red) levels for each. For many of the nutrient requirements, it is not known if they are altered during space flight. Furthermore, in many cases the intake of a nutrient may act as a countermeasure to one or more negative effects of space flight, but these potential countermeasures, too, are not well defined. Thus, we have also documented herein the areas where further research is required.

Accordingly, while this document is intended as a comprehensive summary of our knowledge to date, it is expected that this is the first edition of these requirements and standards. As we learn more about space-flight nutrition, and as relationships between disease and nutrients are further defined in Earth-based populations, this document, and the approach to nutrition in the space rogram, will need to be updated accordingly.

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Introduction

Nutrition has been critical to every phase of exploration, from the early sea voyages on which seafarers were plagued by scurvy to polar expeditions in which explorers died from under-nutrition, or in some cases nutrient toxicities. The role of nutrition in space exploration will be no different, except that space explorers will lack the opportunity to obtain food from the local environment, making their missions even more challenging than the exploration of Earth. The altered gravity environment will also likely alter nutrient requirements, making it even more difficult to meet these requirements. It is very clear that humans on a 1000-day exploration-class mission will require adequate nutrition, and deficiency of any one of the required nutrients could be catastrophic.

To serve as a tool for defining the role of nutrition in exploration is the purpose of this document. The ultimate goal is to define requirements for nutrient intake and standards for assessing nutritional status. To this end, we will define a set of values, or operating bands, that can serve as a guide for setting both required intake levels and nutritional status assessment standards. Use of these operating bands will help NASA to maintain the health and well-being of crew members who explore beyond the surface of Earth.

This document is based on many sources of information that were reviewed at a Nutrition Standards/Operating Bands workshop held March 23–24, 2005 in Houston, Texas. The documents reviewed included the set of nutritional requirements defined in 1991 for Space Station Freedom missions, plus the updated set of requirements developed in 1995 (in collaboration with Russian partners) for Mir flights. The activities of workshop participants included evaluation of the limited data from short-duration Space Shuttle flights, and longer Mir and International Space Station (ISS) flights. The findings from the MR016L/Clinical Nutritional Assessment profile of the first 10 ISS missions were also reviewed, to provide background information about the changes seen in flights of 4 to 6 months (during which time resupply by at least one Progress vehicle occurred). In many cases in this document, we have extrapolated from ground-based space analog studies, and in others we have only the ground-based nutrition literature for support, knowing nothing of the effects of space travel. In this document we also highlight the areas where we are at highest risk, with no evidence base to support the requirements and recommendations. For these areas, targeted research areas are identified as part of the requirement for exploration. The supporting and detailed information have been expanded herein, but the recommendations are based on the panel discussion.

Nutrition is a cross-cutting science, one that influences and is influenced by many other disciplines, and because nutrients are required for the structure and function of every cell and every system, the pervasiveness of nutrient requirements for the adaptation to space travel is no surprise. Key areas of clinical concern for long-duration space flight include loss of body mass (general inadequate food intake), bone and muscle loss, increased radiation exposure, and general depletion of body nutrient

stores because of inadequate food supply, inadequate food intake, increased metabolism, and/or irreversible loss of nutrients. Cardiovascular and/or immune system changes noted during and after space flight may also be related to nutritional issues, but conclusive data are not yet available.

The primary objectives of this document are

- Definition of requirements related to nutrition. This includes nutrient intake requirements as well as other aspects of nutrition.
- Definition of techniques that will be used to evaluate whether the requirement has been met (that is, the standards that must be met).
- For each standard, identification of the operating bands (including success/failure criteria for each) for potential mission impact and severe mission impact.
- Identification of potential differences in operational standards for different mission types (for example, low Earth orbit, lunar, Mars) and durations (6, 12, or 36 months)
- Identification of the effect of mission design elements (such as a traverse, extravehicular activity, or gravity field) on the standards
- Identification of potential differences due to age and sex
- Identification of areas where requirements, though defined, are not well understood or justified. Specific areas are highlighted to point out where research is necessary to better understand the requirement and associated risk.

Document Organization

Recommendations for nutritional status and nutrient intake for exploration must be based on an understanding of the known changes in nutritional status observed during space flight. This document is intended to provide a complete history and rationale for these requirements. Although this will make it more extensive than a typical requirements document, this added information will serve to justify the requirements, and to allow a better understanding of how we have come to the set of requirements described herein.

A section for each nutrient provides a review of that nutrient, and a discussion of the requirements for the nutrient is divided into the following sub-sections:

Physiological function and existing space flight knowledge
This section includes basic background material about the nutrient and its function in the body. It also includes a summary of known space flight and space flight analog studies.

Body stores (if any) **and relative time to depletion**
Background is provided for each nutrient that is stored in the body. Relative time to depletion may be given for a sub-optimal diet, a diet devoid of the nutrient, and special circumstances (such as faster depletion of vitamin C during stress, and depletion of vitamin D during low exposure to ultraviolet light).

Potential implications for flight
This section includes concerns that arise from characteristics of the unique flight environment (for example, potential deficiency caused by radiation exposure and destruction of vitamins in food, or risk that toxicity will result from supplementation).

Targeted research needed
Areas where lack of research limits the ability to characterize requirements are listed. The extramural expert panel recommended that these areas be the targets of further research.

Nominal requirement on Earth
Reference material is provided for each nutrient regarding requirements for it on Earth, and where appropriate, requirements of sub-populations (such as different ages and genders).

Historical space flight requirements
Reference material is provided for each nutrient regarding earlier defined space flight requirements, and the rationale for each.

Requirements, standards, and operating bands

This section consists of definition of the dietary intake requirement per day (average) for each nutrient, techniques for monitoring fulfillment of the requirements, and the sets of values (operating bands) for requirements as well as assessment techniques that will enable human space exploration. Monitoring of fulfillment typically includes a need to verify actual space food content at production, as well as at the planned point of use (because, for example, storage time and environment may affect content) before implementing the program. Fulfillment of intake requirements will be monitored in part by determining dietary intake during flight.

Standards are based on the results of assessment techniques or variables monitored, and serve to determine if requirements have been met. In general, fulfillment of requirements will be assessed before, during, and after flight by determining the levels of status indicators in biological samples.

Nominal operating bands are defined as follows: green/nominal = the nominal amount of intake of a nutrient needed to maintain crew health. Yellow/sub-optimal = the level of intake that, if maintained for prolonged periods, may lead to frank deficiency and disease. Red/deficient = the level that, over a longer period, will lead to symptoms and/or disease. Yellow/supra-optimal = the level of intake that, if maintained for prolonged periods, could lead to toxicity symptoms. Red/toxic = the level that, over a longer period, will lead to toxicity symptoms. These levels are illustrated below:

Dietary Nutrient

	toxic g/d	red
	supra-optimal g/d	yellow
	nominal g/d	green
	sub-optimal g/d	yellow
	deficient g/d	red

Additional sections are included at the end of the document to highlight special issues and concerns for exploration missions. Examples of these are nutritional concerns for extravehicular activity (EVA), and drug/nutrient interactions.

Macronutrients

Energy and Body Composition

Physiological function and existing space flight knowledge

The World Health Organization estimates of energy requirements for moderately active individuals (1) provide a good estimate of inflight requirements (2), and have thus been used as a standard for menu planning. Although composition of the diet (percent of energy intake from protein, carbohydrate, and fat) is acceptable during flight, food and energy intake during flight are generally lower than preflight intake (2-7), despite data indicating that inflight and preflight energy requirements are similar (2) or increased (6). Data from the Apollo program through the more recent flights show that crew member dietary intakes are about 70% of predicted requirements. The gap between energy intake and expenditure is further widened with increased exercise associated with physical countermeasures.

The obvious and immediate reason for concern about reduced dietary intake is the risk of body mass loss and dehydration. Body mass losses of 1%–5% of preflight body mass have been a consistent finding in the history of space flight, and documented losses have occurred on short- and long-duration flights from both the U.S. and Russian space programs (7-10). Indeed, all crew members on Gemini, Apollo, Skylab, and Apollo-Soyuz Test Project missions lost body mass (11). In one study of 13 male Shuttle crew members, body mass losses ranged from 0 to 3.9 kg (2). Body mass loss has also been observed to reach 10–15% of preflight body mass (12). Although a 1% body mass loss can be explained by loss of body water (3), most of the observed loss of body mass is accounted for by muscle and adipose tissue (13, 14). Crew members on the ISS have shown similar patterns of mass loss during and after flight, but some crew members have been able to maintain body mass (15). Results of metabolic experiments on the U.S. Skylab missions showed that ingestion of the prescribed energy intake did not fully ensure maintenance of body mass (16); however, it is clear that reduced energy intake will ensure loss of body mass. Decreased inflight energy intake is also associated with decreased protein synthesis (17).

Insufficient dietary intake, and subsequent body mass loss, is significant not only for crew health, but also for medical and research studies, in which clear interpretation of essentially all other physiological data from malnourished subjects is impossible. That is to say that virtually all space flight data collected on Shuttle, Mir, and ISS missions are confounded by inadequate dietary intake. Investigators who have studied bone and muscle, cardiovascular function, immune response, and other systems during space flight cannot say to what degree undernutrition affected their findings. A recent study in Germany evaluating hypocaloric diets during bed rest (18) will help to identify these issues with greater clarity.

The cause of reduced dietary intake during flight is unknown, but anecdotes provide many potential explanations (4, 7, 19). A common cause of reduced dietary intake during the first days of a mission (20) is space motion sickness (21). Its effects

typically pass after the first several days of flight, but the decreased dietary intake often extends well beyond the first week (4). Anecdotal reports of appetite vary significantly, as indicated in a Russian study in which 40% of Mir crew members reported decreased appetite, 40% reported no change, and 20% reported increased appetite (22). Other flight-related changes in gastrointestinal function may occur. Fluid shifts, in combination with reduced fluid intake, would tend to decrease gastrointestinal motility. Although gastrointestinal transit time has not been systematically studied in flight, during 10 days of −6° head-down bed rest, mouth-to-cecum transit time was significantly longer than during ambulatory control periods (23). Russian studies of gastrointestinal function during actual and simulated space flight, in humans and in animal models, have been reviewed (24).

The palatability of food in the space food system is occasionally identified as a cause of reduced food intake during flight. From the early days of the space program, development of foods for space flight has proven a significant challenge (10, 25-27), yet the design criteria have changed little since the early programs (28). The food systems used on the Space Shuttle and the Russian Mir Station are entirely shelf stable, and are mainly composed of rehydratable or thermostabilized food items (27). Although these foods are known to have lower hedonistic value (palatability) than fresh or frozen foods, ground-based studies have clearly shown that the Shuttle food system can adequately support nutritional requirements (29). Skylab is the only U.S. program to date that has included frozen foods (27). The Skylab crew members ate essentially 100% of their predicted (1) energy requirements (4). Although these crew members were involved in metabolic studies that required complete intake of the prescribed diet (30), this result shows that when astronauts are required to consume the recommended amounts of food during space flight, they can. Thus, hypotheses regarding inability to consume the requisite amount of food because of stomach fullness or other factors are not likely to fully explain decreased inflight dietary intake. It is difficult to determine if the intakes on Skylab were related more to the requirement to consume the food or to the fact that the food was more palatable; however, it would be difficult to argue that increased palatability is not beneficial.

Many anecdotal reports exist of changes in taste and aroma of food during flight (although many long-duration crew members indicate that this is not as significant a problem on long flights). One hypothesis that supports these anecdotes is that fluid shifts and congestion associated with microgravity (especially in the first few days) alter taste and odor perception. However, flight studies have not demonstrated changes in taste or olfaction (31, 32), and ground-based studies of this phenomenon have been equivocal. When tongue taste perception was measured before, during, and after a 30-day −6° head-down bed rest period, subjects reported decreased appetite and lack of taste early in the bed rest phase (33, 34). By day 13 of the bed rest phase, for all tastes (sweet, salt, acidic, bitter), the threshold for taste sensitivity had increased. In contrast, a more recent study found no changes in odor and taste perception after 14 days of head-down bed rest (35), suggesting that multiple factors are likely involved in this process.

It is imperative that adequate resources be provided to support food consumption. A reliable food system must include a variety of palatable foods and the means to process them (such as rehydration, heating, and cooling). Time (for meal preparation, consumption, and clean-up) is another limited resource that often hinders dietary intake.

Initial plans for the ISS included the use of freezers and refrigerators for food storage and preparation. This would have provided a more palatable food system, which would serve to increase dietary intake, as well as provide added psychological support. It is often difficult to balance the intangible potential increase in dietary intake and psychological support against a tangible dollar and power allocation, both of which are typically (if not always) constrained.

Altered energy expenditure is a commonly proposed explanation for loss of body mass. According to early hypotheses, energy expenditure during flight would be less than on the ground, because of the relative hypokinesia in space (19). Lower energy expenditure was observed during extravehicular activity on the lunar surface compared with similar activities at 1 g (36). However, studies of inflight, non-EVA energy expenditure of Space Shuttle crew members showed that inflight energy expenditure was unchanged from preflight levels (2). More recent studies have even shown increased energy expenditure during flight compared to preflight levels, most likely as a result of increased exercise (6). These studies involved Shuttle astronauts and indirect calorimetry techniques to determine total energy expenditure over several days. The doubly-labeled water (water enriched with deuterium and ^{18}O) technique was used to determine oxygen consumption (37). The benefits of this technique are that it is non-invasive and it takes into account the energy cost of all activities over several days. The drawback of the method is that information about the individual components of total energy expenditure (such as resting, sleep, exercise) is not available.

Although it is assumed that less energy is expended moving the body mass around the cabin during flight, energy requirements for other metabolic activities (such as maintaining resting metabolic rate and responding to stress) may increase, to result in an unchanged total energy expenditure. In ground-based studies, during bed rest total energy expenditure was less than before bed rest, but resting energy expenditure did not change (38). Because total energy expenditure during flight is either unchanged (2) from preflight levels or increased (6), bed rest may not be an appropriate model for studies of energy metabolism during flight. One possible explanation for this difference is the lack of a metabolic response to stress during bed rest. Attempts have been made to improve the utility of these ground studies through the administration of a metabolic stressor (such as triiodothyronine or cortisol) to provide a better ground-based model than bed rest for the metabolic effects of space flight on energy and fuel metabolism (39).

Body stores and relative time to depletion

Energy itself is not readily stored in the body, but the substrates for energy are. Energy in the form of heat is obtained by oxidizing carbohydrates, fats, proteins, and alcohol; it is also known as the heat of combustion. Fat provides the most energy of these sources, at about 9 kcal/gram. Carbohydrates and proteins provide about 4 kcal/gram, and alcohol about 7 kcal/gram. Because the body can adapt to different energy sources, large variations in macronutrient intake are generally well tolerated.

Adipose represents the only viable long-term source of stored energy. Carbohydrate stored in liver and muscle as glycogen provides a transient (hours) source of carbohydrate. Protein can be broken down to release amino acids, but this is at the expense of the protein.

Data exist from 2 studies in which subjects were semi-starved, consuming either 580 kcal/d or 1010 kcal/d for 12 and 24 days, respectively (40). In this study, subjects who consumed 580 kcal/d lost 7% of their body mass in 12 days and the subjects who consumed 1010 kcal/d lost 11% of their body mass in 24 days. In another study, starved subjects lost 9% of their body mass after 11 days, 15% by day 18, and 18% by day 43 (41). From these data, it appears that for every 500 kcal consumed per day, about 1% of body mass can be conserved every 12 days. It would not be acceptable, however, to use these numbers for a long-term (>21 days) prediction of body mass loss or conserved body mass loss because after 21 days of starvation the basal metabolic rate of the body decreases (40, 42). This can be and has been accounted for using a mathematical model to predict body mass loss given changes in basal metabolic rate (42), with results estimating that survival on 1000 kcal/day could exceed 3 years (compared with only 6 months without accounting for decreased metabolic rate).

It is difficult to predict the impact of sub-optimal (or lack of) energy intake in otherwise healthy individuals. One issue is that the energy equivalent of the mass lost changes with time, as different body fuels are used at different times during semi-starvation (40, 42). With partial rations available (1000 calories per day), it is reasonable to expect that a person could survive for more than 4 to 6 months, potentially longer if the metabolic rate were to decrease because of decreased intake. Greater restrictions in energy availability would be expected to yield survivability ranging between this amount of time and the 1–2 months possible with no food. These projections obviously include many assumptions, unknowns, and extrapolations. Data from 10 Irish Republican Army hunger strikers, who consumed water ad libitum but no energy, vitamins, or minerals, indicate that an average 25-year-old male could survive no longer than 60 days without energy (43, 44).

Potential implications for flight

On the basis of the small amount of starvation data available, it is speculated that a crew could survive on orbit for 40–60 days without food. With limited rations (1000 calories/d), a crew could survive 4 to 6 months (although physical performance capability might be severely degraded).

Deficiency of energy leads to wasting and ultimately tissue breakdown, or even death. An excess of energy may lead to excess body mass if metabolic rate does not increase. The loss of lean body mass during space flight is significant, and is associated with increased proteolysis and catabolism related to metabolic stress (45). In the high-stress environment of an on-orbit contingency, this would likely be exacerbated, and would shorten projections of survivability from ground-based studies.

Other possible effects of long-term low-calorie intake include decreased motor and cognitive function, both of which could impair an astronaut's ability to perform work-related tasks necessary for landing. According to military survival studies, astronauts would be expected to experience decreased endurance early on, and the decrease in strength would parallel the decrease in lean body mass (46). During total fasting, degradation of coordination, speed, and cognitive function would be evident within the first 2 weeks (46).

The ketosis expected to result from starvation not only would have metabolic effects (including decreased appetite), but might also affect other aspects of the mission (for example, the life support systems may not be able to remove the ketones from the air).

Anecdotal reports from long-duration crew members indicate that a rebound body mass gain occurs after flights on which on-orbit loss of body mass was significant. We are attempting to obtain long-term follow-up body mass data after missions to evaluate these changes. We will also test the hypothesis that metabolic rate decreases on orbit when dietary intake is insufficient, that is, a self-imposed "semi-starvation" state occurs. Compared to the nominal energy requirement of 2000–3000 kcal per day (it varies because of individual factors), this "semi-starvation" would reflect the requirement for approximately 1000 kcal per day of food availability.

Targeted research needed

Further research is warranted to better understand why astronauts typically do not consume 100% of their recommended daily energy intake. Decreased energy intake has numerous negative implications for the body, and is often associated with decreased intake of other nutrients.

Studies of energy expenditure have been conducted only on short-duration (Shuttle) flights (2, 6). Whether the same trends continue on longer flights is not known. Anecdotal reports exist of crew members who have lost significant amounts of body mass during flight and gained excessive amounts after landing. The health implications of this phenomenon need to be determined, and ways to prevent both inflight body mass loss and postflight body mass gain need to be evaluated.

Nominal requirement on Earth

The estimated energy requirement (EER) of an individual on Earth is based on total energy expenditure (TEE) using an activity factor of 1.25 (active) along with the individual's age, body mass (kg) and height (m) in the following calculations:

EER for men 19 y and older

EER = 622 – 9.53 x Age [y] + 1.25 x (15.9 x Wt [kg] + 539.6 x Ht [m])

EER for women 19 y and older

EER = 354 – 6.91 x Age [y] + 1.25 x (9.36 x Wt [kg] + 726 x Ht [m])

Historical space flight requirements

The daily energy requirements for male and female astronauts were defined in 1991 (47), and again in 1995 (48), and are as follows:

Missions of 30–120 days: Energy consumption should be sufficient to maintain body mass and body composition, with continuous monitoring during space flight. A 70-kg man exercising 1 to 2 hours per day is expected to require about 3,000 calories/day (47).

Missions up to 360 days: Intake of energy should be sufficient to maintain body mass and composition, and the extensive activities planned for International Space Station crew members. Energy requirements will be calculated for each individual by using the World Health Organization (1) equations:

Men	18–30 y:	1.7 (15.3M + 679) = calories/day required
	30–60 y:	1.7 (11.6M + 879) = calories/day required
Women	18–30 y:	1.6 (14.7M + 496) = calories/day required
	30–60 y:	1.6 (8.7M + 829) = calories/day required

where M = mass in kg

These equations are to be used for moderate levels of activity. The original space flight requirements included an additional 500 calories/d that would be supplied to the diet during the period when end-of-mission countermeasures (such as more intensive exercise) are being conducted.

On the basis of results from previous space missions, it was also recommended that an additional 500 calories/d be supplied to crew members on days of extravehicular activity (EVA); the extra energy should be similar in nutrient composition to the rest of the diet (48).

Requirements, standards, and operating bands

Req. 1. The estimated energy requirements (EER) for space missions shall be based on total energy expenditure (TEE), using an activity factor of 1.25 (active) along with the individual's age, body mass (kg), and height (m) in the following calculations:

EER for men 19 y and older

EER = 622 – 9.53 x Age [y] + 1.25 x (15.9 x Mass [kg] + 539.6 x Ht [m])

EER for women 19 y and older

EER = 354 – 6.91 x Age [y] + 1.25 x (9.36 x Mass [kg] + 726 x Ht [m])

Energy intake operating bands are defined as a percentage of each individual's EER, as follows:

Energy (% of requirement)

	120%	red
	110%	yellow
	90-100%	green
	80-90%	yellow
	<80%	red

Initial verification that this requirement has been met will be done by proximate analysis of the energy content of space food items, and analysis of crew menus.

Final verification will be completed by determining dietary intake using a food frequency questionnaire or other method of monitoring inflight intake. Standards will be assessed before and after flight (and to the extent possible, during flight) by determining body composition (currently done by dual-energy X-ray absorptiometry) before and after flight, and by determining body mass during flight.

Body Mass (% of preflight)

	>110%	red
	105-110%	yellow
	95-105%	green
	90-95%	yellow
	<90%	red

Body Composition (% of preflight)

	>110%	red
	105-110%	yellow
	95-105%	green
	90-95%	yellow
	<90%	red

Protein

Physiological function and existing space flight knowledge

As the major structural component of all cells in the body, protein includes molecules that perform many essential physiological functions. Amino acids are assembled in various configurations to make proteins that serve as enzymes, hormones, transport carriers, and other important molecules necessary for life. The total energy contribution of protein to the average diet is about 15%. The type of protein, such as animal or vegetable protein, incorporated into the diet may be an important factor to consider in determining protein requirements.

Exposure to microgravity reduces muscle mass, volume, and performance, especially in the legs, on both long (16) and short (49) flights. Muscle biopsy studies demonstrated postflight decreases in cross-sectional area only in type II (fast-twitch) myofibers, the muscle fiber type that responds to resistive exercise (50).

Potassium and nitrogen balances became increasingly negative throughout the Skylab flights, but urinary creatinine did not change (30, 51) despite losses of leg volume (16, 52). Disuse atrophy of muscle in space may be related to changes in whole-body protein turnover. One ground-based study demonstrated that whole-body protein synthesis decreased about 13% during 2 weeks of bed rest, and that half of that decrease could be accounted for by the leg muscles (53). This bed rest study did not include exercise, and body mass was maintained during the bed rest period. In the same study, excretion of 4-pyridoxic acid, a vitamin B_6 metabolite, increased during bed rest (54), suggesting that metabolically active muscle tissue was lost.

Stable isotope turnover studies indicate that during short-term space flight, whole-body protein turnover increases. Protein synthesis increases, but protein breakdown increases even more (55, 56). The increase in synthesis is hypothesized by Stein et al. (57), to be related to physiological stress, as indicated by increased urinary cortisol during flight (3, 58). These findings are similar to those found in catabolic patients. Decreased prostaglandin secretion has also been implicated in the loss of muscle tissue during space flight, secondary to decreased muscle mechanical stress (58).

On long-duration Mir flights, conversely, investigators have noted decreased rates of protein synthesis (6). Protein synthesis was, however, directly correlated with energy intake, suggesting that the reduced protein synthesis was related to inadequate energy intake (6).

Evaluation of plasma and urinary amino acids suggests that they do not provide a clear indication of muscle metabolism. However, an increase in plasma amino acids was noted in cosmonauts after flight (59). Limited Shuttle flight data indicate a tendency for plasma branched-chain amino acids to be increased during flight, compared to preflight levels (60). Data from short-duration flights reveal little or no change in urinary amino acid profiles (20). Skylab studies did reveal increases in excretion of

amino acid metabolites: creatinine, sarcosine, and 3-methylhistidine (61), suggesting that contractile proteins of skeletal muscle are degraded in weightlessness.

Differences between flight and ground studies may relate to a number of variables, identifying potential shortcomings of the analog studies. Dietary intake is one major difference between the two types of studies. On the Spacelab Life Sciences missions, inflight intakes of protein and energy were about 20% less than preflight intakes, and crew members lost about 1 to 1.5% of their body mass (55). Ground-based studies typically have prescribed and controlled dietary intakes or are designed to maintain body mass. Variability in stress levels might explain some of the variability in the results from this type of study, both flight and ground-based. An increase in stress level (as shown by increased cortisol) is typically associated with space-flight studies. Ground-based studies have the potential for increased stress; however, this is not an entirely consistent finding. Lovejoy et al. (1999) (39) have suggested that administration of exogenous thyroid hormone provides a metabolic stress that produces a more accurate ground-based model of space flight. Other groups have used exogenous cortisol as a means to increase muscle catabolism during bed rest (62).

The exercise protocols used to date have not succeeded in maintaining muscle mass or strength, or bone mass, during space flight. On Mir flights, crew members differed significantly with respect to inflight exercise frequency and intensity (related to mission requirements, personal habits, etc.). However, losses of leg muscle volume, detected immediately after flight by magnetic resonance imaging, were almost 20% in all subjects (63). Similar findings (wide variations in exercise, lack of difference in bone loss) have also been documented for bone loss (12). Exogenous testosterone administration during bed rest studies has maintained muscle mass and protein balance, but with no effect on muscle strength (64). Resistive exercise protocols have been proposed to aid in the maintenance of both muscle and bone during flight. Success with these protocols in flight analog studies (65) has yet to be documented in flight.

Body stores and relative time to depletion

Protein is a fundamental component of all cellular and biochemical systems. It is one of the most critical limiting factors when the body is deprived of energy, because essential amino acids are not stored in the body. A complete depletion of energy and protein reserves is said to be the cause of death from starvation. It is estimated that when 33%–50% of total body protein is lost, death results (66). Total body mass loss in excess of 40%–50% of initial body mass is not compatible with life (46, 67). In one case report, individuals on a hunger strike lost 30% of their total body mass and 19% of total body protein before death (43, 44). An adult whose body mass is initially normal can survive 60 to 70 days without consuming any food (68). Protein and energy reserves are much smaller in infants, and a 1000-g infant can survive only 5 days without protein (69).

Potential implications for flight

Maintaining a proper protein intake is critical, as both low-protein and high-protein diets can cause harm (and, at the extreme, death). A low-protein diet (below the recommended dietary allowance) for up to 4 weeks can decrease calcium absorption and induce hyperparathyroidism in otherwise healthy subjects (70, 71). The impact of chronic low protein intakes is not well understood; however, several studies suggest that low-protein diets are associated with loss of bone density (72, 73).

Conversely, high-protein diets increase the risk that renal stones will form. One 5-y study of 120 men found that the relative risk of stone formation on a restricted protein (52 g/d) and salt (50 mEq/d) diet was half that of men on a calcium-restricted diet (400 mg/d) (74). The decreased risk of renal stones on a low-protein diet is not well understood, but several potential mechanisms have been postulated. It is generally well accepted that high-protein diets induce hypercalciuria, and this can contribute to formation of calcium oxalate or calcium phosphate stones. One hypothesis to explain protein-induced hypercalciuria is related to the "acid-ash" hypothesis that excessive animal protein intake provides excess sulfur-containing amino acids that are metabolized to sulfuric acid. Since bone is a large reservoir of base, bone can be broken down to provide carbonate or phosphate to neutralize fixed acid loads. Furthermore, low urinary pH decreases urinary excretion of citrate, which is a potent inhibitor of stone formation. In addition, dietary animal protein represents a rich source of purines that may raise uric acid excretion, which could increase risk of forming uric acid stones (75).

Protein-induced hypercalciuria may also be detrimental to bone. Some studies show that high-protein diets increase calcium absorption (76), but this is currently not well accepted. Several studies show that animal protein increases acid load more than vegetable protein because of the higher sulfur content per serving of food. Vegetable protein itself does not necessarily have less sulfur per gram of protein, but a larger mass of foods containing vegetable protein would have to be consumed to get the same amount of protein as from foods containing animal protein. It can be assumed that foods containing vegetable protein contain less sulfur than foods containing animal protein. In studies with controlled dietary intakes with varying sulfur content, diets consisting of animal protein yielded greater urinary calcium excretion and lower urinary pH than similar diets consisting of mainly vegetable protein (77). Another study comparing the effects of two sources of protein (meat and soy protein), with and without additional supplementation with sulfur amino acids, indicated that dietary meat elicited a greater positive association between protein intake and urinary calcium, sulfur, ammonia, and titratable acids than dietary soy (78). When the soy diet was supplemented with sulfur amino acids, urinary calcium and acid excretion increased. Conversely, the addition of dietary potassium (either as fruit or K^+ supplement) to both diets decreased urinary calcium and acid excretion (78). Other studies have shown that greater amounts of protein or higher ratios of animal protein to potassium are more detrimental when bone health is already compromised (such as during bed rest, and potentially during space flight) (79, 80).

Deficiency of protein leads to muscle loss, weakness, wasting, and ultimately tissue breakdown, or even death. Toxicity of protein has not been well studied.

Targeted research needed

Research continues on the effects of amino acid supplementation as a means to mitigate muscle loss. This needs to continue in order to refine the details (such as dose and timing) and assess the viability of this countermeasure.

The extramural expert panel recommended that further research be done to better understand the effects of protein source (animal vs. vegetable, and the effect of sulfur amino acid content) on bone loss and renal stone risk. Flight proposals reviewed through the NASA research announcement system have received comments supporting the concept that optimizing the protein source would provide a dietary countermeasure to bone loss, with no associated risk of side effects, no additional launch mass, and no stowage requirements. This concept has long been advocated (81), but has yet to be evaluated.

Nominal requirement on Earth

The dietary recommendations for protein are provided as recommended dietary allowances (RDAs), and the current Earth-based daily recommendation for those in the age range of the astronaut population is 56 g/day for men and 46 g/day for women (82). The acceptable macronutrient distribution range (AMDR) is 10%–35% of total energy intake (82).

Historical space flight requirements

The daily protein requirements were defined in 1991 (47), and again in 1995 (48), as follows:

Missions of 30–120 days: 10-15% of total energy intake (47)
Missions up to 360 days: 10-15% of total energy intake (48)

Requirements, standards, and operating bands

Req. 2. The dietary intake of protein shall be 0.8 g/kg per day and not exceed 35% of the total daily energy intake. Approximately 2/3 of the total amount of protein shall be provided in the form of animal protein and 1/3 in the form of vegetable protein.

Protein intake operating bands are defined as

Dietary Protein (% of calories)

	>35%	red
	30-35%	yellow
	15-30%	green
	10-15%	yellow
	<10%	red

Initial verification that this requirement has been met will be done by proximate analysis of the protein content of the planned space food items, and analysis of crew menus.

Final verification will be completed by determining dietary intake using a food frequency questionnaire or other method of monitoring inflight intake. Standards will be assessed before and after flight (and to the extent possible, during flight) by determining levels of 3-methylhistidine (3-MH) (83), total protein (84) , albumin (84), retinol-binding protein (85) (RBP), and transthyretin (86) in biological samples. Serum and urinary creatinine will also be determined; these are included in the "General Chemistry" section.

3-MH (urine)

	>520 µmol/d	red
	320 µmol/d	yellow
	64 µmol/d	green

Total Protein (serum)

	<5.5 g/dL	red
	5.5 g/dL	yellow
	6.2 g/dL	green
	7.8 g/dL	yellow
	>9.0 g/dL	red

Albumin (serum)

	5.2 g/dL	green
	3.7 g/dL	yellow
	<2.8 g/dL	red

Transthyretin (serum)

	40 mg/dL	green
	20 mg/dL	yellow
	<15 mg/dL	red

RBP (serum)

	Women	Men	
	60 mg/L	67 mg/L	green
	32.8 mg/L	39 mg/L	yellow
	<25 mg/L	<25 mg/L	red

Carbohydrate

Physiological function and existing space flight knowledge

Carbohydrates play an important role in the body because they supply the primary source as well as a readily available source of energy. This energy is oxidized and used by various organs and cells in the body, particularly the brain and red blood cells, as they depend solely on carbohydrate for energy.

Dietary carbohydrates are classified into a number of different categories, all based on the number of sugar units present. Monosaccharides are composed of only one sugar unit such as glucose or fructose, and disaccharides are composed of two sugar units, such as sucrose (glucose + fructose) or lactose (glucose + galactose). Longer chains of sugar units, up to 10, are known as oligosaccharides, and polysaccharides contain more than 10 sugar units. Examples of polysaccharides are starch and glycogen, which are the storage forms of carbohydrate for plants and animals, respectively.

The human body stores carbohydrates as glycogen. Glycogen synthesis is triggered in skeletal muscle by a rise in insulin after the consumption of carbohydrates. Most of the total body glycogen is present in skeletal muscle for storage and utilization, with a small portion being stored in the liver for export and maintenance of blood glucose concentrations. *De novo* synthesis of glucose from non-carbohydrate precursors can and does occur in the body, if needed. This allows the liver to maintain adequate blood glucose concentrations. Insulin is required for the uptake of glucose into cells, and various transporter systems are found in different types of tissues that utilize glucose.

Carbohydrate should make up the most significant portion of the diet because it is the main energy source. Space flight requirements for carbohydrate are thought to be similar to those on Earth. However, to date, few investigations have been conducted on the effects of microgravity on the metabolism of dietary carbohydrate. Some data show that bed rest (and theoretically space flight) results in insulin resistance (87-89). Efforts to maintain muscle mass (and presumably correct this) continue, but little research has been done to pursue this as a nutritional issue.

Body stores and relative time to depletion

About 150–500 g of carbohydrate is stored in the body as glycogen, in the liver and skeletal muscle (90). Glycogen stores, especially those in the liver, fluctuate greatly during the day in response to food intake, and these fluctuations may be involved in the regulation of food intake (91). Muscle glycogen stores are used mainly by muscle, whereas liver glycogen stores are used to maintain, store, and export blood glucose. Liver stores are depleted after 12 to 18 hours of fasting (90).

As long as the intake of protein and fat is adequate, the lower limit of dietary carbohydrate that is compatible with life is zero. However, considerable metabolic adjustments (to ketosis) must be made for the body to adapt to using fat and protein

as fuels. The level of carbohydrate required to provide optimal health is not as clearly defined.

Potential implications for flight

Sub-optimal carbohydrate intake before and during space flight may have consequences for the crew's productivity and impede their ability to respond in emergency situations (92).

Deficiency of carbohydrate leads to ketosis. A ketotic state would likely impair performance of the crew, as seen in studies conducted by the military (46). Other aspects of the mission would also be at risk (for example, the life support systems may not be able to remove the ketones from the air). Toxicity of carbohydrate has not been well studied, and would likely be an issue only with regard to displacement of other nutrients (protein and fat).

Targeted research needed

No data are currently available to assess the impact of space flight on carbohydrate metabolism. Observations from space flight as well as ground-based bed rest studies show subtle changes in insulin secretion, insulin resistance, and glucose intolerance (88, 89, 93, 94). Even subtle changes in such important metabolic processes make it critically important to consider the possibilities of altered carbohydrate and insulin metabolism for exploration missions.

Nominal requirement on Earth

Acceptable daily intake of dietary carbohydrate should be between 55 and 75% of the total dietary energy (95). A minimum intake of 140 g/d is required to maintain the needs of organs that require carbohydrate for energy production (96).

Historical space flight requirements

The daily carbohydrate requirement for male and female astronauts was originally defined (47, 48) as follows:

Missions of 30–120 days: 50% of total energy intake (47)
Missions up to 360 days: 50–55% of total energy intake (48)

Most of the carbohydrate should be provided as complex carbohydrates, with less than 10% of total carbohydrate provided as simple sugars.

Requirements, standards, and operating bands

Req. 3. The dietary intake of carbohydrate shall comprise 50–55% of the total daily energy intake. Carbohydrate intake operating bands are defined as

Dietary Carbohydrate (% of calories)

	>65%	red
	55-65%	yellow
	50-55%	green
	45-50%	yellow
	<45%	red

Initial verification that this requirement has been met will be done by proximate analysis of the carbohydrate content of the planned space food items, and analysis of crew menus.

Final verification will be completed by determining dietary intake using a food frequency questionnaire or other method of monitoring inflight intake. Standards will be assessed before, during, and after flight by determining levels of glucose (84) in whole blood.

Glucose (whole blood)

	>200 mg/dL	red
	200 mg/dL	yellow
	70-105 mg/dL	green
	70 mg/dL	yellow
	<50 mg/dL	red

Fat

Physiological function and existing space flight knowledge

Fat is the most energy-dense of all the nutrients, and therefore is a major energy source for the body. Dietary fat comes mainly in the form of triacylglycerols that contain a glycerol backbone with as many as three fatty acids attached. A number of types of fatty acids exist, including saturated, monounsaturated, polyunsaturated, and trans. Dietary fat assists in the absorption of fat-soluble vitamins, and also supplies the body with the two essential fatty acids (EFAs), linoleic acid and linolenic acid. These EFAs are necessary for growth and development, as well as many other biochemical processes, including production of eicosanoids (physiologically active substances derived from arachidonic acid). Lipids, in the form of phospholipids, make up a large proportion of the structural components of the cellular membrane bi-layer. Energy stored as fat is released in the process of fatty acid oxidation, and fat supplies more energy than any other macronutrient because of its higher content of carbon-to-hydrogen bonds.

Body stores and relative time to depletion

Body stores of fat are located mainly in adipose tissue as triacylglycerols. Adipose tissue is dispersed throughout the human body, its distribution differing slightly between genders.

According to case studies, people following fat-free diets can exhibit symptoms of essential fatty acid deficiencies after only 1 month. An infant consuming fat-free total parenteral nutrition (TPN) for 3 months developed skin lesions and had polyunsaturated fatty acid levels less than 10% of control values (97). In another study, an adult consumed fat-free TPN for 7 months and developed a severe dermatitis by the end of the first month. Omega-3 (n-3) fatty acids comprised 0.01% of the fatty acids of this person's plasma phospholipids, which means that the patient was almost completely depleted of n-3 fatty acids (98).

Potential implications for flight

Deficiency of fat leads to essential fatty acid deficiency and ultimately death. Toxic levels of fat lead to high cholesterol, atherosclerotic plaques, and ultimately coronary heart disease, or even death.

Targeted research needed

The role of n-3 fatty acids in cancer prevention is currently being investigated in animal models of space flight radiation effects (99). Not only do n-3 fatty acids show promise in alleviating cancer risk, but these fatty acids also have well documented cardiovascular benefits, have been used in numerous clinical trials, and show promise as a muscle loss countermeasure. The abundant data showing that eicosapentaenoic acid (EPA) can successfully prevent muscle atrophy during other muscle-wasting conditions, such as cancer or sepsis, indicate the likelihood is high that EPA will have the same beneficial effects on muscle atrophy during space flight or ground-based analogs including bed rest. Thus, further research on EPA is warranted. This has been proposed and peer-approved, but not funded.

Nominal requirement on Earth

Currently no RDA or adequate intake (AI) level has been set for total fat because data are insufficient to determine the level of dietary fat that may put one at risk for inadequacy or may contribute to the prevention of chronic disease (82). The AMDR is 20–35% of total energy intake (82).

Historical space flight requirements

The daily total fat requirements for male and female astronauts were evaluated, and were determined to be

Missions of 30–120 days: 30–35% of total energy intake (47)
Missions up to 360 days: 30–35% of total energy intake (48)

Requirements, standards, and operating bands

Req. 4. The dietary intake of fat shall comprise 25–35% of the total daily energy intake. Dietary intake of n-6 and n-3 fatty acids shall be 14 grams/day and 1.1–1.6 grams/day, respectively. Consumption of saturated fat, trans fatty acids, and cholesterol will be as low as possible.

Dietary fat nominal operating bands are defined as

Total Dietary Fat

	>40%	red
	35–40%	yellow
	25–35%	green
	20–25%	yellow
	<20%	red

Initial verification that this requirement has been met will be done by proximate analysis of space food items for fat content, as well as individual fatty acids. The menu content will also be analyzed.

Final verification will be completed by determining dietary intake using a food frequency questionnaire or other method of monitoring inflight intake. Standards will

be assessed before, during (to the extent possible), and after flight by determining levels of cholesterol (84), cholesterol fractions (86, 100), and triglycerides (84) in serum samples.

Cholesterol (serum)

	125 mg/dL	green
	199 mg/dL	yellow
	>350 mg/dL	red

Triglycerides (serum)

	35 mg/dL	green
	149 mg/dL	yellow
	>250 mg/dL	red

HDL Cholesterol (serum)

	>60 mg/dL	green
	40 mg/dL	yellow
	<40 mg/dL	red

LDL Cholesterol (serum)

	<129 mg/dL	green
	159 mg/dL	yellow
	>160 mg/dL	red

Fiber

Physiological function and existing space flight knowledge

Dietary fiber consists of non-digestible food components that are typically carbohydrate and plant-based. Non-starch polysaccharides, including cellulose, gums, pectins, mixed-linkage ß-glucans, and hemicelluloses, are the major components of dietary fiber. Although most dietary fibers are polysaccharides that are made up of 10 units or more, ß-linkage oligosaccharides such as inulin are also included in the definition of dietary fiber because of their physiological similarities. Lignan is also included even though it is a non-carbohydrate component.

A role for dietary fiber has been implicated in decreases in plasma cholesterol, modification of the glycemic response, improvements in large bowel function, and decreases in the bioavailability of some nutrients. Epidemiological evidence also points to relationships between diets high in fiber and decreased incidence of cardiovascular disease and bowel cancer (101).

Body stores and relative time to depletion

By definition, fiber is not stored.

Potential implications for flight

Changes have been described in gastrointestinal function and gut transit time during space flight. Adequate dietary fiber will be essential to maintain gastrointestinal function and decrease the incidence of constipation, because mouth-to-cecum transit times are slower on orbit (92).

Targeted research needed

Several studies have shown that specific dietary fatty acids and types of dietary fiber can reduce radiation-induced cancer risk in animals (99, 102). Further research is warranted to investigate the potential protective effects of fiber on radiation-induced cancer risk in humans exposed to high-linear energy transfer (LET) radiation during space flight.

Nominal requirement on Earth

Recommended intakes of dietary fiber are provided as AIs (82):

Individuals aged 19–50 y	Individuals aged 51–70 y
Men: 38 g/d	Men: 30 g/d
Women: 25 g/d	Women: 21 g/d

Historical space flight requirements

The daily total fiber requirements for male and female astronauts were defined earlier as follows:

Missions of 30–120 days: 10–15 g, in soluble and insoluble forms (47)
Missions up to 360 days: 10–25 g, in soluble and insoluble forms (48)

Requirements, standards, and operating bands

Req. 5. The dietary intake of fiber shall be 10–14 grams/1000 kcal. The nominal operating bands for dietary fiber are defined as

Dietary Fiber

	21-38+ g/d	green
	20 g/d	yellow
	<20 g/d	red

Verification that this requirement has been met will be done by proximate analysis of the fiber content of the planned space food items, and analysis of crew menus.

Fluid, Electrolytes and Renal Stone Risk

Fluid

Physiological function and existing space flight knowledge

Adequate fluid intake is necessary to maintain the body's normal hemodynamic state and normal fluid osmolality, which is important for cardiovascular health and maintenance of fluid and electrolyte homeostasis. Water is a structural component of the body and the solvent for transportation of nutrients and waste. Fluid and electrolytes may be lost from the body by a variety of routes and for a variety of reasons. Fluid and electrolytes are excreted in sweat, urine, and feces, and in abnormal situations excessive amounts can be lost by these routes and others. Significant losses may occur through the gastrointestinal tract as a result of diarrhea, vomiting, or gastric drainage. Loss through the skin increases with fever, increased metabolism, sweating, and burns (103).

Fluid and electrolyte homeostasis is significantly altered during space flight, and this has been extensively reviewed (3, 104-112). The hypothesis originally proposed was that upon entering weightlessness, the human body would experience a headward shift of fluids, with subsequent diuresis and dehydration. A series of experiments was conducted to assess fluid and electrolyte homeostasis during space flight; the most comprehensive of these took place on the two Spacelab Life Sciences missions in the early 1990s.

Within hours of the onset of weightlessness (the earliest available data point), a reduction in both plasma volume and extracellular fluid volume occurred, accompanied by the "puffy" faces typically observed early in flight (3, 113). Initially, the decrement in plasma volume (~17%) was larger than the decrement in extracellular fluid volume (~10%), suggesting that interstitial fluid volume (the other four-fifths of extracellular fluid) is conserved proportionally more than plasma volume (3). Conservation of interstitial fluid volume is supported by rapid decreases in total circulating protein, specifically albumin (3). This shift of protein, and associated oncotic pressure, from the intravascular to the extravascular space would also facilitate the initial changes in plasma volume (3).

Following the initial adaptation, extracellular fluid volume decreased between the first days of flight and 8 to 12 days of flight, from the initial ~10% below preflight levels to ~15% below preflight levels (3). Plasma volume was partially restored during this period, from the initial ~17% below preflight levels to ~11% below preflight levels (3), and it has been found to remain 10%–15% below preflight levels even for extended-duration flights (114).

It is hypothesized that the extravascular shift of protein and fluid represents an adaptation to weightlessness, and that after several days, some of the extravascular albumin has been metabolized, with a loss of oncotic force and a resulting decreased extracellular fluid volume and increased plasma volume (3). This loss of extracellular

protein (either intra- or extravascular), and associated decreased oncotic potential, probably plays a role in postflight orthostatic intolerance, which has been considered to result partly from reduced plasma volume at landing (115). Furthermore, the loss of protein may explain why fluid loading alone does not restore circulatory volume (116, 117), as no additional solute load exists to maintain the fluid volume.

The effect of space flight on total body water has been evaluated to assess hydration. Shuttle and Skylab astronauts had approximately 1% decreases in total body water during flight (3, 118, 119), and the percent of body mass represented by water did not change. Thus, the often-proposed weightlessness-induced dehydration does not exist. This has also been shown by European investigators (111, 120-122).

Diuresis is also typically not observed during flight (13, 104, 105, 122-125), for a number of possible reasons. Operational constraints have made it difficult to document urine volume accurately on the first day of space flight. However, on the Spacelab Life Sciences missions, urine volume on the first 3 days of flight was significantly less than preflight volume, and tended to be less than preflight values throughout the flight (3). Urine volumes on a week-long flight to Mir were also less than preflight volumes (124). During the first week of the 59- and 84-d Skylab flights (30), urine volume was less than it was before flight, and for the remainder of the mission it was unchanged from preflight levels. Decreased fluid intake likely accounts for the decreased urine volume, which was accompanied by little or no change in total body water. Diuresis has been documented in bed rest studies (126), suggesting differences in fluid metabolism between analog studies and actual space flight.

As mentioned above, the percent of body mass represented by total body water is relatively unchanged during flight (3). However, on a volume basis, the change in extracellular fluid volume was found to be greater than the change (or lack of change) in total body water (3). Thus, by difference, intracellular fluid volume increased during space flight. This had been previously hypothesized from ground-based studies (127) and observed in postflight studies of Apollo crew members (13). The mechanism for a space flight-induced increase in intracellular fluid volume is unknown. One possible explanation is that a shift in fuel utilization results in altered glycogen storage, a condition known to increase cellular water content.

Body stores and relative time to depletion

Total body water makes up about 50%–70% of body mass (128).

Fluid requirements increase with metabolic rate and heat stress. Death from dehydration from depriving the body of all water can occur within weeks (129).

Potential implications for flight

Inadequate fluid intake increases the risk of renal stone formation and dehydration, and may be a consequence of reduced thirst during space flight (92). Fluid intakes during flight are typically less than preflight levels, and are often below the recommended quantities. Although no space flight-induced dehydration occurs, care

must be taken to ensure adequate fluid intake and hydration status. This is critical for closed flight vehicles where water is often a limiting resource. Rationing of water should be avoided wherever possible.

Deficiency of fluid leads to dehydration and ultimately death. Likewise, an excess of fluid intake leads to water intoxication or even death.

Targeted research needed

Studies described above have documented that total body water is unchanged during flight, but an apparent shift of fluid from the extracellular to the intracellular compartment occurs. The effect of this on cell size and cell function (such as the effect of a change in the density of receptors on cell membranes) has not been evaluated. This might be responsible for some of the changes noted in other systems (such as the endocrine, cardiovascular, and immune systems).

Nominal requirement on Earth

Recommended intakes of total water (including that contained in food, beverages, and drinking water) are provided as AIs (130):

Men, 19 y and older: 3.7 L/d
Women, 19 y and older: 2.7 L/d

Historical space flight requirements

The daily total fluid requirements for male and female astronauts were defined earlier as follows:

Missions of 30–120 days: Water intake should be adequate to reduce the incidence of kidney stones; a tentative guideline could be 1 mL/kcal of consumed energy (47).

Missions up to 360 days: Intake of fluid shall be sufficient to reduce the incidence of kidney stones and prevent dehydration. The daily fluid requirement is estimated to be 1.0–1.5 mL/kcal consumed (at least 2000 mL/day). It is imperative for health of the crew that fluid intake be maintained (48).

Requirements, standards, and operating bands

Req. 6. The dietary intake of fluid shall be 1–1.5 mL/kcal, with a minimum intake of 2000 mL. The nominal operating bands are defined as

Fluid Intake

	1-1.5 mL/kcal	green
	2 L/d	yellow
	<2 L/d	red

Initial verification that this requirement has been met will be done by proximate analysis of space food items for water content, as well as by analysis of the selected menus.

Final verification will be completed by determining fluid intake using a food frequency questionnaire or other method of monitoring inflight intake. Standards will be assessed before, during (to the extent possible), and after flight by determining blood protein and electrolyte levels in blood and serum samples (operating bands for these are described in other sections).

Sodium

Physiological function and existing space flight knowledge

Sodium is the major cation of extracellular fluid (103). Together with chloride, sodium is utilized by the body to maintain normal water distribution, osmotic pressure, and anion-cation balance in the extracellular fluid compartment (131). Electrolyte concentrations in the body are critical for proper cardiovascular function and are under renal and hormonal control (132). Increases in blood sodium levels can be caused by diabetes, renal polyuria, diarrhea, insufficient water intake, excessive sweating, or increased dietary sodium intake. Sodium levels decrease with edema, excessive water intake, vomiting, diarrhea, diuretic therapy, renal tubular damage, hyperaldosteronism, or lower dietary intake.

Inflight sodium intakes during Skylab and Shuttle missions averaged 4 – 5 g, and were not dissimilar from the astronauts' preflight intakes (133). The current food system is high in dietary sodium, and typical intakes on the ISS have been in excess of 4.5 g, even with sub-optimal food intake (15). Although sodium homeostasis and blood sodium levels are maintained during real and simulated space flight (134), excessive intake of sodium can affect bone and renal health (135).

Body stores and relative time to depletion

For the normal adult, total body sodium averages about 60 mmol/kg body weight. Forty to 45% of total sodium resides in bone, with the balance found in extracellular and intracellular fluid. These sodium stores are classified as either exchangeable (42 mmol/kg body weight) or non-exchangeable, the former being composed of all cellular and less than half of bone sodium (136). Exchangeable sodium becomes available by diffusion when plasma sodium levels become low, and in states of edema, the exchangeable sodium stores absorb sodium.

Animal studies show that symptoms of a sodium deficiency occur after 3 to 4 weeks of dietary sodium restriction (137). During acute starvation, urinary sodium excretion decreases to less than 0.2 g within 10 days (138), and can be affected by the amount of sweat (139). Plasma sodium levels are maintained fairly well during acute starvation: an initial decrease is followed by a return toward normal values (140). Maintenance of blood sodium is also observed during semi-starvation. During the Minnesota Experiment, plasma sodium levels in samples taken after the 6-month semi-starvation period were 0.6 ± 7.3% higher than baseline levels (n=4) (139). Six days of under-nutrition resulted in large negative balances of sodium chloride (–12.8 ± 3.6 g/d), likely related to changes in water balance (data from (139)).

Potential implications for flight

Dietary sodium is known to affect calcium homeostasis (141, 142). High salt intakes are typically found during space flight, and have potential consequences for renal stone risk and microgravity-induced osteoporosis. Changes in plasma volume, extracellular fluid volume, and cardiovascular function have also been observed during space flight (3).

On Earth, excessive sodium intake has been associated with increased bone turnover (143). In a review of the interaction between dietary salt, calcium, and bone, Massey and Whiting (144) suggest that habitual excessive salt intake contributes to bone loss and increases risk of renal stone formation (as reviewed in (145-147), and that the effects of dietary sodium are different in different subpopulations (for example, renal calcium stone formers are more responsive to a change in dietary salt than are non-stone formers).

Increased risk of renal stone formation during and after space flight is well documented (148, 149), and crew intakes of sodium are typically high even when energy intakes are inadequate (15). Dietary sodium also seems to exacerbate the calciuric responses to musculoskeletal unloading in weightlessness. Bed rest subjects consuming a low-sodium (100 mmol/d) diet had no change in urinary calcium, while those on a high-sodium diet (190 mmol/d) had hypercalciuria (150). The high sodium content of the current space food system makes it particularly important to monitor and restrict dietary sodium intake of astronauts to maintain their bone and renal health. Thus, the research emphasis for food system development for exploration-class missions should include a focus on low-sodium, long-shelf-life, palatable foods (151).

Deficiency of sodium leads to hyponatremia and hypotension, or even death. Conversely, an excess of sodium leads to hypernatremia and hypertension, or even death.

Targeted research needed

The extramural expert panel recommended that further research be done to investigate potential effects of high sodium intake during space flight, since the space food system currently has very high sodium levels. The impact of high sodium intake on bone, calcium, and pH is not well understood, and adjustments in sodium intake may serve as a viable countermeasure to bone loss. Furthermore, the role of high-sodium diets in potassium homeostasis is not well understood. This may prove to be an area where nutrition and cardiovascular effects of space flight may interact, and study of the interaction may produce a dietary countermeasure.

Nominal requirement on Earth

The recommendations for sodium intake are provided as AIs (130):

Men and women, 19–50 y: 1.5 g/d
Men and women, 51–70 y: 1.3 g/d

Historical space flight requirements

The intake for male and female astronauts was defined as 1.1–3.3 g/d on missions of 30 to 120 days in duration, and 1.5–3.5 g/d on missions up to 360 days (23, 152). The food system was unable to support this requirement, and intakes were often much higher (intakes as high as 7–10 g Na per day have been observed).

Requirements, standards, and operating bands

Req. 23. The dietary intake of sodium shall be 1500–2300 mg/day for both women and men. The nominal operating bands are defined as

Dietary Sodium

	>3500 mg/d	red
	3500 mg/d	yellow
	1500-2300 mg/d	green
	500-1500 mg/d	yellow
	<500 mg/d	red

Initial verification that this requirement has been met will be done by proximate analysis of space food items for sodium content, as well as by analysis of the crew menus.

Standards will be assessed before, during (to the extent possible), and after flight by determining levels of sodium in blood (84, 153, 154) samples. Determination of urinary sodium allows indirect assessment of the level of sodium intake (153, 154), although this is considered supporting data and not a standard *per se*. Normal ranges for urinary sodium are documented in the General Chemistry section.

Sodium (serum)

	>155 mmol/L	red
	144-155 mmol/L	yellow
	135-144 mmol/L	green
	128-135 mmol/L	yellow
	<128 mmol/L	red

Potassium

Physiological function and existing space flight knowledge

As the major intracellular cation, potassium has a significant role in several physiological processes (132). Potassium is critical to regulation of acid-base balance, energy metabolism, blood pressure, membrane transport, and fluid distribution within the body. It is also involved in the transmission of nerve impulses and cardiac function (155). Disordered potassium metabolism because of excess or deficient circulating levels has negative consequences for cardiac, muscle, and neurological function.

Body stores and relative time to depletion

Total body potassium averages 45 mmol/kg body weight, totaling about 3150 mmol (1230 g) of potassium in a reference 70-kg person. Two percent of body potassium (~60 mmol) is distributed in the extracellular fluid, and intracellular fluid levels are typically maintained at 140–150 mmol/L).

Potassium levels cannot be maintained at intakes under 10–20 mmol/day (156). Moderate depletion of potassium in humans is associated with clinically significant impaired active relaxation of the left ventricle (157). In the referenced study, healthy adults were placed on a potassium-depletion diet for 7 days. At the end of 7 days, isovolumic relaxation time and deceleration time of flow through the mitral valve were significantly increased.

Potential implications for flight

Increased levels of urinary potassium may be related to muscle disuse atrophy and inadequate intake during space flight (134).

Deficiency of potassium leads to hypokalemia, muscle weakness, constipation, and fatigue, or even death. There is no evidence of adverse effects associated with toxicity of potassium from naturally occurring sources. However, supplemental intake may cause hyperkalemia (and associated weakness, cardiac arrest, paralysis), metabolic acidosis, decreased neuromuscular functions, or even death.

Targeted research needed

The extramural expert panel recommended that the relationship between bone health and the protein:potassium ratio in the diet be further investigated, along with the role of potassium in cardiovascular health during flight. The loss of lean body mass, along with high sodium intake, may result in potassium depletion.

Nominal requirement on Earth

The recommended intake for potassium is provided as AIs (130):

Men and women, 19–70 y: 4.7 g/d

Historical space flight requirements
The intake of potassium for male and female astronauts was defined as approximately 3500 mg/day (47, 48).

Requirements, standards, and operating bands
Req. 24. The dietary intake of potassium shall be 4.7 g/d. The nominal operating bands are defined as

Dietary Potassium

	4.7 g/d	green
	3.5-4.7 g/d	yellow
	<3.5 g/d	red

Initial verification that this requirement has been met will be determined by proximate analysis of space food items for potassium content, as well as by analysis of the crew menus.

Standards will be assessed before, during (to the extent possible), and after flight by determining levels of potassium in blood (84) and urine (153) samples. Determination of urinary potassium allows indirect assessment of the level of potassium intake (130), although this is considered supporting data and not a standard *per se*. Normal ranges for urinary potassium are documented in the General Chemistry section.

Potassium (serum)

	>5.8 mmol/L	red
	5.2-5.8 mmol/L	yellow
	3.7-5.2 mmol/L	green
	3.0-3.7 mmol/L	yellow
	<3.0 mmol/L	red

Renal Stone Risk

Physiological function and existing space flight knowledge

In-flight data show that there is an increased risk for renal stones during space flight (148, 158, 159). Urinary components, such as decreased citrate, decreased potassium, increased calcium, and increased relative supersaturation of calcium oxalate and brushite (148) contribute to an increased renal stone risk among crewmembers during flight.

Ground-based clinical data show that certain dietary components have a major impact on renal stone-forming risk. High sodium diets, excess animal protein in the diet, and excess dietary oxalate increase calcium excretion, decrease citrate excretion, increase urinary uric acid, and decrease the inhibitor activity against calcium oxalate crystallization in the urine (160, 161).

Potential implications for flight

It is imperative that renal stone risk be minimized prior to space flight, and that recommended fluid and dietary guidelines are followed during flight to minimize risk. If crewmembers have an increased risk of renal stones prior to space flight because of dietary habits or other factors, then exposure to microgravity and the resultant bone loss, hypercalciuria, increased urinary sodium and decreased urinary output, may further exacerbate their risk of renal stone formation (148, 149).

Targeted research needed

It is not uncommon for astronauts to consume 4-8 g sodium per day during flight (15, 148). A high sodium diet is associated with elevated urinary calcium and sodium excretion, and decreased urinary citrate (144, 147, 148, 160-162). It is not known whether increased risk from high dietary sodium and protein intake have an additive effect with the increased risk from space flight itself, therefore further studies are warranted. It is ideal if renal stone risk could be mitigated through dietary changes alone to minimize potential side effects from pharmacological agents, but this approach needs to be investigated during flight for its efficacy.

Nominal requirement on Earth

Clinical experience has demonstrated that a program of monitoring urinary parameters related to renal stone risk and estimating the risk for renal stone development can virtually lead to total control of renal stone disease (163, 164). Meeting DRIs for fluid intake, dietary calcium, sodium, phosphorus, magnesium, and protein are recommended for reducing renal stone risk (82, 130, 165).

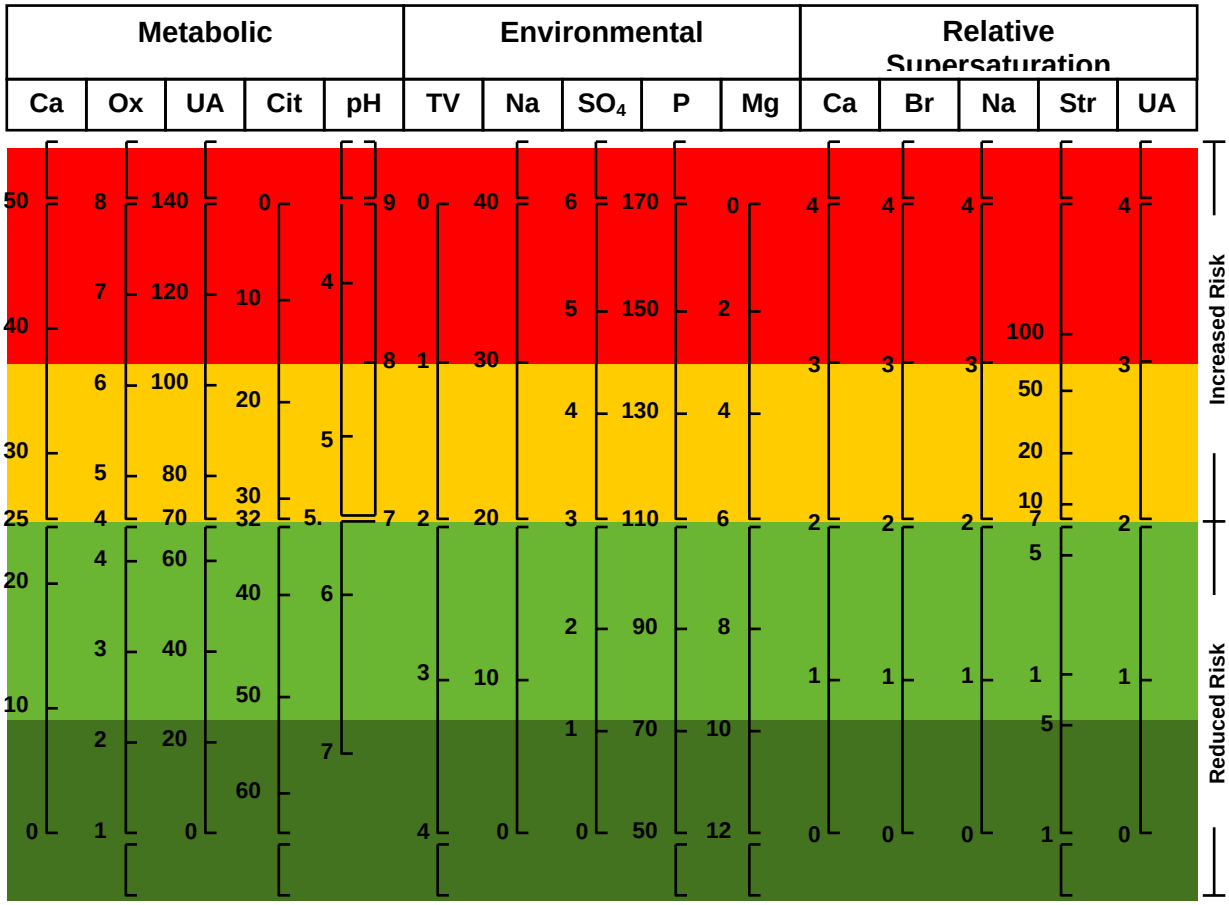
Historical space flight requirements
The renal stone risk profile has been evaluated extensively on Shuttle, Mir, and ISS crews (148, 149, 159), and was included as part of the nutritional assessment profile from the inception (166).

Requirements, standards, and operating bands
The renal stone risk profile shall be assessed in order to minimize risk of stone formation.

Metabolic factors and limits are: urinary calcium shall not exceed 375 mg per day; urinary oxalate shall not exceed 62 mg per day; urinary uric acid shall not exceed 1000 mg per day; urinary citrate shall be greater than 160 mg per day; and urinary pH shall not be greater than 8.

Environmental standards and limits are: the total volume of urine shall be at least 1 liter per day; urinary sodium shall not exceed 300 meq per day; urinary sulfate (SO_4) shall not exceed 45 mmol per day; urinary phosphorus shall not exceed 1400 mg per day; urinary magnesium shall be greater than 30 mg per day.

Relative supersaturation standards and limits are: urinary calcium oxalate supersaturation shall not exceed 3; urinary brushite supersaturation shall not exceed 3; sodium urate supersaturation shall not exceed 3; struvite supersaturation shall not exceed 750; uric acid supersaturation shall not exceed 3.


Metabolic
Environmental
Relative Supersaturation
Ca
Ox
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pH
TV
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SO4
P
Mg
Ca
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Na
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UA
Increased Risk
Reduced Risk

Fat-Soluble Vitamins

Vitamin A

Physiological function and existing space flight knowledge
Vitamin A is a general term that refers to a family of fat-soluble compounds that are structurally similar to retinol and share its biological activity. Among these are retinol, α-carotene, β-carotene, and retinyl palmitate. Trans-retinol is the primary biologically active form of vitamin A. Many carotenoids, such as β-carotene, can be converted to trans-retinol and thus contribute to vitamin A activity. Collectively, these carotenoids are termed provitamin A carotenoids and are measured in retinol equivalents (REs). Vitamin A is directly involved in vision, gene expression, reproduction, embryonic development, and immunity. Vitamin A and β-carotene serve as biological antioxidants and have been shown in multiple studies to reduce the risk of cancer and coronary heart disease (167, 168). Vitamin A also plays a role, albeit sometimes indirectly, in the function of almost all of the body's organs (169).

Serum levels of retinol and retinol-binding protein are significantly decreased after long-duration space flight (15).

Body stores and relative time to depletion
Vitamin A is stored mainly (80%) in the liver, with the remainder stored in peripheral organs and tissues. Total body stores range from 1.05 to 3.14 nmol (300 to 900 mg) in normal adults (170).

Liver stores of vitamin A are severely depleted when levels are less than 20 μg (171). A study of vitamin A depletion in baboons found a 59% decrease in hepatic vitamin A after 4 months of a chronic ethanol diet (172). After 24 to 48 months, the researchers found a 95% decrease in hepatic vitamin A stores, which was accompanied by fibrosis and cirrhosis of the liver. Alcoholism is often associated with vitamin A deficiency because retinol and ethanol are competing substrates for the same enzymes (173).

Potential implications for flight
Oxidant stress is increased during space flight, and this could affect cardiovascular health and cancer risk. Vitamin A status may play a critical role in maintaining antioxidant health during space flight.

Deficiency of vitamin A leads to xerophthalmia, loss of appetite, drying and keratinization of membranes, infection, or even death.

Acute toxicity of vitamin A leads to nausea, vomiting, headache, blurred vision, and muscular incoordination. Chronic toxicity of vitamin A leads to rapid reduction in bone mineral density, liver abnormalities, or even death.

Targeted research needed
The extramural expert panel recommended that vitamin A content and stability in the space food supply be determined.

Nominal requirement on Earth
The RDA for vitamin A is 900 μg RE/d for men aged 19 and older, and 700 μg RE/d for women aged 19 and older (174). Upper limits exist for vitamin A (3000 μg RE/d), and β-carotene supplementation is advised only in situations where there is a risk of vitamin A deficiency.

Historical space flight requirements
The daily vitamin A requirements for male and female astronauts were determined earlier, and are as follows:

Missions of 30 – 120 days (47):
Males 1000 μg RE/d
Females 800 μg RE/d
Missions up to 360 days (48):
Males 1000 μg RE/d
Females 1000 μg RE/d
RE = retinol equivalents; 1 RE = 1 μg retinol or 6 μg β-carotene

Requirements, standards, and operating bands
Req. 7. The dietary intake of vitamin A shall be 700–900 μg/day. The nominal operating bands are defined as

Dietary Vitamin A

	>3000 μg/d	red
	700-900 μg/d	green
	500-700 μg/d	yellow
	<500	red

Initial verification that this requirement has been met will be determined by proximate analysis of space food items for vitamin A content, as well as by analysis of the crew menus.

Final verification will be completed by determining vitamin A intake using a food frequency questionnaire or other method of monitoring inflight intake. Standards will be assessed before, during (to the extent possible), and after flight by determining levels of retinol (85)and retinyl palmitate (175) in blood samples. Blood levels of retinyl palmitate are measured to identify any evidence of vitamin A toxicity. Chronic and acute vitamin A toxicities are associated with increased plasma retinyl esters because excess retinol in the blood is converted to this less toxic form (174).

Retinol

	1.2 µg/mL	green
	0.3 µg/mL	yellow
	<0.1 µg/mL	red

Retinyl Palmitate

	0-0.19 µg/mL	green
	>0.20 µg/mL	red

β-carotene

	0.04-0.373 µg/mL	green

Vitamin D

Physiological function and existing space flight knowledge

The major function of vitamin D is to maintain normal blood levels of calcium and phosphorus. The liver converts vitamin D_3 to 25-hydroxyvitamin D_3, which is typically the gold standard measurement for determining vitamin D status. 25-hydroxyvitamin D_3 is converted to 1,25-dihydroxyvitamin D_3 in the kidney, and from there it is transported systemically to target organs. Classic target organs include bone, intestine, and kidney. Numerous other tissues are affected by vitamin D status because their cell nuclei contain receptors for 1,25-dihydroxyvitamin D_3. Some of these tissues are adipose tissue, bone marrow, brain, breast, cancer cells, cartilage, lung, muscle, ovary, placenta, prostate, stomach, testis, thymus, and uterus (176).

The 2005 Dietary Guidelines for Healthy Americans reports that optimal serum 25-hydroxyvitamin D may be as high as 80 nmol/L (177). These guidelines recommend that people in high-risk groups (elderly and those exposed to little sunlight) have substantially higher intakes of vitamin D (25 µg or 1000 IU) than the general population, to maintain serum 25-hydroxyvitamin D values at 80 nmol/L (177). These findings were based, in part, on numerous studies showing that for individuals with little sun exposure, dietary intake is insufficient to maintain vitamin D status and parathyroid hormone (PTH) suppression (178).

Decreased vitamin D status is one of the most striking nutritional changes that occurs during space flight (15, 179). In several different studies, crew members on the Russian space station Mir had serum 25-hydroxyvitamin D_3 concentrations that were 32%–36% less during and after long-duration (3- to 4-month) missions than before the missions (12, 179). Ground-based studies of bed rest subjects (180) and subjects living in closed-chamber facilities for extended periods also support these data (181). Attempts to supplement with vitamin D have not been successful in correcting the problem. Specific examples of this include data from individual Skylab missions showing that crew members on the longest mission (Skylab 4, 84 days), but not the shorter missions (28 and 59 days), had decreased serum 25-hydroxyvitamin D_3 at landing despite daily vitamin D supplementation (30), and similar data from ISS crew members, for whom supplementation did not seem to correct the problem of vitamin D status (15). Another important observation was related to the relationship between PTH and 25-hydroxyvitamin D_3 before and after flight. Before launch, 25-hydroxyvitamin D_3 was inversely correlated with PTH ($r = -0.72$, $P < 0.05$), but this relation was not evident after landing, suggesting that the body's normal response to changes in vitamin D was altered (15).

Body stores and relative time to depletion
7-Dehydrocholesterol is present in the skin, and can be converted to vitamin D_3 by ultraviolet (UV) light. Vitamin D is also present in the liver and kidney, where hydroxylation reactions occur to produce the active form of vitamin D.

The classic indications of vitamin D deficiency are rickets and osteomalacia. During space flight, vitamin D status was decreased after long missions (84 to 195 d), but not after shorter missions (28 to 59 d) (15, 30).

Potential implications for flight
Since the current space food system includes very few dietary sources of vitamin D, and vitamin D cannot be synthesized endogenously due to lack of UV light, decreased vitamin D status is a serious concern for exploration missions that could last up to 1000 d. Decreased vitamin D status could lead to fragile or brittle bones upon return to Earth. Furthermore, decreased vitamin D status is related to increased risk for multiple diseases (182), including cancer and multiple sclerosis, probably because the cells in a variety of tissues contain 1,25-dihydroxyvitamin D_3 nuclear receptors (183, 184).

Deficiency of vitamin D leads to osteomalacia and osteoporosis, which could lead to life-threatening fractures and even death. Toxicity of vitamin D leads to hypercalcemia caused by hypervitaminosis D, nephrocalcinosis, arteriosclerosis, irreversible calcification of soft tissue, or even death.

Targeted research needed
The extramural expert panel expressed concern that vitamin D status is decreased during space flight, despite vitamin D supplementation. They recommended that vitamin D levels be determined in the food system, and that the stability of vitamin D in the food system be investigated. Furthermore, additional research is needed to understand whether supplementation (and what level of supplementation) can maintain vitamin D stores.

Nominal requirement on Earth
The AI for vitamin D recommended by the 1998 Food and Nutrition Board of the Institute of Medicine is 200 IU/d (5 µg/d) for adults < 51 y. For adults > 51 y, the AI is 400 IU/d (10 µg/d) (185).

The 2005 Dietary Guidelines for Healthy Americans recommend that people in high-risk groups (elderly and those exposed to little sunlight) have substantially higher intakes of vitamin D (25 µg or 1000 IU) to maintain serum 25-hydroxyvitamin D values at 80 nmol/L (177).

Historical space flight requirements
The space flight requirements for vitamin D were defined as 10 µg/d for men and women. This was higher than the requirement for the general population, where about 50% of the daily requirement for vitamin D was expected to be obtained from

sun exposure. This 10 µg per day was designed to augment vitamin D stores in light of decreased (or lack of) exposure to ultraviolet light (and thus, decreased endogenous production) (4, 15, 186)

Requirements, standards, and operating bands

Req. 8. The dietary intake of vitamin D shall be 25 µg per day. The nominal operating bands are defined as

Dietary Vitamin D

	>50 µg/d	yellow
	25-50 µg/d	green
	10-25 µg/d	yellow
	<10 µg/d	red

Initial verification that this requirement has been met will be done by proximate analysis of space food items for vitamin D content, as well as by analysis of the crew menus.

Final verification will be completed by determining vitamin D intake using a food frequency questionnaire or other method of monitoring inflight intake. Standards will be assessed before, during (to the extent possible), and after flight by determining levels of 25-OH vitamin D (154, 187) and 1,25-$(OH)_2$ vitamin D (154, 187) in serum samples.

25-Hydroxy Vitamin D

	>400 nmol/L	red
	138 nmol/L	yellow
	25-138 nmol/L	green
	12 nmol/L	Yellow
	<12 nmol/L	red

1,25-Dihydroxy Vitamin D

	48 pmol/L	green
	100 pmol/L	yellow
	>206 pmol/L	red

Vitamin K

Physiological function and existing space flight knowledge

Vitamin K occurs naturally in 2 forms: phylloquinone (vitamin K_1) and menaquinone (vitamin K_2). Menaquinones are produced by bacteria, while phylloquinone is synthesized in plants. Phylloquinone represents the main source of dietary vitamin K in Western countries (188).

The function of vitamin K was originally assumed to be strictly limited to involvement in blood coagulation, but an increasing amount of evidence indicates that this vitamin affects multiple physiological systems. Vitamin K is a cofactor in the post-translational synthesis of gamma-carboxyglutamic acid (GLA). Gamma-carboxyglutamic acid is common to all vitamin K-dependent proteins, and its role is related to increasing the affinity of the proteins for calcium (189). Vitamin K-dependent proteins include blood coagulation proteins (prothrombin; factors VII, IX, and X; and proteins C and S) and bone proteins (osteocalcin, matrix GLA protein, and protein S).

The limited data available show that vitamin K status is decreased during space flight. Data from 11 U.S. astronauts from Expeditions 1–8 (mission durations of 128 to 195 d during 2000–2004) reveal that on landing day serum phylloquinone (vitamin K1) was 42% less than it was before flight, whereas urinary GLA did not change (15). Other studies show that vitamin K supplementation during space flight elevates urinary GLA and decreases urinary undercarboxylated osteocalcin, suggesting that vitamin K status is lower during space flight (190, 191).

Body stores and relative time to depletion

The main storage depot for vitamin K is the liver. Large amounts of vitamin K are also present in cortical and trabecular bone (192).

Vitamin K stores are very small compared to those of other fat-soluble vitamins, and hepatic vitamin K is rapidly depleted when dietary vitamin K is restricted (193). One study found that undercarboxylated osteocalcin was elevated (a sign of vitamin K insufficiency) as early as the 8^{th} day of space flight, and remained high during 21- and 180-d missions (190).

Potential implications for flight

Decreased vitamin K status has serious implications for space flight because it is related to bone health. Studies on the EuroMir 95 mission demonstrated that markers of vitamin K status were decreased after 12.5 weeks of space flight, and vitamin K supplementation (10 mg/d for 6 weeks) reversed these effects (191). These data, along with data from ISS crew members (15), suggest that vitamin K status during long-duration space flight is sub-optimal.

Elevated undercarboxylated osteocalcin has been associated with increased fracture risk in certain populations, and evidence exists that vitamin K antagonists increase the risk of fracturing vertebrae and ribs in a time-dependent manner (194, 195).

Deficiency of vitamin K is not common in adults, as the intestinal microflora synthesize vitamin K. The reliability of this source of vitamin K during flight is unknown, and expert panels have recommended having higher intake requirements because of this uncertainty. Given the (limited) space flight data documenting the improvement in bone marker status with vitamin K supplementation, clearly more needs to be known before exploration missions are undertaken.

Toxicity of vitamin K in the form of menadione leads to fatal anemia and severe jaundice.

Targeted research needed

The extramural expert panel expressed concern that phylloquinone levels are decreased after long-duration space flight, and that research from the European Space Agency has found evidence for increased amounts of undercarboxylated osteocalcin during flight. They recommended that vitamin K levels and stability in the space food system be determined.

Nominal requirement on Earth

The recommended AI for vitamin K is 120 µg/d for men and 90 µg/d for women (174). No upper limit has been established.

Historical space flight requirements

The space flight requirement for vitamin K for males and females was determined to be 80 µg/d (47, 48).

Requirements, standards, and operating bands

Req. 9. The dietary intake of vitamin K shall be 90 and 120 µg per day for women and men, respectively. The nominal operating bands are defined as

Dietary Vitamin K

	Women	Men	
	90 µg/d	120 µg/d	green
	60 µg/d	90 µg/d	yellow
	45 µg/d	60 µg/d	red

Initial verification that this requirement has been met will be done by proximate analysis of space food items for vitamin K content, as well as by analysis of the crew menus.

Standards will be assessed before, during (to the extent possible), and after flight by

determining levels of phylloquinone (154, 196, 197) and γ-carboxyglutamic acid (198-200) in blood and urine samples.

Phylloquinone (serum)

	1.51 nmol/L	green
	0.38 nmol/L	yellow
	0.1 nmol/L	red

GLA (urine)

	>6.5 µmol/mmol creat	red
	5 µmol/mmol creat	yellow
	4 µmol/mmol creat	green
	2.3 µmol/mmol creat	yellow
	<1.75 µmol/mmol creat	red

Vitamin E

Physiological function and existing space flight knowledge

Vitamin E is a lipid-soluble, chain-breaking antioxidant found in body tissues, and is also the first line of defense against lipid peroxidation reactions. Eight naturally-occurring compounds have vitamin E activity: four tocopherol derivatives (alpha-, gamma-, delta-, and beta-tocopherol) and four tocotrienol derivatives (alpha-, gamma-, delta-, and beta-tocotrienol) (201). The tocopherols that are most abundant in biological systems are alpha- and gamma-tocopherol, but small amounts of delta-tocopherol and alpha-tocopheryl quinine are also present. About 90% of the tocopherol found in human plasma is in the form of alpha-tocopherol (202).

Vitamin E helps protect cell membranes in the early stages of free-radical attack because of its free-radical quenching activity. Free radicals attack polyunsaturated fatty acids found in membrane phospholipids, causing damage to cellular membranes and possibly cell death. The interception of a free radical by vitamin E produces a tocopheroxyl radical that can be reduced by vitamin C or another reducing agent to return vitamin E to its reduced state. The extent of regeneration and recycling of vitamin E in human tissue has not been well established (201, 203).

After crew members have spent 4 to 6 months in space, their plasma γ-tocopherol is 50% less than preflight levels (15). No change in α-tocopherol occurred in these subjects.

Body stores and relative time to depletion

Vitamin E is stored mainly in the adipose tissue and is also found in phospholipid membranes. Results of studies conducted to determine vitamin E tissue levels have shown that tissue α-tocopherol concentrations are largely reflected by changes in plasma α-tocopherol concentrations.

Vitamin E deficiencies in humans are rare; however, fat malabsorption syndromes, genetic abnormalities, and protein-energy malnutrition are specific cases when a vitamin E deficiency is likely to occur. Symptoms include neurological problems associated with nerve degeneration in the extremities (202). Vitamin E depletion has been detected when markers of lipid peroxidation were elevated. However, the lowering of levels of these lipid peroxidation markers has not been shown to have any health benefits, and therefore they have not been used to establish α-tocopherol requirements.

Potential implications for flight
Because oxidative stress can increase in a microgravity and high-radiation environment, it may be necessary to provide enough vitamin E for astronauts' blood levels of the vitamin to be higher during space flight than on Earth. The antioxidant properties of vitamin E may help to counteract the free-radical damage caused by high linear energy transfer radiation in space. Pretreatment with antioxidants may help decrease radiation damage during missions (204).

Deficiency of vitamin E leads to neurological disorders, hemolytic anemia, retinopathy, and abnormal platelets and lymphocytes, or even death. Toxicity of vitamin E from naturally occurring sources has not been shown to occur.

Targeted research needed
The extramural expert panel recommended that vitamin E content of space foods, along with the stability of vitamin E in these foods, be determined.

Nominal requirement on Earth
The dietary reference intake for vitamin E is 15 mg/d for men and women. No upper limit has been established because the highest level of daily intake is not likely to pose serious health risks to the majority of individuals (202).

Historical space flight requirements
The space flight requirement for vitamin E, in tocopherol equivalents (TE), for males and females was defined as 20 mg TE/d (47, 48).

Requirements, standards, and operating bands
Req. 10. The dietary intake of vitamin E shall be 15 mg/day. The nominal operating bands are defined as

Dietary Vitamin E

	15 mg/d	green
	7.5-15 mg/d	yellow
	<7.5 mg/d	red

Initial verification that this requirement has been met will be done by proximate analysis of space food items for vitamin E content, as well as by analysis of the crew menus.

Standards will be assessed before, during (to the extent possible), and after flight by determining levels of α-tocopherol (86) in serum samples. Markers of oxidative status [total antioxidant capacity (205, 206), superoxide dismutase (205, 207, 208), glutathione peroxidase (207, 209-211) and antioxidant damage [8-hydroxy-2'-deoxyguanosine (212-214), malondialdehyde (215), 4-hydroxynonenal (216)] will also be measured.

The health benefits of γ-tocopherol (217) are unknown (as opposed to the well-studied α-tocopherol), but several studies suggest potential beneficial effects. Plasma γ-tocopherol was strongly and inversely correlated with risk of prostate cancer in men with the lowest quintile of γ-tocopherol (218). Other studies show lower γ-tocopherol concentrations in coronary heart disease patients compared with controls (219, 220). The low γ-tocopherol in these studies could be a secondary effect of the accompanying condition; therefore, until further research is done to conclusively determine primary effects of low serum γ-tocopherol, a critical level of γ-tocopherol will not be defined.

α-Tocopherol (serum)

	18 μg/mL	green
	5.5 μg/mL	yellow
	<3.0 μg/mL	red

γ-Tocopherol (serum)

	3.9 μg/mL	green
	0.47 μg/mL	yellow

Total Antioxidant Capacity

	1.77 mmol/L	green
	1.30 mmol/L	yellow
	<1.20 mmol/L	red

Superoxide Dismutase

	>1600 U/g Hgb	red
	1567 U/g Hgb	yellow
	1295 U/g Hgb	green
	1024 U/g Hgb	yellow
	<763 U/g Hgb	red

Glutathione Peroxidase

	88 U/g Hgb	green
	29 U/g Hgb	yellow
	<27.5 U/g Hgb	red

8-OH-2'-Deoxyguanosine

	0.17 μg/g creat	green
	5.9 μg/g creat	yellow
	>15μg/g creat	red

Malondialdehyde

	0 μmol/L	green
	3 μmol/L	yellow
	>5 μmol/L	red

4-Hydroxy-2(E)-nonenal

	<1 nmol/L	green
	2 nmol/L	yellow
	>4 nmol/L	red

Water-Soluble Vitamins

Vitamin C

Physiological function and existing space flight knowledge

The term "vitamin C" actually refers to two different compounds, both of which have anti-scorbutic activity: ascorbic acid and dehydroascorbic acid. Vitamin C functions as an antioxidant because it acts as a reducing agent for most physiologically relevant reactive oxygen species, reactive nitrogen species, singlet oxygen, and hypochlorite. It serves as a cofactor for enzymes involved in the biosynthesis of collagen, carnitine, and neurotransmitters. Vitamin C also provides antioxidant protection by returning α-tocopherol to its biologically active state during lipid oxidation. The reducing agents glutathione and either reduced nicotinamide adenine dinucleotide (NADH) or reduced nicotinamide adenine dinucleotide phosphate (NADPH) regenerate the oxidation products of ascorbate.

It has been suggested that vitamin C requirements should be greater in persons who are under excessive physical or emotional stress, given the role of ascorbate in the biosynthesis of steroid hormones and neurotransmitters. However, no substantial data show that vitamin C metabolism is altered in healthy subjects under mental or emotional stress (202).

One concern for space flight is the possibility that vitamin C could be degraded in foods during extended-duration missions when space foods are exposed to large amounts of radiation and undergo long-term storage (up to 5 years). The stability of vitamin C has been studied in food supplies, and it is generally unstable at a neutral or alkaline pH, or in high-oxygen environments (221). Vitamin C is also unstable when exposed to light or heat (221), and in irradiated foods (222, 223). Salem (223) found that gamma irradiation of fresh onion bulbs significantly reduced their vitamin C content. This group also found that vitamin C content of onion bulbs had decreased about 50% after 6 months of storage. The destructive effects of gamma-irradiation (10 kGy) on vitamin C are also evident in commercial spices such as basil, black pepper, cinnamon, nutmeg, oregano, parsley, rosemary, and sage (224). Gamma-ray exposure of these spices for >3 months resulted in a marked increase of quinone radicals.

Body stores and relative time to depletion

The total body pool of vitamin C varies with intake. Higher concentrations are found in the pituitary and adrenal glands, liver, spleen, heart, kidneys, lungs, pancreas, leukocytes, eye tissues and humors, and the brain, while lower concentrations are found in the saliva, muscle, and plasma. Blood cell and tissue concentrations become saturated at intakes from 100 to 140 mg/day, and steady-state plasma vitamin C concentrations occur with intakes of 200 mg/day. Catabolic turnover varies from 10 to 45 mg/day and with low intakes, turnover is reduced. Maximum body pools of ascorbate are ~2 grams.

Vitamin C deficiency most commonly presents itself as any of an array of symptoms commonly referred to as scurvy. Scurvy is seen in adults within 45 to 80 days of stopping vitamin C intake. Intake below the RDA can cause a deficiency once the body pools fall below ~300 mg of ascorbic acid. The length of time until scurvy symptoms develop when intake is sub-optimal depends on the size of the individual's body pool of vitamin C before intake was decreased.

Potential implications for flight

Free-radical formation is increased in space because greater amounts of radiation are present than on Earth. Because of this and increases in other oxidative stressors, antioxidants such as vitamin C are in greater demand by the body to act as buffers and minimize the oxidative damage. Studies have shown that supplementation with vitamin C and other antioxidants can modify human tissue radiosensitivity and protect DNA against damage (225, 226). Just as important to consider, however, is the possibility that vitamin C could induce DNA damage. Cai and colleagues (226) found that vitamin C can act as an antioxidant to prevent DNA damage caused by ionizing radiation, but in the presence of copper, it can also act as a reducing agent to induce DNA damage. Because vitamin C can reduce redox-active metals such as iron and copper, this "antioxidant" can increase the pro-oxidant chemistry of these metals (227). Thus, vitamin C can serve as both a pro-oxidant and an antioxidant.

Vitamin C assessments from the ISS have not been completed yet, but they will be available soon and may raise additional questions.

Deficiency of vitamin C leads to fatigue, depressed immune function, and ultimately scurvy (fatigue, muscle cramps, bruised and/or bleeding gums), or even death. Toxicity of vitamin C leads to gastrointestinal distress.

Targeted research needed

The extramural expert panel recommended that vitamin C levels and stability be determined in the space food supply. The panel also suggested that vitamin C supplementation during exposure to oxygen or high-LET radiation be investigated before making recommendations for supplement use during flight.

Nominal requirement on Earth

The RDAs for vitamin C for men and women aged 19 and older are 90 mg/day and 75 mg/day, respectively. They are set by assuming a coefficient of variation of 10 percent because information about the standard deviation is unavailable. The RDA is defined as equal to the estimated average requirement (EAR) plus twice the coefficient of variation, to cover the needs of at least 98% of the population (202).

Historical space flight requirements

Because of the increased level of stress predicted for orbiting crews, the requirement for vitamin C was initially defined as 100 mg/day for males and females (47, 48).

Requirements, standards, and operating bands

Req. 11. The dietary intake of vitamin C shall be 90 mg/day. The nominal operating bands are defined as

Dietary Vitamin C

	>2000 mg/d	red
	90 mg/d	green
	30-90 mg/d	yellow
	<30 mg/d	red

Initial verification that this requirement has been met will be done by proximate analysis of space food items for vitamin C content, as well as by analysis of the crew menus.

Standards will be assessed before, during (to the extent possible), and after flight by determining levels of vitamin C (228) in blood samples.

Vitamin C (serum)

	>96 µmol/L	red
	>85 µmol/L	yellow
	23-85 µmol/L	green
	<23 µmol/L	yellow
	<11 µmol/L	red

Vitamin B_{12}

Physiological function and existing space flight knowledge

Vitamin B_{12} functions as a coenzyme in two metabolic forms: adenosylcobalamin and methylcobalamin. Vitamin B_{12} works as a cofactor for 3 different enzymatic reactions: 1) the conversion of homocysteine to methionine, 2) the conversion of L-methylmalonyl-coenzyme A (CoA) to succinyl-CoA, and 3) the isomerization of L-leucine and ß-leucine. B_{12} deficiency may cause the accumulation of folate in the serum due to the reduction in B_{12}-dependent methyltransferase, also known as the methyl-folate trap (229). Vitamin B_{12} also functions in the synthesis of choline, which can be converted to the neurotransmitter acetylcholine.

No data are available on vitamin B_{12} status during or after long-duration space flight.

Body stores and relative time to depletion

Unlike other water-soluble vitamins, vitamin B_{12} can be stored in the body for years. The vitamin is stored predominantly in the liver, but smaller amounts can also be found in the muscles, kidneys, bones, heart, brain, and spleen. About 2–5 mg of vitamin B_{12} is stored (230). The size of B_{12} stores remains relatively stable, partly because urinary and fecal excretion decrease in direct relationship to decreases in the body pools.

The half-life of vitamin B_{12} is 350 to 400 days in humans (230).

Potential implications for flight

No evidence of toxicity has been found with vitamin B_{12} supplementation in amounts greater than the RDA (230). If a person went for many years without adequate intake and/or supplementation, body stores could be depleted. Other factors that could contribute to a vitamin B_{12} deficiency include a decrease in gastric acidity, the presence of atrophic gastritis, and bacterial overgrowth accompanied by malabsorption of food-bound B_{12} (231).

Deficiency of vitamin B_{12} leads to pernicious anemia or even death. However, no adverse effects are reported to be caused by an excess of vitamin B_{12}.

Targeted research needed

The extramural expert panel recommended that vitamin B_{12} levels and stability be determined in the space food supply.

Nominal requirement on Earth

The required amount of vitamin B_{12} for both men and women aged 19 years and older is 2.4 µg/day (230).

Historical space flight requirements

Intake of vitamin B_{12} was originally defined as 2.0 µg/day for males and females (23, 152).

Requirements, standards, and operating bands

Req. 12. The dietary intake of vitamin B_{12} shall be 2.4 μg/day. The nominal operating bands are defined as

Dietary Vitamin B12

	100 μg/d	red
	2.4 μg/d	green
	1.2-2.4 μg/d	yellow
	<1.2 μg/d	red

Initial verification that this requirement has been met will be done by proximate analysis of space food items for vitamin B_{12} content, as well as by analysis of the crew menus.

The extramural expert panel concluded that if dietary sources of vitamin B_{12} are adequate, definition of a standard to ensure that vitamin B_{12} requirements are met is unnecessary. Accordingly, no biochemical measures of vitamin B_{12} status are required for exploration missions.

Vitamin B_6

Physiological function and existing space flight knowledge

Vitamin B_6 comprises a group of three compounds and their 5′-phosphates (P): pyridoxal (PL) and PLP, pyridoxine (PN) and PNP, and pyridoxamine (PM) and PMP. These vitamers of B_6 serve as coenzymes in many transamination reactions by forming a Schiff's base with the ε-amino group of lysine and the carbonyl group of PLP (230, 232). They can also function in decarboxylation reactions, such as the formation of gamma-aminobutyric acid from glutamate and serotonin from 5-hydroxytryptophan, and they function in trans- and desulfhydration, where cysteine is synthesized from methionine and pyruvate is generated from cysteine, respectively. The vitamers also function in cleavage reactions, racemization of D- and L-amino acids, synthesis of multiple compounds, glycogen catabolism (where vitamin B_6 is required for the activity of glycogen phosphorylase), and steroid hormone action (where the vitamers decrease the actions of steroids) (233).

According to data from astronauts on 4- to 6-month space flights, no change occurs in red blood cell (RBC) transaminase activation (15). Plasma PLP has not been determined after long-duration space flight. Bed rest studies have demonstrated reductions in body pools of vitamin B_6, most likely related to loss of muscle mass (54).

Body stores and relative time to depletion

Approximately 80% of vitamin B_6 is stored in muscle tissue and 10% is stored in the liver, with the rest being stored in the plasma pool. Data from studies have shown that total body stores are about 1,000 μmol or 167 mg (230).

Overall body half-lives of the vitamers of vitamin B_6 are about 25 days (230, 234).

Potential implications for flight

Weightlessness has been shown to reduce the cross-sectional area of muscle fibers and is associated with a change from type I to type II muscle fibers (235). Since vitamin B_6 is stored mainly in muscle tissue, a decrease in muscle cross-sectional area could reduce the amount of the vitamin that is stored. A deficiency in vitamin B_6 causes a decrease in the synthesis of serotonin and catecholamines, which has been shown to be associated with depression (236).

Deficiency of vitamin B_6 leads to dermatitis, microcytic anemia, convulsions, altered mental status, hyperhomocysteinemia, or even death. Toxicity of vitamin B_6 leads to sensory neuropathy or even death.

Targeted research needed

The extramural expert panel recommended that vitamin B_6 levels and stability be determined in the space food supply. The panel also recommended that plasma PLP be added to the list of indicators used to determine B_6 status.

Nominal requirement on Earth
The vitamin B_6 requirement for all adults over age 19 years is 1.3 mg/day (230).

Historical space flight requirements
Intake of vitamin B_6 was originally defined as 2.0 mg/day for males and females (47, 48).

Requirements, standards, and operating bands
Req. 13. The dietary intake of vitamin B_6 shall be 1.7 mg/day. The nominal operating bands are defined as

Dietary Vitamin B6

	100 mg/d	red
	1.7 mg/d	green
	0.8-1.2 mg/d	yellow
	<0.8 mg/d	red

Initial verification that this requirement has been met will be determined by proximate analysis of space food items for vitamin B_6 content, as well as by analysis of the crew menus.

Standards will be assessed before, during (to the extent possible), and after flight by determining levels of RBC transaminase (85, 154, 237), urinary 4-pyridoxic acid (154), and plasma PLP (85, 153, 238).

RBC Transaminase

	>85% activation	red
	70% activation	yellow
	0% activation	green

4-Pyridoxic Acid (urine)

	>5.0 µmol/d	green
	3 µmol/d	yellow
	<1 µmol/d	red

PLP (plasma)

	>30 nmol/L	green
	20 nmol/L	yellow
	<20 nmol/L	red

Thiamin

Physiological function and existing space flight knowledge

Thiamin functions as a coenzyme in the metabolism of carbohydrates and branched-chain amino acids. The coenzyme form of thiamin, thiamin pyrophosphate (TPP), functions in the decarboxylation of pyruvate and α-ketoglutarate. Without these decarboxylations, synthesis of both adenosine triphosphate (ATP) and acetyl-CoA would be inhibited. TPP also functions as part of a major enzyme involved in the hexose monophosphate shunt, the pathway by which 6-carbon sugars are converted to pentoses and NADPH. Thiamin pyrophosphate is also believed to be involved in nerve conduction and nerve membrane function, although its role is not completely clear (233). Very little is known about thiamin status during space flight.

Body stores and relative time to depletion

Approximately 30 mg of thiamin is stored in the human body (230). About half of the body's thiamin is stored in the skeletal muscle, with the rest being stored in the heart, liver, kidney, and brain.

Thiamin in excess of tissue needs and storage capacity is excreted in the urine. The biological half-life of thiamin is in the range of 9 to 18 days.

Potential implications for flight

Thiamin deficiency first became prevalent in the 19th century in rice-growing countries when steam-powered rice mills were becoming more efficient. The milling process removed the aleurone layer that contained most of the rice's thiamin content. Beriberi, a polyneuritic paralysis that affects the lower limbs, was first characterized in these populations. This historical information illustrates the importance of every nutrient. A deficiency in one nutrient can be devastating. It is well known that thiamin is highly susceptible to destruction by radiation (239, 240) and processing in foods (241). It will be crucial to determine if thiamin can survive a 3-year-plus mission to deep space.

Deficiency of thiamin ultimately leads to beriberi (enlarged heart, muscle weakness, anorexia, apathy, reduction in nerve impulse transmission), or even death. There are no known toxicity symptoms of excess thiamin.

Targeted research needed

The extramural expert panel recommended that thiamin levels and stability be determined in the space food supply, particularly since thiamin is highly susceptible to degradation from radiation exposure.

Nominal requirement on Earth

The thiamin RDA is 1.2 mg/day for men aged 19 and older and 1.1 mg/day for women (230).

Historical space flight requirements

The daily thiamin intake was originally defined as 1.5 mg/day for males and females (47, 48).

Requirements, standards, and operating bands

Req. 14. The dietary intake of thiamin shall be 1.1 and 1.2 μmol/day for women and men, respectively. The nominal operating bands are defined as

Dietary Thiamin

	Women	Men	
	1.1 μmol/d	1.2 μmol/d	green
	0.8-1.0 μmol/d	0.8-1.0 μmol/d	yellow
	<0.8 μmol/d	<0.8 μmol/d	red

Initial verification that this requirement has been met will be done by proximate analysis of space food items for thiamin content, as well as by analysis of the crew menus.

Standards will be assessed before, during (to the extent possible), and after flight by determining levels of erythrocyte transketolase (ETK) (85)activation in blood samples.

RBC Transketolase (ETK)

	0% activation	green
	15% activation	yellow
	>25% activation	red

Riboflavin

Physiological function and existing space flight knowledge

The most important biologically active forms of riboflavin are flavin mononucleotide and flavin adenine dinucleotide (FAD). These cofactors participate in a range of redox reactions in numerous metabolic pathways (242). Some of these pathways are niacin-dependent and independent dehydrogenations, reactions with sulfur-containing compounds, hydroxylations, oxidative decarboxylations, dioxygenations, and reduction of oxygen to hydrogen peroxide. The cofactors also play a role in the formation and function of some vitamins, including folate, vitamin B_{12}, and vitamin B_6 (242).

There is no evidence that riboflavin status is altered during 4- to 6-month space flights (15).

Body stores and relative time to depletion

The highest concentrations of stored riboflavin are found in the liver, kidneys, and heart (230), and almost all riboflavin in tissues is enzyme-bound, such as FAD covalently bound to succinic dehydrogenase (243). Unbound flavins are labile and are rapidly hydrolyzed to release free riboflavin. Excess free riboflavin is excreted in the urine (242).

The total body stores of riboflavin are enough to meet the demands of the body for 2 to 6 weeks (230).

Potential implications for flight

There is no evidence that riboflavin status is altered during 4- to 6-month space flights (15); however, riboflavin content in the space food supply needs to be investigated to ensure that riboflavin will not degrade during long-duration storage. Riboflavin is relatively heat-stable, but it is readily degraded by light (242, 244). It does not seem to be degraded by gamma-radiation of foods (240, 245).

Riboflavin deficiency affects ferritin iron mobilization and iron absorption. Other symptoms of riboflavin deficiency include peripheral nerve demyelination, neurologic abnormalities, and anemia. Cataract incidence is higher in space travelers than the general population (246), and cataracts have also been described in riboflavin-deficient animal models (242, 247).

No toxicity symptoms of excess riboflavin are known.

Targeted research needed

The extramural expert panel recommended that riboflavin content and stability be determined in the space food supply.

Nominal requirement on Earth
The RDA for riboflavin for men and women aged 19 and older is 1.3 and 1.1 mg/day, respectively (230).

Historical space flight requirements
The daily requirement for riboflavin was defined as 2.0 mg/day for males and females (47, 48).

Requirements, standards, and operating bands
Req. 15. The dietary intake of riboflavin shall be 1.3 mg/day. The nominal operating bands are defined as

Dietary Riboflavin

	1.3 mg/d	green
	1.0 mg/d	yellow
	<0.8 mg/d	red

Initial verification that this requirement has been met will be done by proximate analysis of space food items for riboflavin content, as well as by analysis of the crew menus.

Standards will be assessed before, during (to the extent possible), and after flight by determining levels of erythrocyte glutathione reductase (EGR) (85) activation in blood samples.

RBC Glutathione Reductase (EGR)

	0% activation	green
	20% activation	yellow
	40% activation	red

Folate

Physiological function and existing space flight knowledge

Folate is the general term used to describe folic acid and other compounds that have activity similar to that of folic acid. Folic acid is the form of the vitamin used in vitamin supplements and fortified food products, but it is rarely found to occur naturally in food.

Folate is in its active form when folic acid and dihydrofolate are reduced by a cytosolic enzyme to generate tetrahydrofolate (THF). THF accepts single-carbon groups from reactions in amino acid metabolism to form derivatives of THF. These THF derivatives function in amino acid metabolism in the reversible reaction of serine synthesis from glycine, methionine synthesis from homocysteine, and histidine metabolism. Folate is essential in cell division because the THF derivatives play important roles in purine and pyrimidine synthesis. THF derivatives play a major role in the formation of thymidylate, which is a substrate needed for DNA synthesis.

It is evident from previous long-duration space flight research (4 to 6 months) that folate status decreases significantly (15). It is unknown whether this is related to the food, the stability of folate in food during flight, or alterations in absorption, metabolism, or excretion.

Body stores and relative time to depletion

About 50% of all folate is stored in the liver. The average liver concentration of folate is about 8 μg/g (248). Estimated total body folate stores are between 12 and 28 mg (230). Very little folate is excreted in the urine or feces. Most of the absorbed folate is secreted by the liver into the bile, which is then reabsorbed through enterohepatic recirculation. Most of the folate excreted in feces is synthesized by intestinal bacteria.

Low folate intake will cause red blood cell folate concentrations to diminish within 4 months. Bone marrow cells become megaloblastic and anemia occurs after 4 to 5 months of low folate intake (233). As outlined in **Figures 1 and 2**, folate deficiency in humans has 4 stages (249, 250):

> *Stage 1*: Early negative balance is accompanied by serum folate <3.5 ng/mL.
>
> *Stage 2*: Serum folate continues to be low, and RBC folate decreases to below 160 ng/mL.
>
> *Stage 3*: Defective DNA synthesis can be detected. Deoxyuridine (dU) suppression tests are abnormal, and homocysteine levels are elevated.
>
> *Stage 4*: Clinical folate deficiency is manifested by macroovalocytosis, elevated mean corpuscular volume (MCV), and large, nucleated embryonic cells

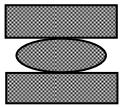
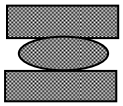
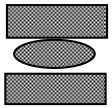
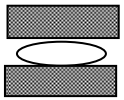
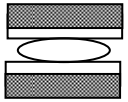
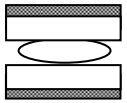
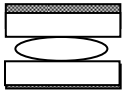
				Negative Balance			
	Positive balance		Normal	Depletion		Deficiency	
	Stage II	**Stage I**		**Stage I**	**Stage II**	**Stage III**	**Stage IV**
	Excess	Early positive folate balance	Normal	Early negative folate balance	Folate depletion	Metabolic damage: folate deficiency erythropoiesis	Clinical damage: folate deficiency anemia
Liver folate **Plasma folate** **Erythron folate**							
Serum folate	>10	>10	>5	<3	<3	<3	<3
RBC folate	>400	>300	>200	>200	<160	<120	<100
Diagnostic dU suppression	Normal	Normal	Normal	Normal	Normal	Abnormal	Abnormal
Liver folate	>5	>4	>3	>3	<1.6	<1.2	<1
Homocysteine	Normal	Normal	Normal	Normal	Normal	High	High
Eythrocytes	Normal	Normal	Normal	Normal	Normal	Normal	Macroovalocytic
MCV	Normal	Normal	Normal	Normal	Normal	Normal	Increased
Hemoglobin	>12	>12	>12	>12	>12	>12	<12
Plasma clearance of intravenous folate	Normal	Normal	Normal	Normal	Normal	Increased	Increased

Figure 1. Sequence of events in developing folate deficiency. Earliest abnormalities are boxed. Adapted from Herbert 1999 (250).

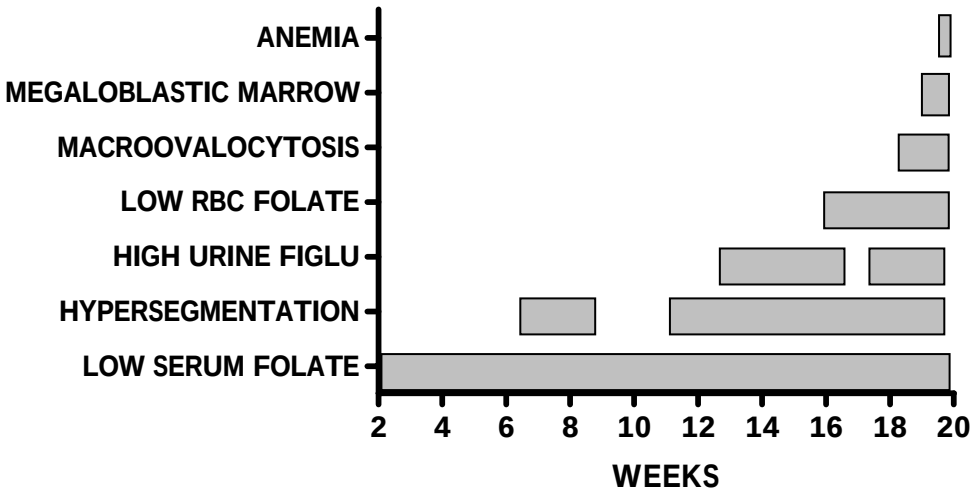


Figure 2. Biochemical sequence of events in developing dietary folate deficiency in humans (adapted from Herbert (250)). FIGLU is formiminoglutamic acid.

Potential implications for flight

It has been suggested that folate may influence the metabolism of certain neurotransmitters. Folate deficiency is associated with irritability, forgetfulness, and hostile or paranoid behavior (250). Radiation exposure and inadequate dietary consumption can lead to inadequate intake of folate (230).

Deficiency of folate leads to megaloblastic anemia or even death. The upper limit of folate is set because very high doses of folate can mask a deficiency of vitamin B_{12}.

Targeted research needed

The extramural expert panel recommended that folate levels in the space food system be determined. If the diet does in fact provide 400 μg/d, then they recommended that further research be done to understand the stability of folate during radiation exposure.

Nominal requirement on Earth

The RDA for all individuals aged 14 and older is 400 μg/day of dietary folate equivalents (DFEs). Using DFEs adjusts for the 50% reduction in food folate bioavailability compared to that of folic acid. 1 μg/d DFE = 0.6 μg of folic acid from fortified food or as a supplement taken with meals = 1 μg food folate = 0.5 μg of a supplement taken on an empty stomach.

Historical space flight requirements

Intake of folate was defined as 400 μg/day for males and females (47, 48).

Requirements, standards, and operating bands

Req. 16. The dietary intake of folate shall be 400 μg/day. The nominal operating bands are defined as

Dietary Folate

	1000 μg/d	red
	400 μg/d	green
	200 μg/d	yellow
	<200 μg/d	red

Initial verification that this requirement has been met will be done by proximate analysis of space food items for folate content, as well as by analysis of the crew menus.

Standards will be assessed before, during (to the extent possible), and after flight by determining serum (154, 251) and RBC folate (86, 154) in blood samples.

Folate (RBC)

	600 ng/mL	green
	150 ng/mL	yellow
	<140 ng/mL	red

Folate (serum)

	5.4-40 ng/mL	green
	3.4-5.3 ng/mL	yellow
	<3.3 ng/mL	red

Niacin

Physiological function and existing space flight knowledge

The term "niacin" includes nicotinamide, nicotinic acid, and their derivatives that have the biological activity of nicotinamide (230). In its coenzyme forms, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), niacin has many different metabolic roles in the human body. The nicotinamide moiety accepts hydride ions in numerous biological redox reactions. NAD functions in respiration and as a co-dehydrogenase with enzymes involved in the oxidation of fuel molecules. NAD is converted to NADH, which transfers electrons from the Krebs cycle through the electron transport chain. NAD also acts as a donor of adenine dinucleotide phosphate-ribose for the posttranslational modification of proteins (233). The coenzyme NADP has a role in fatty acid, cholesterol, and steroid syntheses, and as a co-dehydrogenase in the pentose phosphate pathway. Conversion of folate to its active forms also requires NADP.

Very little is known about niacin metabolism during space flight. One concern for exploration missions is the stability of niacin in the food system, particularly because of reports showing that the niacin content of foods decreases after exposure to 6 kGy of radiation (252).

Body stores and relative time to depletion

Niacin is stored in the liver as NAD. This storage NAD can be converted from tryptophan, nicotinic acid, or plasma nicotinamide.

Limited data show that after 80 to 135 days of ingesting a low-niacin diet, subjects' urinary excretion of N^1-methylnicotinamide is at a level representing deficiency status (251).

Potential implications for flight

Niacin in the amount of 3 g/day or more has been associated with toxic effects (230). Flushing, gastrointestinal problems, hepatotoxicity, glucose intolerance, and ocular effects have all been associated with high doses of the vitamin. However, many of these toxic effects have been shown to occur only after treatment over long periods and in amounts that far exceed the RDA.

Deficiency of niacin leads to dermatitis, glossitis, growth retardation, and ultimately pellagra (diarrhea, dermatitis, dementia), or even death. Likewise, toxicity from mega doses of niacin can cause vasodilatory effects (flushing), gastrointestinal distress, hepatotoxicity, glucose intolerance, and blurred vision.

Targeted research needed

The extramural expert panel recommended that niacin levels and stability be determined in the space food supply.

Nominal requirement on Earth

The niacin requirement for men aged 19 and older is 16 mg/day of niacin equivalents and for women aged 19 and older the requirement is 14 mg/day of niacin equivalents (230). One niacin equivalent is equal to approximately 60 mg of the amino acid tryptophan and can be obtained from 6 grams of high-quality protein (233). The RDA for niacin can be met from the actual niacin content of the diet or by conversion of tryptophan in the diet.

Historical space flight requirements

Intake of niacin was defined as 20 mg NE/day for men and women (NE = niacin equivalent; 1 NE = 1 mg niacin or 60 mg dietary tryptophan) (47, 48).

Requirements, standards, and operating bands

Req. 17. Based on the current recommendations for Earth (230), the dietary intake of niacin shall be 16 mg NE/day. The nominal operating bands are defined as

Dietary Niacin

	35 mg NE/d	red
	16 mg NE/d	green
	12 mg NE/d	yellow
	<12 mg NE/d	red

Initial verification that this requirement has been met will be done by proximate analysis of food items for niacin content, as well as by analysis of the crew menus.

Standards will be assessed before, during (to the extent possible), and after flight by determining levels of NAD/NADP (85), N^1-methylnicotinamide (153, 251), and 2-pyridone (154) in blood and urine samples.

Erythrocyte NAD/NADP

	>1.5	green
	1	yellow
	<1	red

N^1-methyl Nicotinamide (urine)

	46.7 µmol/d	green
	17.5 µmol/d	yellow
	<5.8 µmol/d	red

2-Pyridone (urine)

	>4.0 mg/g creatinine	green
	2.0 mg/g creatinine	yellow
	<2.0 mg/g creatinine	red

Biotin

Physiological function and existing space flight knowledge

Biotin is a required cofactor for pyruvate carboxylase, acetyl-CoA carboxylase isoforms 1 and 2, propionyl-CoA carboxylase, and β-methylcrotonyl-CoA carboxylase. The five biotin-dependent enzymes are involved in carbohydrate, fatty acid, and amino acid metabolism.

No data currently exist regarding biotin intake or status during or after space flight.

Body stores and relative time to depletion

Biotin exists freely or bound to proteins. Approximately 81% of biotin in the human body is free biotin in serum, and 10% is free in tissues (253).

Low-biotin diets administered to 10 healthy subjects who also consumed large amounts of avidin (an egg-white protein that binds biotin very tightly) showed signs of decreased biotin status by the third day (254). Urinary excretion of biotin and its metabolites decreased significantly and urinary excretion of 3-hydroxyisovaleric acid increased significantly after 3 d; however, these decreases were not out of the normal range until days 7 and 17, respectively. Serum biotin did not decrease significantly, and it was suggested that serum biotin is not an early and sensitive indicator of marginal biotin deficiency (255). Animal studies indicate that a biotin deficiency, marked by urinary biotin excretion, generally occurs about 2 to 3 weeks after beginning consumption of a biotin-free diet (256, 257).

Potential implications for flight

Despite the observation that frank signs of deficiency are rare, there is growing appreciation of genetic, physiologic, and pharmacologic conditions that marginally impair biotin status (258-260). This suggests that the lack of physiologic manifestations of biotin deficiency may not be a reliable measure to gauge biotin status. Marginal changes in biotin status have been shown to affect a range of metabolic factors, from carboxylase activity to the expression of non-biotin-dependent enzymes such as glucokinase, ornithine transcarbamoylase, and phosphoenolpyruvate carboxykinase (261-263).

Frank biotin deficiencies are associated with neurological and dermatological manifestations, which are likely caused by the loss of function of biotin-dependent enzymes. Seizures, hearing loss, optic atrophy, dermatitis, and aciduria (associated with elevated blood concentrations of organic acids) are common symptoms of a frank biotin deficiency.

There is no evidence of toxicity of biotin at high intake levels.

Targeted research needed
The extramural expert panel recommended that biotin levels in the space food system be determined. The lack of data on biotin status, and the fact that gastrointestinal changes during space flight may lead to changes in microbial synthesis of biotin, warrant further study. Furthermore, the interaction of biotin with some pharmacological agents (such as phenobarbital) included in the medical kit supplied to astronauts during space flight has been shown to yield biotin deficiencies in other populations (259).

Nominal requirement on Earth
The dietary reference intake for biotin has been based only on adequate intake (AI) data (251). To date, no RDA has been reported for biotin due to lack of data and a general consensus that colonic bacteria synthesize biotin that contributes to the daily supply. Because microbial synthesis of biotin takes place in the lower part of the intestine, where nutrient absorption is limited, controversy exists about how much of the biotin produced by colonic bacteria is available for host metabolism. The AI for adults is extrapolated from the AI for healthy infants consuming breast milk, and has been determined to be 30 μg/d for men and women >19 years. No upper limit has been set for biotin because of lack of symptoms of biotin toxicity when it is administered at high doses.

Historical space flight requirements
Intake of biotin was defined as 100 μg/day for males and females (47, 48).

Requirements, standards, and operating bands
Req. 18. The dietary intake of biotin shall be 30 μg/day. The nominal operating bands are defined as

Dietary Biotin

	30 μg/d	green
	10 μg/d	yellow
	<10 μg/d	red

Initial verification that this requirement has been met will be done by proximate analysis of space food items for biotin content, as well as by analysis of the crew menus.

The extramural expert panel concluded that if dietary sources of biotin are adequate, definition of a standard to ensure that biotin requirements are met is unnecessary. Accordingly, no biochemical measures of biotin status are required for exploration missions.

Pantothenic Acid

Physiological function and existing space flight knowledge

The primary function of pantothenic acid is in its role as a precursor of coenzyme A (CoA) and as a component of acyl carrier protein (ACP). Pantothenic acid, in the form of CoA and ACP, is required for numerous lipid, carbohydrate, and protein metabolic reactions. CoA is necessary for acetyl and acyl transfer reactions associated with catabolism, and it acts as a precursor to ACP. ACP is a coenzyme in fatty acid synthase complex.

No data regarding pantothenic acid intake or status during or after space flight are currently available.

Body stores and relative time to depletion

Free pantothenic acid is found in various parts of the body: 10–15 μmol/L in the liver, ~100 μmol/L in the heart, 1–5 μmol/L in plasma, 50–100 μmol/L as CoA, and 10 μmol/L as ACP. About 70%–90% of CoA is found in the mitochondria. Any excess pantothenic acid is excreted in urine. (264)

Since pantothenic acid is widely distributed in foods, deficiencies are reported only in cases where semisynthetic diets or antagonists to the vitamin were used. Individuals became deficient after 63 days on a diet virtually devoid of the vitamin (265).

Potential implications for flight

No space flight data are available to determine effects of microgravity on pantothenic acid status. It is also unknown whether conditions of long-term space flight (such as extended storage time and exposure to high-LET radiation) will affect the stability of pantothenic acid in the food supply. The stability of pantothenic acid under these conditions will have to be determined in order to minimize risk for pantothenic acid deficiency symptoms.

Deficiency of pantothenic acid leads to dermatologic manifestations and neurological, immunological, hematological, reproductive, and gastrointestinal symptoms.

There is no conclusive evidence that adverse effects occur from high intakes of pantothenic acid.

Targeted research needed

The extramural expert panel recommended that pantothenic acid levels in the space food system be determined.

Nominal requirement on Earth

The dietary reference intake for pantothenic acid has been based only on adequate intake (AI) data (251). No RDA has been reported for pantothenic acid. The AI for adults is based on mean intakes and is 5 mg/d for men and women >19 years. No

upper limit has been reported for pantothenic acid, but doses of the vitamin as high as 10–20 g/d have been well tolerated with occasional diarrhea reported (264). Since pantothenic acid is required in numerous metabolic reactions, deficiency of the vitamin can cause neurological, immunological, hematological, reproductive, and gastrointestinal dysfunctions. Specific symptoms include dermatitis, growth retardation, numbness and burning of hands and feet, impaired antibody production, headache, fatigue, insomnia, increased sensitivity to insulin, and intestinal disturbances. Pantothenic acid deficiency is rare because of its presence in a wide variety of foods of both plant and animal origin. Deficiency of the vitamin is frequently associated with multi-nutrient deficiencies, making it difficult to detect specific symptoms of pantothenic acid deficiency.

Historical space flight requirements

Intake of pantothenic acid was defined as 5 mg/day for males and females (266).

Requirements, standards, and operating bands

Req. 19. The dietary intake of pantothenic acid shall be 30 mg/day. The nominal operating bands are defined as

Dietary Pantothenic Acid

	30 mg/d	yellow
	5 mg/d	green
	1 mg/d	yellow
	<1 mg/d	red

Initial verification that this requirement has been met will be done by proximate analysis of space food items for pantothenic acid content, as well as by analysis of the crew menus.

The panel concluded that if dietary sources of pantothenic acid are adequate, definition of a standard to ensure that pantothenic acid requirements are met is unnecessary. Accordingly, no biochemical measures of pantothenic acid status are required for exploration missions.

Minerals

Calcium

Physiological function and existing space flight knowledge

Calcium is critical for maintaining the body's structural and mechanical functions, and it makes up 37%–40% of the bone mineral hydroxyapatite in the body (267). In addition to its obvious role in the musculoskeletal system, calcium also has a critical role in modulating the function of important proteins and regulation of metabolic processes. Calcium binding is responsible for the activation of a wide range of proteins, including those involved in cell motility, blood coagulation, muscle contraction, neural transmission, glandular secretion, and cell division (154, 268). Circulating calcium levels are under tight control and are maintained within a narrow range (269).

Bone loss is one of the main health concerns of long-duration space flight (270). It is estimated that the rate of bone mineral loss during space flight is about 0.5%–1% per month (135, 271, 272). During the 84-d Skylab 4 mission, calcium balance was –200 mg/d (51, 273), but no significant calcium losses occurred during the 28-d Skylab 2 mission (135, 274). The Skylab studies showed that during space flight, bone mineral is not uniformly lost from all parts of the skeleton. Loss of bone tissue is most profound in weight-bearing bones such as the *os calcis*. Of the 3 men aboard the 59-day Skylab 3 mission, 1 lost a significant amount of *os calcis* bone mineral (–7.4%) but the other 2 did not (+2.3% and +1.4 %). Calcium excretion in the urine was 200% of the preflight value for the man who lost *os calcis* and 50% of the preflight values for the other 2 men (274).

The ability to understand and counteract weightlessness-induced bone loss will be critical for crew health and safety during and after extended-duration space station and exploration missions (275-278). As a result of skeletal unloading during flight (274, 279-283), bone mineral is lost, leading to increased urinary excretion of calcium (51, 274, 282). The bone loss and an increased risk of renal-stone formation during and after flight (148, 149) are significant. Inflight and ground-based analog studies have shown that the loss of calcium from bones varies between sites in the same subject, and that the nature and degree of loss over time varies between subjects (279, 284). Long-term follow-up data on bone recovery are lacking (285).

Negative calcium balance was observed during the Skylab (30, 51, 274, 282, 286, 287) and Mir (12, 179) missions. Increased urinary and fecal calcium excretion accounted for most of the deficit (12, 30, 51, 148, 179, 274, 282, 287). During the Skylab 4 mission, calcium losses correlated roughly with mineral losses in the os calcis (288) and increases in the excretion of hydroxyproline.

If the rate of bone calcium loss is constant throughout a flight (a reasonable assumption judging by collagen crosslink excretion data (12, 179, 289), then about 250 mg of bone calcium are lost per day (12, 51, 179, 290). The rate of postflight

recovery, also if assumed to be constant (reasonable according to ground-based (284) and flight (12, 179) data), is approximately +100 mg/d (12, 179). By these estimates, on flights up to about 6 months, it will take 2 to 3 times the mission duration to recover the lost bone. For longer flights, however, the usefulness of these assumptions comes into question as space flight data are not available. Although more data clearly are required to validate this hypothesis, it nevertheless has significant implications as mission durations increase. For planetary missions, the ability of a terrestrial partial *g* force (such as Mars' 0.38 *g*) to reduce bone loss, or even begin recovery, is unknown. Although no data on partial *g* responses are available, the general consensus among investigators is that forces less than 0.5 *g* are likely to be of little value.

Bone resorption increases during space flight, as shown by the concentrations of bone markers (289, 291, 292) and by the results of calcium tracer kinetic studies (12, 179). Urinary hydroxyproline was elevated 33% after 84 days of flight (51, 61). Urinary collagen crosslinks, also markers of bone resorption, were elevated >100% during space flight compared to preflight levels (12, 289). Calcium tracer kinetic data indicated that bone resorption increased about 50% during flight (12).

Bone formation either remains unchanged or decreases during space flight (12, 135, 179). As indicated by serum concentrations of bone-specific alkaline phosphatase and osteocalcin, bone formation was unchanged during Mir flights, but increased 2 to 3 months after landing (12, 179). Trends toward decreased levels of bone formation markers were noted in 2 Mir studies with 1 subject each (291, 292). Studies, using calcium tracer techniques, of bone formation in 3 Mir crew members (12, 179) were equivocal (formation unchanged or decreased).

Together, increased resorption and decreased or unchanged formation yield an overall negative calcium balance (12, 179). A number of related factors likely contribute to the loss of bone mineral during weightlessness. Decreased calcium absorption has been observed among Mir astronauts (12, 179), which likely resulted from the decreased concentration of circulating 1,25-dihydroxyvitamin D that was also observed in these crew members (12, 179).

Space flight analog studies (such as bed rest) with humans have shown qualitative effects on bone and calcium homeostasis similar to those shown in flight studies, with quantitative effects generally showing reductions. These include loss of bone mass (284, 293, 294), decreased calcium absorption (295), increased urinary calcium (282, 295-302), increased risk of renal stone formation (299, 300), and decreased serum concentrations of parathyroid hormone (180, 297) and 1,25-dihydroxyvitamin D (180, 295, 297, 303).

Bone resorption increases during bed rest, as measured by histomorphometry (294, 304) or biochemical markers of bone metabolism. Hydroxyproline excretion of bed-rest subjects (295) is elevated. Collagen crosslink excretion during bed rest (289, 295) is elevated about 50% above control levels, compared with the greater than 100%

increase during flight (12, 289). These data suggest that bed rest, although it is an analog of space flight, may not result in the same magnitude of bone changes.

According to histomorphometry data from bone biopsies, bone formation decreases during bed rest (294, 297, 304), but the concentrations of biochemical markers (180, 293, 295) indicate that it is unchanged. This difference likely reflects the difference between site-specific (biopsy) and systemic (biochemical markers) indices of bone formation. After ambulation following bed rest, bone formation is generally increased (293, 295).

Bone loss and altered calcium metabolism occur in paralyzed individuals (as reviewed by (305), and there are a number of similarities between these changes and those associated with space flight (306-309). Although the loss of bone that occurs after spinal cord injury seems to stabilize after about 25 weeks (310), studies of bone metabolism have not been possible during space missions of this duration, and the limited postflight bone assessment does not allow determination of the rate of loss.

Changes in the endocrine regulation of bone metabolism seem to reflect adaptation to the weightless environment. Decreases in calcium absorption and plasma levels of parathyroid hormone and 1,25-dihydroxyvitamin D are expected physiological responses to increased resorption of bone that may occur as the body adapts to an environment in which bones bear less weight. This evidence, and the lack of improvement provided by earlier dietary countermeasures, indicate that supplemental nutrients such as calcium and vitamin D will not correct this problem (311). Adequate nutrition will, however, be a required component in the success of whatever countermeasures are identified and implemented (276, 312).

Body stores and relative time to depletion

Bone acts as the body's reserve for calcium. Total skeletal calcium is on average 1100–1500 g, and inadequate calcium intakes have significant impact on adult bone (165). About 1% of the body's calcium stores resides in the intracellular structures, cell membranes, and extracellular fluids (154).

Calcium depletion is not uncommon in many subgroups of the population. During acute starvation, urinary calcium remains constant; the largest amounts of calcium loss occur in feces, with much of the mineral lost apparently coming from bone (139). Gamble et al. (1923) (140) examined blood mineral concentrations in children during acute starvation and showed that calcium levels did not change after 4 days of fasting. Studies in dogs and cats indicate that significant changes occur only when more than 35% of body mass is lost (313). Blood calcium levels after chronic semi-starvation are variable, but most studies indicate that plasma or serum calcium levels decrease (139). Controlled calcium balance studies during semi-starvation provide more variable results, with individual calcium balances ranging from positive to negative (139).

Calcium absorption may be decreased in a variety of disease states, including Crohn's disease, diabetes, chronic renal failure, and malabsorption syndromes (154). Although the daily calcium intake requirement rises with age, many of the elderly and other population groups have inadequate intakes. Assessment of calcium deficiency by clinical laboratory analyses is difficult because circulating calcium is tightly regulated over a wide range of intakes (154). Imaging techniques (such as dual-energy X-ray absorptiometry and quantitative computed tomography) that enable determination of bone mineral content may provide a good indicator of long-term calcium nutritional status.

Deficiency of calcium leads to reduced bone mass and osteoporosis. An excess of calcium leads to kidney stones, hypercalcemia, and ultimately renal insufficiency or even death. Intakes up to 2500 mg/d are considered safe under normal conditions (154).

Potential implications for flight

The effect of near-weightlessness on the human skeletal system is one of the greatest concerns in safely extending space missions (186, 270). Adequate intake of dietary calcium will be critical for maintaining skeletal health. Both dietary protein (amount and type) and dietary sodium affect calcium metabolism. In addition, the use of pharmacological countermeasures may have implications for calcium homeostasis. Specifically, the bisphosphonates exert their effects by inhibiting osteoclast-mediated bone resorption, lowering serum calcium in subjects who are normocalcemic or hypercalcemic (314). It is recommended that subjects receiving bisphosphonates have adequate vitamin D status before therapy, and that their calcium status be monitored (315-317).

Although it is unlikely that diet is solely responsible for the bone mineral loss associated with space flight, even modest protective effects from a balanced diet would benefit crew health. Using diet modification as a countermeasure has several advantages, including no additional costs and no additional time required by astronauts during flight. Maintaining a diet balanced in acid and base precursors would involve food choices, and could be done with the help of a dietitian planning the menus. The ratio of acid and base precursors in the diet could be an important predictor for the extent of bone loss during space flight, and could be determined from the menu choices before flight. Furthermore, until inflight resources for research are available, a pre- and postflight investigation of the relationship between diet and bone metabolism could provide a basis for defining optimal nutritional recommendations during recovery after space flight.

Targeted research needed

To determine calcium requirements for long-duration space flight, it will be necessary to define the mechanisms by which calcium metabolism is altered during flight. Critical questions, including those addressing differences in calcium absorption during space flight (Risk #1: Accelerated Bone Loss and Fracture Risk; Research and Technology Question 1h: does the hypogravity environment change the nutritional requirements for optimal bone health? and Risk #16: Inadequate Nutrition; Research and Technology Question 16c: what are the decrements in nutritional status due to long term LEO, lunar, and exploration missions?), need to be addressed.

Nominal requirement on Earth

The dietary recommendations for calcium are provided as AIs, and the current Earth-based daily recommendation for the astronaut population is 1000 mg for men and women under age 50 y and 1200 mg for men and women 51 y and older (187).

Historical space flight requirements

The daily calcium requirements for male and female astronauts were defined as follows:

Missions of 30–120 days:	800–1200 mg (47)
Missions up to 360 days:	1000–1200 mg (48)

Requirements, standards, and operating bands

Req. 20. The dietary intake of calcium shall be 1200–2000 mg/day. The nominal operating bands are defined as

Dietary Calcium

	>2500 mg/d	red
	2000-2500 mg/d	yellow
	1200-2000 mg/d	green
	1000-1200 mg/d	yellow
	<1000 mg/d	red

Initial verification that this requirement has been met will be done by proximate analysis of space food items for calcium content, as well as by analysis of the crew menus.

Standards will be assessed before, during (to the extent possible), and after flight by determining levels of bone-specific alkaline phosphatase (BSAP)(318-320), intact parathyroid hormone (153, 321), calcium (85, 86, 100), n-telopeptide (NTX) (153), helical peptide (HP)(322), deoxypyridinoline (DPD) (323), osteocalcin (total (324) and undercarboxylated (197-199) (325-327), serum calcium (100), and ionized calcium (84, 153) in biological samples. Helical peptide is a new marker of bone resorption, and a sensitive indicator for bone resorption, but full evaluations on normal reference ranges (particularly for men) have yet to be published.

There is clear within-subject evidence that a 2-fold increase in bone marker excretion is associated with a high rate of bone loss (328-330). Because the bone resorption markers have considerable within- and between-subject variability, and because their concentrations are affected by the type of urine collection (such as single void or 24-hour pool) (331), it is important to collect appropriate sample types (e.g., 24-h pools) and to evaluate within-subject changes as well as changes in the group of subjects compared with population means. The operating bands presented below are based on available normal ranges (153, 322, 323) and serve as a useful guide; however, it may be more important to observe changes in a given subject.

Serum Intact PTH

	>100 pg/mL	red
	100 pg/mL	yellow
	65 pg/mL	green
	10 pg/mL	yellow
	<50 pg/mL*	red

*Hypoparathyroidism is defined as intact PTH <50 pg/mL and serum calcium <8mg/dL.

Urinary Calcium

	>350 mg/d	red
	240 mg/d	yellow
	100 mg/d	green

Serum Calcium

	>13.0 mg/dL	red
	10.5 mg/dL	yellow
	8.6 mg/dL	green
	6.0 mg/dL	yellow
	<6.0 mg/dL	red

Urinary NTX

	Women PreMenopause	Women PostMenopause	Men	
	>130 nmol/mmol creat*	>250 nmol/mmol creat	>200 nmol/mmol creat	red
	65 nmol/mmol creat	124 nmol/mmol creat	>86 nmol/mmol creat	yellow
	5 nmol/mmol creat	26 nmol/mmol creat	<86 nmol/mmol creat	green

* creat = creatinine.

Urinary Helical Peptide

	Women PreMenopause	Women PostMenopause/Men	
	>200 µg/mmol creat	>200 µg/mmol creat	red
	200 µg/mmol creat	200 µg/mmol creat	yellow
	<50 µg/mmol creat	<100 µg/mmol creat	green

Urinary DPD

	Women	Men	
	>15 nmol/mmol creat	>15 nmol/mmol creat	red
	7.4 nmol/mmol creat	5.4 nmol/mmol creat	yellow
	3 nmol/mmol creat	2.3 nmol/mmol creat	green

Serum Osteocalcin (total)

	>19.8 ng/mL	red
	19.8 ng/mL	yellow
	12.8 ng/mL	green
	6.4 ng/mL	yellow
	< 5 ng/mL	red

Serum Osteocalcin (undercarboxylated)

	10 %	green
	30 %	yellow
	>70%	red

Serum BSAP

	Women	Men	
	>46 U/L	>51 U/L	red
	42.7 U/L	51 U/L	yellow
	30.6 U/L	41.3 U/L	green
	14.2 U/L	15 U/L	yellow
	<11.6 U/L	<15 U/L	red

Whole Blood Ionized Calcium

	>1.45	red
	1.32-1.45	yellow
	1.12-1.32 mmol/L	green
	1.07-1.12 mmol/L	yellow
	<1.07 mmol/L	red

Phosphorus

Physiological function and existing space flight knowledge

Phosphorus is an important component of cell membranes and bone mineral. It is a critical element of most enzymes, cellular messengers, and carbohydrate fuels. Osteomalacia, a defect in bone mineralization, often occurs as a result of long-term phosphorus deficiencies. Inadequate intake of phosphorus can cause the release of calcium from bone, a reduction in chemotactic, phagocytic, and bactericidal properties of granulocytes, and cardiomyopathy (332). Excessive phosphorus intake has been shown to affect calcium absorption by increasing endogenous calcium excretion in the feces (333).

Long-duration space flight data show that urinary phosphorus concentrations are about 45% less after landing than before launch (15).

Body stores and relative time to depletion

Phosphate accounts for about 60% of bone mineral (267), and most (80%) of the body's extracellular phosphorus is present in the bone as hydroxyapatite (332).

Human studies show that phosphorus can be depleted by daily antacid treatment with either magnesium-aluminum hydroxide (60 mL, 4 times per day) or aluminum hydroxide (30 mL, 4 times per day) (334). Serum calcium of these subjects was elevated within 12 days of treatment, and by day 20 phosphorus balance was negative (334).

Animal studies have shown that symptoms of a phosphorus deficiency occur after 11 days on a low-phosphorus diet. Twelve hours after growing pigs had started consuming an experimental low-phosphorus diet, a marked fall occurred in their growth rate, plasma phosphorus, plasma growth hormone, and renal 24-hydroxylase activity levels (335). Additional animal studies have demonstrated that the removal of phosphate from the diet rapidly produces hypercalcemia, hypercalciuria, and hypophosphaturia. Rats fed a low-phosphate diet showed signs of deficiency after 11 days (336).

Potential implications for flight

Adequate phosphorus intake before and during flight will be critical for preserving bone quality and quantity. In addition, calcium:phosphorus ratios greater than 1.5 are known to decrease calcium absorption, which could impair skeletal integrity. Because serum phosphorus rises with increasing phosphorus intake and can result in calcification of the kidney if hyperphosphatemia occurs, ensuring optimal phosphorus intake during flight becomes very important (135). Maintaining adequate nutritional status during flight will be critical for preventing impaired performance on landing, which could limit crew capability for emergency egress.

Deficiency of phosphorus leads to hypophosphatemia, which causes cellular dysfunction and can lead to anorexia, muscle weakness, bone pain, and ultimately

rickets, or even death. Likewise, an excess of phosphorus leads to hyperphosphatemia, interference with calcium absorption, ectopic calcification of the kidney, or even death.

Targeted research needed

Nominal determinations of phosphorus content of the space food system were recommended by the extramural expert panel, as well as further investigation of the mechanism and implications of decreased phosphorus excretion after long-duration space flight.

Nominal requirement on Earth

The RDA for phosphorus (165) is 700 mg/d for men and women 19 years of age and older.

Historical space flight requirements

The daily phosphorus requirement for male and female astronauts was defined as 800–1200 mg/d for missions of 30 to 120 days (47). There was no specific phosphorus recommendation for missions up to 360 days (48); however, both sets of space flight dietary requirements indicate that phosphorus intake should not exceed 1.5 times the calcium intake.

Requirements, standards, and operating bands

Req. 21. The dietary intake of phosphorus shall be 700 mg/day, and shall not exceed 1.5 times the calcium intake. The nominal operating bands are defined as

Dietary Phosphorus

	4000 mg/d	red
	700 mg/d	green
	580-700 mg/d	yellow
	<580 mg/d	red

Initial verification that this requirement has been met will be done by proximate analysis of space food items for phosphorus content, as well as by analysis of the crew menus.

Standards will be assessed before, during (to the extent possible), and after flight by determining levels of phosphorus in blood (154, 187, 334) and urine (84, 86, 154) samples.

Phosphorus (serum)

	1.50 mmol/L	yellow
	1.41 mmol/L	green
	0.87 mmol/L	yellow
	<0.3 mmol/L	red

Phosphorus (urine)

	>1300 mg/d	red
	1300 mg/d	yellow
	800 mg/d	green
	600 mg/d	yellow
	<50 mg/d	red

Magnesium

Physiological function and existing space flight knowledge

Magnesium is the fourth most abundant cation in the body and within the cell is second only to potassium (337). It is required as a cofactor for over 300 enzyme systems and serves as a substrate for phosphate transfer reactions in all cells. Adequate intake of magnesium is necessary to prevent hypocalcemia, resistance to vitamin D, and resistance to parathyroid hormone. Excessive intake has been shown to impair calcium absorption (338). Several studies show that magnesium metabolism may be altered during long-duration space flight (15, 30, 339). After crew members have spent 4 to 6 months in space, their urinary magnesium is about 45% less than it was before flight (15).

Body stores and relative time to depletion

More than half of the body's magnesium is contained in bone, about 30% in muscle, and the remainder mostly in soft tissue (338).

Few studies have addressed experimental magnesium depletion in humans. Consuming a diet containing 10 mg/d for 110 days led to a steady decline in plasma magnesium to levels 10–30% of control values, and urinary magnesium levels were negligible (< 1 mEq/d) within 7 days (338). Abnormal neuromuscular signs occurred in 5 of 7 subjects after 25 to 110 days of magnesium deficiency (338).

Potential implications for flight

Adequate magnesium intake before and during flight will be critical to reduce the potential for altered magnesium status, and to help preserve bone quality and quantity. Maintaining adequate nutritional status during flight will be critical for preventing impaired performance on landing, which might limit crew capability for emergency egress.

Deficiency of magnesium leads to neuromuscular hyperexcitability, seizures, cardiac complications, or even death (165). No evidence has been reported of adverse effects associated with toxicity from naturally occurring sources of magnesium, but mega doses may cause gastrointestinal distress.

Targeted research needed

Nominal determinations of magnesium content of the space food system were recommended by the extramural expert panel. Significant decreases in urinary magnesium excretion after 4- to 6-month space flights (15) also warrants further investigation.

Nominal requirement on Earth

The RDA for magnesium (165) is as follows:

Men,	19–30 y: 400 mg/d	Men,	31–70 y: 420 mg/d
Women,	19–30 y: 310 mg/d	Women,	31–70 y: 320 mg/d

Historical space flight requirements

The daily magnesium requirement for male and female astronauts was defined as follows:

Missions of 30–120 days (47)
Male: 350 mg/d
Female: 280 mg/d

Missions up to 360 days (48)
Male and female: 350 mg/d

Requirements, standards, and operating bands

Req. 22. The dietary intake of magnesium shall be 320 and 420 mg/day for women and men respectively. The upper limit for both genders is defined as 350 mg/d from supplements only (not from dietary sources). The nominal operating bands are defined as

Dietary Magnesium

	Women	Men	
	350 mg/d*	350 mg/d*	red
	320 mg/d	420 mg/d	green
	231 mg/d	350 mg/d	yellow
	<230 mg/d	<350 mg/d	red

*Upper red band is for supplement intake only

Initial verification that this requirement has been met will be done by proximate analysis of space food items for magnesium content, as well as by analysis of the crew menus.

Standards will be assessed before, during (to the extent possible), and after flight by determining levels of magnesium in serum (154) and urine (85, 153, 154) samples.

Magnesium (urine)

	5 mmol/d	green
	3 mmol/d	yellow
	<2 mmol/d	red

Magnesium (serum)

	1.25 mmol/L	green
	0.75 mmol/L	yellow
	<0.75 mmol/L	red

Trace Elements

Iron

Physiological function and existing space flight knowledge

Iron is an essential element involved in oxygen transport, oxidative phosphorylation in carbohydrate and lipid metabolism, and electron transport in cytochromes and cytochrome oxidase (340). Iron deficiency is the most common nutritional deficit worldwide, but iron toxicity is also of concern. Iron deficiency results in reduced work capacity and impaired temperature regulation, behavior and intellectual performance, and immune function (341-343). The toxic potential of iron derives from its ability to exist in two oxidative states (ferrous and ferric forms). Iron serves as a catalyst in redox reactions; however, when these reactions are not properly modulated by antioxidants or iron-binding proteins, cellular damage can occur (344).

Decreased red blood cell mass is a consistent finding after short- and long-term flights (114, 345-348). This "space-flight anemia" was observed as early as Gemini missions of the 1960s (349). Although the decrease in RBC mass is significant (reaching 10%–15% below preflight levels within 10 to 14 days of flight), this appears to be an adaptation to space flight with no documented functional consequences.

A confounding factor in the early flights (before Skylab) was the increased cabin partial pressure of oxygen (348). The possibility of hyperoxia-induced RBC membrane peroxidation was considered (114). This was ruled out, however, when changes in erythropoiesis were also observed during Skylab (114, 350) and Shuttle missions (346, 347), where the partial pressure of oxygen was similar to that of the Earth's atmosphere (4, 114).

Decreased release of mature red blood cells into the circulation is associated with a decrease in circulating erythropoietin concentrations. An early hypothesis for the cause of decreased RBC mass was that RBC synthesis was under-stimulated compared to synthesis on the ground (348). However, iron turnover is unchanged during flight (346, 347), indicating that synthesis of hemoglobin and red blood cells is unchanged.

During the first several days of space flight, hematocrit is either unchanged (351) or slightly elevated (345-347). When elevation is noted, it is not as great as would be predicted from the decrease in plasma volume (3). The initial decrease in red blood cell mass occurs at the rate of slightly greater than 1% per day, with an eventual loss of 10%–15% (345-347). Although removal of mature red cells from the circulation is unchanged during flight (347, 352-354), the release of new red cells is halted upon entry into weightlessness (346, 347, 355). Additionally, newly released red blood cells are selectively removed from the circulation (355). These nascent cells are larger than the more mature circulating red blood cells, allowing their selective destruction (355).

The inflight changes in body fluid volumes and red blood cell mass seem to be adaptive and reach a new plateau after the first weeks of flight, as shown by data from long-duration flights (4, 16, 356, 357). The triggering mechanism for these changes is unknown. The body seems to sense a decreased requirement for blood volume, and adapts accordingly. This may be related to changes in fluid (circulatory) dynamics and reduced gravitational strain on the circulatory system during flight. One consequence of the decreased RBC mass is that the iron released when the RBCs are destroyed is processed for storage. This interpretation is based on findings of increased serum ferritin concentrations during and after both short- and long-duration flights. Serum iron concentrations are normal to elevated during and after flight (346, 347). The implications of excess stored iron during extended-duration space flights are currently unknown. Current space food systems provide excessive amounts of dietary iron (about 20 mg/d (4, 358)), which have the potential to cause deleterious effects during extended-duration space missions. Studies of dietary iron absorption have not been conducted, but could alleviate concern about iron overload during extended-duration space flight.

Another consequence of the reduced blood volume and red cell mass occurs after return to gravity. A dilutional "anemia" often occurs after flight (351), with the disproportionate return of plasma volume before the repletion of red blood cells. For example, a 3%–5% decrease in hematocrit between R+0 and R+3 is common after both short- and long-duration flight (351).

Bed-rest studies have not proven suitable models for the hematological changes of space flight. Although red blood cell mass decreases during bed rest, erythropoietin is unchanged, and hematocrit increases (359), suggesting that the mechanisms that bring about hematological changes during bed rest are different from those that act during flight. If the reduced red blood cell mass during flight is caused by the reduced gravitational load on the circulatory system, it is reasonable to assume that bed rest alone would not alleviate these forces, but would only reposition them. In studies involving changes in altitude, however, the descent from high to low altitude induces changes similar to those observed for space flight (decreased red cell mass, increased iron storage) (360).

Indices of iron metabolism and erythropoiesis return toward normal relatively quickly (days), although the replenishment of red blood cell mass may take several weeks. The efficient postflight recovery suggests that the inflight "anemia" represents an adaptation to weightlessness, probably in response to either the easier delivery of oxygen to tissues without the influence of gravity or to the decreased plasma volume and an increased concentration of RBCs in the first few days of space flight.

Body stores and relative time to depletion

Body iron comprises hemoglobin iron (67% of total) and storage iron (27%). Storage iron includes ferritin and hemosiderin, tissue iron (3.7%), a labile iron pool (2.2%) and transport iron (<1%) (340).

Storage iron may be completely deleted before the development of iron-deficiency anemia (344). As a result of this, tissue iron deficiency occurs before anemia.

Potential implications for flight

Pathological conditions in which involvement of iron-related radicals is suspected and that have specific relevance to space flight include ionizing radiation and inflammatory-immune injury (361). Free-radical involvement subsequent to elevations in iron stores has also been linked to cardiovascular disease and cancer. A correlation between coronary heart disease and iron status has been described in a number of recent studies (362-366). Although the evidence supporting this thesis is contradictory (367, 368), an association between increased iron stores (as measured by serum ferritin) and increased incidence of myocardial infarction has been observed (363, 366). Increased risk of all cancer types combined and colorectal cancer in particular was associated with high iron stores in a prospective Finnish study (369). The relationship between iron, lipids, and cancer has also been documented in the Framingham study (370). A relationship has also been indicated between excessive iron stores and ascorbic acid deficiency; when reductions in ascorbic acid occur, vitamin A and selenium tend to exacerbate iron-induced peroxidation processes (371). These data suggest that the alterations in erythropoiesis and iron metabolism that occur in microgravity could cause significant changes affecting crew health.

Deficiency of iron leads to anemia, fatigue, impaired performance, heart palpitations, congnitive deficits and memory loss, impaired thermoregulation, decreased immune function, or even death. Toxicity of iron may lead to tissue damage or cancer. High iron intakes have also been related to gastrointestinal distress.

Targeted research needed

The extramural expert panel recommended that iron metabolism be further investigated because of the high levels of dietary iron and the potential for iron to act as an oxidizing agent during space flight, complicated by increased radiation levels. An experiment to study this was approved for flight on the ISS but was later deselected because of resource constraints.

Nominal requirement on Earth

The recommended intakes for iron are provided as RDAs (174):

Men, 19–70 y:	8 mg/d
Women, 19–50 y:	18 mg/d
50+ y:	8 mg/d

Historical space flight requirements

Missions of 30–120 days:

Because space flight has been associated with decreased erythropoiesis and increased serum ferritin concentrations, the use of iron supplementation should be prohibited, and the maximum intake held at the male RDA (10 mg/day) (47).

Missions up 360 days:

Iron intake requirements were defined to not exceed 10 mg/d for males and females. This is based on space-induced changes in iron storage, and is designed to prevent iron overload, a situation that may lead to oxidative tissue damage (48).

The food system was unable to support this requirement, and intakes have often been much higher (intakes as high as 20–25 mg iron per day have been observed).

Requirements, standards, and operating bands

Req. 25. The dietary intake of iron shall be 8–10 mg/day. The nominal operating bands are defined as

Dietary Iron

	35 mg/d	red
	15-35 mg/d	yellow
	8 mg/d	green
	5-8 mg/d	yellow
	3-5 mg/d	red

Initial verification that this requirement has been met will be done by proximate analysis of space food items for iron content, as well as by analysis of the crew menus.

Standards will be assessed before, during (to the extent possible), and after flight by determining levels of hemoglobin (84), hematocrit (84), mean corpuscular volume (MCV) (84), iron (84, 100), ferritin (84, 153, 154), ferritin iron (153, 372), ferritin % saturation (153), transferrin receptors (174), and C-reactive protein (an indicator of inflammation, which could affect iron status indicators) (86) in blood or serum samples.

Ferritin (serum)

	Women	Men	
	>200 ng/mL	>300 ng/mL	red
	120-200 ng/mL	250-300 ng/mL	yellow
	120 ng/mL	250 ng/mL	green
	10 ng/mL	20 ng/mL	yellow
	<10 ng/mL	<12 ng/mL	red

Ferritin Iron (serum)*

	>200 ng/mL	red
	35 ng/mL	green
	10 ng/mL	yellow
	<5.3 ng/mL	red

* For ferritin values ≥150 ng/mL

Transferrin (serum)

	318 mg/mL	green
	196 mg/mL	yellow
	<196 mg/mL	red

Transferrin Receptors (serum)

	2.9 µg/mL	green
	8.3 µg/mL	yellow
	>8.5 µg/mL	red

Hemoglobin (whole blood)

	Women	Men	
	19.0 g/dL	20.0 g/dL	red
	14.8 g/dl	16.5 g/dL	green
	11.6 g/dL	13.3 g/dL	yellow
	9.0 g/dL	10.0 g/dL	red

Hematocrit (whole blood)

	Women	Men	
	57.0%	60.0%	red
	43.5%	49.1%	green
	33.5%	39.7%	yellow
	27.0%	30.0%	red

MCV (whole blood)

	106 fL	red
	98 fL	green
	84 fL	yellow
	70 fL	red

Iron (serum)

	>250 µg/dL	red
	177-250 µg/dL	yellow
	46-177 µg/dL	green
	20-46 µg/dL	yellow
	<20 µg/dL	red

hs C-Reactive Protein (serum)

	<1.0 mg/L	green
	1.0-3.0 mg/L	yellow
	>3.0 mg/L*	red

*Greater than 10 mg/L indicates inflammatory response.

Copper

Physiological function and existing space flight knowledge

Copper is an essential cofactor for enzymes involved in energy production, metabolism of oxygen and iron, maturation of the extracellular matrix and neuropeptides, and neuroendocrine signaling. Deficiencies in copper have implications for bone health, the nervous system, immune function, the cardiovascular system, and lipid metabolism.

Body stores and relative time to depletion

Copper is not usually stored in tissues, but liver, brain, and kidney typically contain the largest amounts per unit tissue mass (373). Total body copper is about 50–120 mg (0.79–1.9 mmol) (374). Frank copper deficiency in humans is rare; however, copper deficiencies have been noted in infants fed milk formulas, infants recovering from malnutrition and fed cow's milk, and patients receiving total parenteral nutrition for a prolonged period (174). A copper deficiency developed in 6 patients fed an enteral diet containing 15 μg copper/100 kcal for 12 to 66 mo (375).

Potential implications for flight

The role of copper in maintaining normal immune function seems to be altered during space flight (90, 376). Additionally, the well documented (12, 51) changes in bone status during space flight may be exacerbated by copper deficiencies. Anemia of space flight is manifested as a reduction in circulating red blood cell mass with elevations in serum ferritin and iron concentrations (4, 347). Since copper is required for iron mobilization and absorption, alterations in copper status may affect iron and red blood cell changes during flight. Although deficiencies are rare in populations consuming a normal diet, no information about copper absorption and metabolism during space flight is available.

Deficiency of copper leads to normocytic, hypochromic anemia, leucopenia, neutropenia, defects in connective tissue that lead to vascular and skeletal problems and central nervous system dysfunction, or even death (174). Heartbeat irregularities have also been reported in cases of copper deficiency (377). Deficiency symptoms, including macrocytic anemia, bone abnormalities, and decreased neutrophil production, have been reported in subjects with serum copper concentrations ranging from 0.9–7.2 μmol/L (375). Toxicity of copper leads to gastrointestinal distress, liver damage, or even death.

Targeted research needed

Existing knowledge of copper metabolism seems adequate; other than the nominal determinations of copper content of the space food system, no other specific research is required.

Nominal requirement on Earth

The recommended intake for copper is provided as an RDA (174):
Men and women, 19–70 y: 900 μg/d

Historical space flight requirements
Intake of copper was defined as 1.5–3.0 mg/day for males and females (47, 48).

Requirements, standards, and operating bands
Req. 26. The dietary intake of copper shall be 0.5–9 mg/day. The operating bands are defined as

Dietary Copper

	10 mg/d	red
	0.5-9 mg/d	green
	0.3-0.5 mg/d	yellow
	<0.3 mg/d	red

Initial verification that this requirement has been met will be done by proximate analysis of space food items for copper content, as well as by analysis of the crew menus.

Standards will be assessed before, during (to the extent possible), and after flight by determining indices of copper status (86, 174) and ceruloplasmin (174) in blood samples.

Copper (serum)

	1.55 μg/mL	green
	0.70 μg/mL	yellow
	0.02 μg/mL	red

Ceruloplasmin (serum)

	43 mg/dL	green
	22 mg/dL	yellow
	18 mg/dL	red

Manganese

Physiological function and existing space flight knowledge

Manganese can function as an enzyme activator and as part of metalloenzymes. It is involved in the activation of enzyme-catalyzed reactions by causing conformational changes in the enzyme that it binds to. Manganese can also bind directly to the substrate.

Transferases, including kinases, hydrolases, oxido-reductases, ligases and lyases, all can be activated by manganese. However, these enzymes can also be activated by other divalent cations in the presence of a manganese deficiency. Activating these enzymes gives manganese a role in formation of components of connective tissue, urea formation, arginase activity, gluconeogenesis, the prevention of lipid peroxidation by superoxide radicals in the mitochondria, and the conversion of pyruvate to oxaloacetate in the tricarboxylic acid (TCA) cycle. Studies are currently being conducted to look at the role that manganese may play in second-messenger pathways in tissues and the regulation of calcium-dependent processes (233).

Body stores and relative time to depletion

Only trace amounts of manganese are found in animal tissues. Humans store about 10 to 20 mg of the nutrient. Although it is found in most organs and tissues, the highest concentrations are found in bone and the liver, pancreas, and kidneys (233).

In one study, when adult men were fed a purified diet with only 0.11 mg manganese per day for 39 days, all of them developed a finely scaling rash, along with decreased serum cholesterol, increased serum calcium and phosphorus, and increased alkaline phosphatase (378). Otherwise, signs of a manganese deficiency in humans have not been firmly established.

Potential implications for flight

Considering manganese's function in preventing lipid peroxidation and the increase in lipid peroxidation during space flight, ensuring adequate manganese intake on long space flights is vital to preventing and/or minimizing oxidative stress.

Manganese is one of the least toxic trace minerals when it is taken orally. At excessively high intakes of manganese, absorption decreases and excretion increases to protect against toxicity. Manganese and iron compete for binding sites. At low iron intakes, manganese is absorbed at a greater rate than at higher iron intakes, so that higher iron intake inhibits manganese absorption. Likewise, higher manganese intake can inhibit iron absorption.

Deficiency of manganese has not been shown to cause any overt clinical symptoms due to the fact that other cations can perform the same role. However, toxicity of manganese leads to neurotoxicity.

Targeted research needed
Existing knowledge of manganese metabolism seems adequate; other than the nominal determinations of manganese content of the space food system, no other specific research is required.

Nominal requirement on Earth
The AI for manganese for men 19 and older is 2.3 mg/day and for women 19 and older it is 1.8 mg/day (174).

Historical space flight requirements
Intake of manganese was defined as 2–5 mg/day for males and females (47, 48).

Requirements, standards, and operating bands
Req. 27. The dietary intake of manganese shall be 1.8 and 2.3 mg/day for women and men respectively. The nominal operating bands are defined as

Dietary Manganese

	Women	Men	
	11 mg/d	11 mg/d	red
	1.8 mg/d	2.3 mg/d	green
	1.6 mg/d	2.1 mg/d	yellow
	<1 mg/d	<1 mg/d	red

Initial verification that this requirement has been met will be done by proximate analysis of space food items for manganese content, as well as by analysis of the crew menus.

The extramural expert panel concluded that if dietary sources of manganese are adequate, definition of a standard to ensure that manganese requirements are met is unnecessary. Accordingly, no biochemical measures of manganese status are required for exploration missions.

Fluoride

Physiological function and existing space flight knowledge

Fluoride in bone exists in a rapidly exchangeable pool and a slowly exchangeable pool. In the rapidly exchangeable pool, fluoride is present in the hydration shell on bone crystallites, where it is exchanged isoionically or heterionically with other ions nearby (187). The slowly exchangeable pool is mobilized during the process of bone remodeling. Fluoride has also been shown to influence the function of osteoblasts, enabling new bone to be made.

Body stores and relative time to depletion

Ninety-nine percent of fluoride is stored in mineralized tissues, predominantly in bone.

Because specific signs of fluoride deficiency have not been fully elucidated for higher animals and humans, it is not possible to estimate a relative time to depletion.

Potential implications for flight

An increase in fluoride absorption increases the amount absorbed by the hard tissue, but urinary excretion also increases. With the loss of bone mass associated with weightlessness, adequate fluoride is necessary to ensure that the bone apatite remains intact.

Toxicity with fluoride supplementation is rare but can occur when fluoride concentrations are greater than 10 mg/day for at least 10 years (165). The toxic side effects are skeletal fluorosis and osteosclerosis.

Fluoride deficiency increases the development of dental caries and may reduce the integrity of skeletal tissue (233). Toxicity of fluoride leads to enamel and skeletal fluorosis.

Targeted research needed

Existing knowledge of fluoride metabolism seems adequate; other than the nominal determinations of fluoride content of the space food system, no other specific research is required.

Nominal requirement on Earth

The AI for fluoride for men 19 y and older is 4 mg/day and for women 19 and older it is 3 mg/day (174).

Historical space flight requirements

The original space requirement for fluoride was defined as 4.0 mg/d for males and females (47, 48).

Requirements, standards, and operating bands

Req. 28. The dietary intake of fluoride shall be 3 and 4 mg/day for women and men respectively. The nominal operating bands are defined as

Dietary Fluoride

	Women	Men	
	3.0 mg/d	4.0 mg/d	green
	1.5 mg/d	2.0 mg/d	yellow
	1.0 mg/d	1.5 mg/d	red

Initial verification that this requirement has been met will be done by proximate analysis of space food items for manganese content, as well as by analysis of the crew menus.

The extramural expert panel concluded that if dietary sources of fluoride are adequate, definition of a standard to ensure that fluoride requirements are met is unnecessary. Accordingly, no biochemical measures of fluoride status are required for exploration missions.

Zinc

Physiological function and existing space flight knowledge

Zinc is a component of many enzymes, which depend on it for their catalytic activity. RNA polymerases, alcohol dehydrogenase, carbonic anhydrase, and alkaline phosphatase are all zinc metalloenzymes. Its role with these metalloenzymes is to provide structural integrity to the enzyme by binding to amino acids, and it may participate directly in the reaction at the catalytic site (233).

Tissue or cell growth, cell replication, bone formation, skin integrity, cell-mediated immunity and generalized host defense are all functions of zinc. In tissue growth it is involved directly with the regulation of protein synthesis. Zinc helps to regulate transcription by binding to promoter sequences of specific genes. Cell membranes require zinc for protein-to-protein interactions and membrane proteins' conformation. It may also affect the activity of enzymes attached to plasma membranes. Zinc stabilizes membrane structure by maintaining phospholipids and thiol groups in their necessary reduced state. It also prevents oxidation of the membrane by occupying sites that might otherwise be occupied by pro-oxidant metals and protects against oxidation by its role in metallothionein.

Zinc is an integral part of the hormone insulin and plays a role in carbohydrate metabolism.

Body stores and relative time to depletion

About 1.5 to 2.5 grams of zinc is stored in the human body (174). It is found intracellularly in all organs, tissues, and body fluids, but mostly in bone, liver, kidneys, muscle, and skin (233). Over 85% of zinc is found in skeletal muscle and bone (233, 379).

Even when dietary zinc is sub-optimal, the zinc stored in muscle, brain, lung, and heart is not released. Also, the apatite of bones releases zinc slowly and this does not greatly affect the zinc supply (174). When zinc intake is sub-optimal or non-existent, plasma enzymes containing zinc and metallothionein are catabolized to provide the necessary zinc (174).

The greatest losses of zinc occur through the intestine. In men, the average daily loss of zinc from sources other than the intestine remains relatively constant at 1.27 mg/day, even when individuals consume an inadequate amount of the nutrient. For women, calculation of this value has been based on the difference in average surface area and menstruation, and is 1.0 mg/day (174).

Because the stores of zinc in the body are small, inadequate intake can quickly lead to exhaustion of the zinc supply. This may cause a need for catabolism of the zinc metalloenzymes, which would bring about a decrease in enzyme activity (233).

Zinc deficiency can cause decreased glucose tolerance by decreasing insulin response. Basal metabolic rate has been shown to be decreased in individuals who were receiving a zinc-deficient diet (380).

Zinc toxicity can occur with excessive intakes. Acute toxicity has been shown to produce metallic taste, nausea, vomiting, epigastric pain, abdominal cramps, and bloody diarrhea. Long-term toxicity can cause copper deficiency because zinc and copper compete for absorption by the intestine (233).

Deficiency of zinc leads to arrested growth and development and decreased immune function. There is currently no evidence of adverse effects associated with toxicity from naturally occurring sources. However, supplemental intake of zinc may cause suppression of immune response, decreased high-density lipoprotein (HDL) cholesterol, reduced copper status, or even death.

Potential implications for flight

Many different compounds exist in food that can complex with zinc and decrease its absorption. Phytates, oxalates, polyphenols, fibers, and other nutrients including vitamins can all inhibit zinc absorption.

The release of zinc from bones (due to demineralization) has been noted in bed rest studies (381, 382). Similarly, increases in urinary zinc have been noted with increased muscle catabolism in cases of starvation or trauma (174). The importance of this phenomenon for space flight has not been evaluated (and furthermore, the release of other heavy metals from bone during flight has not been evaluated).

Targeted research needed

Existing knowledge of zinc metabolism seems adequate; other than the nominal determinations of zinc content of the space food system, no other specific research is required.

Nominal requirement on Earth

The AI for zinc is 11 mg/day for men and 8 mg/day for women (174).

Historical space flight requirements

The original space flight requirement for zinc was defined as 15 mg/day for males and females (47, 48).

Requirements, standards, and operating bands

Req. 29. The dietary intake of zinc shall be 11 mg/day. Nominal operating bands are defined as

Dietary Zinc

	40 mg/d	red
	11 mg/d	green
	6-11 mg/d	yellow
	<6 mg/d	red

Initial verification that this requirement has been met will be done by proximate analysis of space food items for zinc content, as well as by analysis of the crew menus.

Standards will be assessed before, during (to the extent possible), and after flight by determining levels of zinc in serum (86, 100, 154) and urine (86) samples.

Zinc (serum)

	>1.5 µg/mL	red
	1.5 µg/mL	yellow
	1.2 µg/mL	green
	0.9 µg/mL	yellow
	<0.7 µg/mL	red

Zinc (urine)

	1200 µg/d	green
	200 µg/d	yellow
	<200 µg/d	red

Selenium

Physiological function and existing space flight knowledge

Selenium has been shown to play a role in the maintenance or induction of cytochrome P450, pancreatic function, DNA repair, enzyme activation, immune system function, and detoxification of heavy metals. Selenium also plays a role as a cofactor for glutathione peroxidase (GPX). GPX plays a role in the reduction of organic peroxides and hydrogen peroxide. Selenium has also been shown to be necessary for iodine metabolism.

Selenium absorption can be enhanced by vitamins A, C, and E and reduced glutathione. Selenium absorption can be reduced by chelation and precipitation of the mineral by heavy metals, such as mercury and phytates.

Deficiency of selenium leads to decreased selenoenzyme activity, which may lead to biochemical changes that predispose to illness or even death. Selenium deficiency has been associated with Keshan disease, which is characterized by cardiomyopathy and heart tissue necrosis. It has also been shown to be associated with Kashin-Beck's disease, which is characterized by osteoarthropathy of the joints and epiphyseal-plate cartilages of the legs and arms (233).

Toxicity of selenium is called selenosis. Nausea, vomiting, fatigue, hair and nail brittleness and loss, changes in nail beds, interference in sulfur metabolism and inhibition of protein synthesis have all been demonstrated.

Long-duration space-flight data provide evidence that serum selenium is about 10% lower after flight than before launch (15).

Body stores and relative time to depletion

Total body selenium stores are in the amount of about 15 mg (233). There are two selenium pools in the body. One is the selenium present as selenomethionine and the other is the selenium present as glutathione peroxidase.

In rats, symptoms of acute selenium deficiency have been shown to appear as early as 20 days. This was presented as a reduction in GPX activity, but no change in blood enzymes was seen (202).

Potential implications for flight

Little or no data are available regarding selenium during space flight. The Clinical Nutritional Assessment profile has documented a significant reduction in serum selenium concentrations after flight. Whether this is related to intake or metabolism is not known.

Targeted research needed
The extramural expert panel recommended that selenium levels in the space food system be determined. They also recommended that the potential role for selenium in protecting against oxidative stress during space flight be further investigated.

Nominal requirement on Earth
The recommended intake for selenium is provided as an RDA (202):
Men and women, 19 y and older: 55 μg/d

Historical space flight requirements
Intake of selenium was defined as 70 μg/day for males and females (47, 48).

Requirements, standards, and operating bands
Req. 30. The dietary intake of selenium shall be 55–400 μg/day. The nominal operating bands are defined as

Dietary Selenium

	400 μg/d	red
	55-400 μg/d	green
	45-55 μg/d	yellow
	<45 mg/d	red

Initial verification that this requirement has been met will be done by proximate analysis of space food items for selenium content, as well as by analysis of the crew menus.

Standards will be assessed before, during (to the extent possible), and after flight by determining levels of selenium in serum (85, 150, 163). Determination of urinary selenium provides supporting data (85) and not a standard per se. Normal ranges for urinary selenium are documented in the General Chemistry section.

Selenium (serum)

	1000 ng/mL	red
	200 ng/mL	green
	100 ng/mL	yellow
	<65 ng/mL	red

Iodine

Physiological function and existing space flight knowledge

The main function of iodine occurs in its ionic form, iodide. It serves in the production of the thyroid hormones T_3 and T_4.

Body stores and relative time to depletion

About 15–20 mg iodide is stored in the human body (233). The element tends to concentrate itself in the thyroid and in the salivary and gastric glands, with some iodide being found in the mammary glands, ovaries, placenta, and skin. The thyroid gland traps the iodide and it is here that 70 to 80 percent of the total body iodide is stored.

During a 4-week study in which rats were submitted to varying degrees of iodine deficiency, the most severely depleted rats showed an increase in thyroid mass after 4 days (383).

Insufficient dietary iodine has been shown to cause goiter. This is due to over-stimulation of the thyroid gland by TSH. Iodine deficiency can also cause the iodine deficiency disorders, which include mental retardation, hypothyroidism, goiter, cretinism, and other growth and development abnormalities or even death.

No toxic side effects have been reported when intakes in the amount of 2.0 mg/day have been ingested (233). However, with prolonged intakes of greater than 18 mg/day, the risk of goiter increases, as does the risk of thyroid cancer (174, 187). Other symptoms of iodine toxicity when intakes are on the order of several grams per day include gastrointestinal distress, thyroiditis, goiter, sensitivity reactions, thyroid papillary cancer, or even death (187).

Potential implications for flight

Although providing adequate amounts of dietary iodine is not a critical issue with regard to space flight, there is much discussion regarding the effects of the iodine used in the water systems on orbit (where iodine is often used as a bactericide) (384).

Targeted research needed

Existing knowledge of iodine metabolism seems adequate; other than the nominal determinations of iodine content of the space food system, no other specific research is required.

Nominal requirement on Earth

The recommended intake for iodine is provided as an RDA (174):
Men and women, 19 y and older: 150 μg/d

Historical space flight requirements

Intake of iodine was defined as 150 μg/day for males and females (47, 48).

Requirements, standards, and operating bands

Req. 31. The dietary intake of iodine shall be 150 µg/d. Nominal operating bands are defined as

Dietary Iodine

	150 µg/d	green
	95-150 µg/d	yellow
	<95 µg/d	red

Initial verification that this requirement has been met will be done by proximate analysis of space food items for iodine content, as well as by analysis of the crew menus.

Standards will be assessed before, during (to the extent possible), and after flight by determining levels of iodine in urine (100, 154) samples. It is also assumed that serum thyroid stimulating hormone and serum thyroid hormone concentrations will be determined in the routine clinical assessment.

Iodine (urine)

	50 µg/g creatinine	green
	25 µg/g creatinine	yellow
	<25 µg/g creatinine	red

Chromium

Physiological function and existing space flight knowledge

Chromium is thought to complex with nicotinic acid and amino acids to form glucose tolerance factor, which initiates the disulfide bridging between insulin and its receptor (233). This allows the insulin hormone to be more effective and therefore increases cellular glucose uptake and intracellular carbohydrate and lipid metabolism.

Chromium may also play a role in pancreatic insulin secretion, internalization of insulin through decreasing membrane fluidity, and regulation of the insulin receptor. It also may increase insulin sensitivity by activating insulin receptor kinase.

Chromium deficiency may result in insulin resistance, which is characterized by hyperinsulinemia. This has been shown to be a risk factor for coronary heart disease.

Severe trauma and stress may increase the need for chromium. Stress causes the release of the stress hormones, including cortisol and glucagon. These hormones alter glucose metabolism and, in effect, chromium.

Cr^{6+} is more toxic than Cr^{3+} when ingested orally. Liver damage, skin ulcerations, dermatitis, and respiratory disease may all result from a chromium intake greater than 1,000 μg/day (233).

Deficiency of chromium leads to impaired glucose tolerance, or even death. Toxicity of chromium leads to chronic renal failure, hepatic dysfunction, rhabdomyolysis, or even death.

Body stores and relative time to depletion

The human body can store 4 to 6 mg of chromium. Tissues having the greatest amounts of chromium are the liver, kidney, muscle, spleen, heart, pancreas, and bone. It is possible that chromium is stored along with ferric iron because of its transport by transferrin.

Several months of sub-optimal chromium intake will lead to deficiency symptoms such as hyperglycemia and glycosuria (385). One study found that 9 weeks on a low-chromium diet (5 μg/1000 kcal) was long enough to yield changes in glucose tolerance (386).

Potential implications for flight

Little or nothing is known about chromium in space travelers. Chromium deficiency may result in insulin resistance, which has also been observed after space flight or bed rest (87-89). Whether or not these are related is unknown.

Targeted research needed
Existing knowledge of chromium metabolism seems adequate; other than the nominal determinations of chromium content of the space food system, no other specific research is required.

Nominal requirement on Earth
The recommended intake for chromium is provided as AI (174):

Men, 19–50 y:	35 μg/d
50 y and older:	30 μg/d
Women, 19–50 y:	25 μg/d
50 y and older:	20 μg/d

Historical space flight requirements
Chromium requirements were originally set at 100–200 μg/day (47, 48).

Requirements, standards, and operating bands
Req. 32. The dietary intake of chromium shall be 35 μg/day. The nominal operating bands are defined as

Dietary Chromium

	35 μg/d	green
	14 μg/d	yellow
	<14 μg/d	red

Initial verification that this requirement has been met will be done by proximate analysis of space food items for chromium content, as well as by analysis of the crew menus.

The extramural expert panel concluded that if dietary sources of chromium are adequate, definition of a standard to ensure that chromium requirements are met is unnecessary. Accordingly, no biochemical measures of chromium status are required for exploration missions.

General Chemistry and Supporting Analytes

Several supporting factors need to be evaluated in addition to the nominal nutritional assessment parameters. While all of these do not have standard "red" values, these are important in understanding and interpreting other findings. One example: blood pH (100, 387, 388) has a direct effect on ionized calcium concentrations. Having one without the other would yield uninterpretable data. In addition, urine pH can change the risk for renal stone risk (389, 390).

pH (urine)

	>8	red
	7	yellow
	5.5	green
	4.5	yellow
	<4.5	red

pH (blood)

	7.35-7.45	green
	<7.35	red

Creatinine is another example of supporting measures. Serum creatinine is a marker of kidney function (391), and urinary creatinine is a marker of muscle mass (86). Furthermore, the concentrations of many other analytes are normalized to creatinine.

Creatinine (serum)

	0.6 mg/dL	green
	1.8 mg/dL	yellow
	2.0 mg/dL	red

Creatinine (urine)

	Women	Men	
	700-1600 mg/d	1000-2500 mg/d	green

Determination of urinary sodium (153, 154), potassium (130), and selenium (154) allows indirect assessment of the level of dietary intake.

Sodium (urine)

	40-220 mmol/d	green

Potassium (urine)

	25-125 mmol/d	green

Selenium (urine)

	0-200 µg/d	green

Special Issues

The following sections represent specific issues related to nutrition, although they are not related to a specific nutrient.

Supplements

It is generally agreed that nutrients should be provided to astronauts in standard foods, as opposed to supplements (4, 47, 48, 392). This is critical, as natural foods provide other non-nutritive substances such as fiber and carotenoids as well as a sense of palatability and psychological well-being that will be important during long missions. The need for more detailed information about the "psychophysiology of hunger and eating" was noted decades ago during the early space programs (19) but has yet to be studied in detail. It is clear from astronauts' experience on the Mir that when humans are in an isolated environment far from home, food becomes a very supportive psychological factor.

The question of dietary supplements is often raised, but NASA currently does not recommend general nutritional supplements during flight, for several reasons. Experience to date indicates that crew members do not consume the recommended amount of energy intake, and accordingly, intake of many individual nutrients is therefore also inadequate. Unfortunately, the concept of a vitamin/mineral supplement to remedy this is unwarranted, as the primary problem—inadequate dietary/energy intake—will not be resolved by a supplement. This situation may even be worsened, as crew members may believe that taking the supplement reduces the need for adequate food consumption, and thus eat even less. Furthermore, many nutrients when provided as oral supplements are not metabolized by the body as they are when in foods. Changes in bioavailability and metabolism can increase the risk of malnutrition. Vitamin or mineral supplements should be used only when the nutrient content of the nominal food system does not meet the requirements for a given nutrient (as is currently done with vitamin D supplementation), or when data show that the efficacy of single (or multiple) nutrient supplementation is advantageous.

Nutrient-Drug Interactions

An understanding of interactions between pharmacotherapeutics and nutrients is necessary to implement safe and effective medical care and clinical intervention operations for astronauts on long-duration missions. The most commonly and well-studied interactions between pharmacological agents and nutrients concern their effects on a nutrient or drug's absorption, distribution, biotransformation, and excretion.

Normally, drugs must undergo biotransformation to allow excretion or activation. To terminate drug activity through excretion, the compound must be made water-soluble by this process. For most drugs, biotransformation yields a water-soluble compound that is less active than the original compound. There are 2 phases of reactions in the process of biotransformation. Phase I is an oxidation or hydrolysis reaction to expose a functional group on a parent compound or introduce a functional group to that compound. Cytochrome P450 enzymes are involved in this process. Humans have 12 families of cytochrome P450 enzymes, but CYP1, CYP2, and CYP3 are the most commonly used forms in drug metabolism (393). Cytochrome P450 enzymes are unique in their ability to use a wide range of substrates (394). Phase II involves the conjugation of the parent compound to a polar group (acetate, glucuronides, sulfates, amino acids, glutathione). This process inactivates most drugs.

Dietary factors

Dietary factors can influence enzyme induction or inhibition, and they are required for phase I and phase II biotransformations. In phase I, three things are required: a sufficient energy source (because of the high energy demands of this system), a protein source for enzyme formation, and iron for cytochrome formation (395). Phase II requires glucose, sulfur-containing amino acids, and glutathione (395).

The effects of nutrients on drug metabolism have been well studied in animal models; however, relatively few dietary factors have been studied in humans (395, 396). Results from animal studies must be carefully weighed because of some differences in cytochrome P450 enzymes.

One of the most well-documented food-drug interactions is between grapefruit juice and a number of medications (397, 398). Flavonoid compounds such as naringin, naringenin, limonin, and obacunone, which are present in grapefruit juice, act as substrates for particular intestinal cytochrome P450 enzymes (CYP3A4 and CYP1A2). Grapefruit juice induces a sustained decrease in CYP3A4 protein expression within 4 hours of ingestion, lasting up to 24 hours (399, 400). The decrease in CYP3A4 results in decreased capability for drug metabolism, and therefore increased drug bioavailability.

Other foods or nutrients with compounds known to affect phase I and II biotransformations and cytochrome P450 enzymes include protein, carbohydrate, lipids, certain vitamins, minerals, char-broiled foods, red wine, monosodium

glutamate and aspartate, and herbs such as St. John's wort (395, 396, 401-404). Generally, high-protein diets increase drug metabolism, and low-protein diets decrease drug metabolism. For instance, antipyrine and theophylline are metabolized more rapidly when subjects are on a high-protein diet (396). Other macronutrients, including carbohydrate, can elicit effects on phase I and phase II biotransformation reactions when intakes are very high or low. Theophylline (for asthma) is particularly sensitive to dietary protein:carbohydrate ratios; increasing the ratio can decrease effectiveness of the drug, and decreasing the ratio may lead to toxicity of the drug (405). Fatty acids are metabolized by cytochrome P450 enzymes. Specifically, CYP2E1 is responsible for lipid peroxidation, and this enzyme is enhanced in the presence of highly polyunsaturated fatty acids such as fish oils.

Nutrient metabolism

Certain nutrients are metabolized by cytochrome P450 enzymes; therefore, drugs or other nutrients that alter the activity of these enzymes can alter nutrient metabolism. Vitamin D and vitamin A are two examples of nutrients whose metabolism involves cytochrome P450 enzymes.

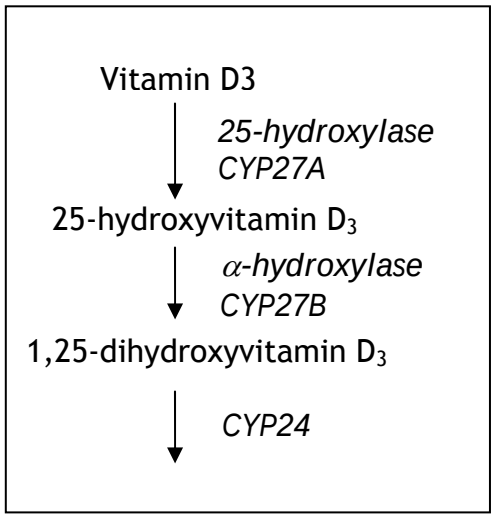


Figure 3. Diagram of vitamin D metabolism.

Exposure of 7-dehydrocholesterol to sunlight converts the substrate to previtamin D_3. Previtamin D_3 undergoes an isomerization to form vitamin D_3, a biologically inactive compound. CYP27A is a mitochondrial mixed-function oxidase that is responsible for hydroxylating vitamin D_3 to form 25-hydroxyvitamin D_3 (**Figure 3**) (406). Recently, CYP3A4 has been found to be a 25-hydroxylase as well (407). CYP27B converts 25-hydroxyvitamin D_3 to 1,25 dihydroxyvitamin D_3. CYP24 is a 24-hydroxylase that hydroxylates the vitamin D side chain and ultimately terminates hormonal activity. Inhibition of CYP24 has recently been targeted in the development of novel anti-cancer drugs. Because 1,25-dihydroxyvitamin D_3 exerts antiproliferative and differentiating effects on many cell types including cancer, preventing its metabolism by inhibiting CYP24 activity may show to be beneficial in treating cancer (408). Certain drugs are known to activate CYP24 activity, including rifampin, isoniazid, and

phenobarbital (409, 410). Several studies show a relationship between the use of these drugs and osteomalacia (411, 412). The discovery of the involvement of CYP3A4 may implicate and/or explain the effects of numerous other drugs on vitamin D metabolism, including inducers or inhibitors of this enzyme (e.g., grapefruit juice, erythromycin, omeprazole, carbamazepine, dexamethasone).

Vitamin A metabolism involves the actions of CYP1A2 and CYP4A4 in the conversion of retinol to retinoic acid (413, 414). Inducers of CYP1A2 (cigarette smoke, cruciferous vegetables, broiled beef, rifampin) may affect vitamin A metabolism.

Monoamine oxidase inhibitors

First-generation monoamine oxidase (MAO) inhibitors include agents such as antidepressants (phenelzine, tranylcypromine, pargyline, and selegiline), chemotherapeutic drugs (procarbazine), antiprotozoal drugs (furazolidone), and analgesics (meperidine). Monoamine oxidase is responsible for metabolizing dietary phenylethylamines, including tyramine, in the gastrointestinal tract and in the liver. Inhibitors of MAO prevent the breakdown of these compounds, and therefore the compounds are taken up in brain. In the brain, tyramine displaces norepinephrine from storage vesicles and this results in release of a flood of norepinephrine at synapses. Acute hypertension and the potential for stroke or myocardial infarction are the implications of this process (395). Fermented foods and protein-rich foods that have begun to spoil are rich in phenylethylamines (395). A list of foods rich in tyramines is included in **Table 1**.

Tyramine-Rich Foods	
Ale	Liver (beef or chicken)
Avocados	Raspberries
Bananas	Raisins
Beans (lima beans, butter beans, bean pods)	Sour cream
Caviar	Soy beans or sauce
Cheese	Tofu
Coffee	Wines (especially red)
Figs	Yeast preparations
Fish (smoked or pickled herring)	Yogurt
Processed meat (bologna, fermented meat, salami, pepperoni, summer sausage)	

Table 1. Foods containing a large amount of tyramine (395, 415).

Antacids and proton pump inhibitors

By altering the pH of the stomach, chronic antacid or proton pump medications can negatively affect the bioavailability of several nutrients, including phosphate, thiamin, folate, vitamin B_{12}, vitamin C, and vitamin A (395, 416, 417). Antacids can precipitate folic acid at a pH greater than 4.0, thus rendering it insoluble and not available for absorption (418). A high pH also affects thiamin bioavailability because the vitamin is not stable at high pH (395). Similarly, at a neutral pH, the action of

vitamin C on dietary nitrites is hindered because of its instability. Normally, dietary nitrite is quickly reduced to nitric oxide by ascorbic acid in the acidic gastric juice, where it is then absorbed by the mucosa; however, at neutral pH, the nitrite does not react with ascorbic acid and accumulates in the stomach (417). These changes are mostly observed in *Helicobacter pylori*-infected subjects taking proton-pump inhibitors (417). Elevated nitrite concentrations in the stomach can predispose to the formation of potentially carcinogenic N-nitroso compounds.

Vitamin B_{12} and vitamin A are also malabsorbed at higher pH because the acidic environment is essential for their release from dietary proteins. Because large stores of vitamin B_{12} exist in the body, this is problematic mainly when a subject has been taking proton pump inhibitors chronically for at least 2 years (416). This would be particularly harmful if vitamin B_{12} stores were low before initiation of therapy.

Coumarin anticoagulants

Anticoagulants such as warfarin, a coumarin-based anticoagulant, are administered to create a partial vitamin K deficiency to reduce risks of abnormal blood clotting (419). Dosing with warfarin must be closely monitored for optimal efficacy and safety. Generous or poor intake of vitamin K can interact with the actions of warfarin to yield non-therapeutic anticoagulation or life-threatening hemorrhagic complications (420, 421). Some foods that are rich in vitamin K are listed in **Table 2**.

Vitamin K-Rich Foods
Alfalfa tablets
Broccoli
Brussels sprouts
Cabbage
Cauliflower (raw)
Green leafy vegetables (spinach, collard greens)
Green tea
Liver
Soybeans
Vegetable oils (canola, soybean)
Watercress

Table 2. Foods containing a large amount of vitamin K (395, 422).

Implications for space flight

Currently no data are available for specific drug-nutrient interactions during space flight. The main concerns for a long-duration mission include those pharmacological agents that are taken chronically. Side effects will be especially harmful if nutritional status of all nutrients is not adequate at the beginning of a long-duration mission.

Nutritional Recommendations for Extravehicular Activity

Extravehicular activity (EVA) is a unique situation from a nutritional perspective, because the EVA suit does not easily allow food consumption. On early Shuttle missions, a 165-kcal fruit bar was custom-made to fit in the EVA suit, but it was typically not consumed, and is no longer included for EVA missions. As a result of the requirements of EVA preparation and EVA itself, crew members can go up to 8 to 10 hours without food. Recommendations were designed to help maximize crew performance and efficiency. When reviewed in 1991, the recommendations for EVA crew members was that they should consume an additional 500 kcal on days of EVA (47). This was designed to account for the metabolic cost of EVA (~200 kcal/hr).

In 2000, another review of this situation was requested by Flight Medicine. The resulting recommendation was to provide food items for consumption during EVA preparation (as close as possible to the donning of helmets). The food items should contain 300–500 kcal, with about 70–100 g of carbohydrate, and a high soluble fiber content. Candidate items are reviewed to ensure that in the attempt to meet the basic criteria, other undesirable nutrients or additives are not included, and that crew preferences are accounted for. It was also recommended that crew members reconsider use of the in-suit food bar, or that alternatives be sought.

Fluid intake during EVA is also a concern. Crew members lose 6–8 oz fluid/h during an EVA. The current EVA suit contains either a 24- or 32-ounce drink bag. Only water is used (early EVAs included flavored beverages, but a problem during a lunar EVA resulted in a programmatic decision to only include water). Provision of in-suit fluid is an important factor in suit design. For the current suit, use of the 32-ounce drink bag is recommended. The development of a larger, disposable drink bag is highly encouraged. The disposable drink bag should be designed so that a flavored drink (such as the current Shuttle food system beverages) could be used to increase palatability and intake, assuming that the technical concerns can be eliminated.

Although the issue of nutritional support during EVA was reviewed only briefly at the 2005 Standards and Operating Bands meeting, no recommendations were made to change the 2000 guidelines. As suits are developed for exploration mission transit and planetary EVAs, meeting the suggestions above would alleviate problems deemed too complicated given the existing suit used on Shuttle and ISS.

Along with food and fluid issues associated with EVA, the hyperoxic environment also has the potential for causing additional damage to the body. The prebreathe protocol for U.S. astronauts typically includes a 2.5-h prebreathe of >95%–100% oxygen (423) to reduce risk for decompression sickness. After the 2.5-h prebreathe, astronauts are typically exposed to hypobaric 100% oxygen for 6 to 8 h during EVA. Studies from saturation dives show that oxidative damage is evident under similar conditions (424). Judging by the results of numerous ground-based studies with hyperoxia, the potential exists for nutritional countermeasures to mitigate some of oxidative damage (425-427).

APPENDIX A. Abbreviations, Acronyms, Definitions

4-PA	4-pyridoxic acid
ACP	acyl carrier protein
AI	adequate intake
AMDR	acceptable macronutrient distribution range
ATP	adenosine triphosphate
BSAP	bone-specific alkaline phosphatase
CoA	coenzyme A
DFE	dietary folate equivalent
DPD	deoxypyridinoline
DRI	dietary reference intake
dU	deoxyuridine
EAR	estimated average requirement
EER	estimated energy requirement
EFA	essential fatty acid
EGR	erythrocyte glutathione reductase
EPA	eicosapentaenoic acid
ETK	erythrocyte transketolase
EVA	extravehicular activity
FAD	flavin adenine dinucleotide
FIGLU	formiminoglutamic acid
GLA	γ-carboxyglutamic acid
GPX	glutathione peroxidase
HDL	high-density lipoprotein
HP	helical peptide
ISS	International Space Station
LDL	low-density lipoprotein
LET	linear energy transfer
MAO	monoamine oxidase
MCV	mean corpuscular volume
3-MH	3-methylhistidine
NAD	nicotinamide adenine dinucleotide
NADH	nicotinamide adenine dinucleotide, reduced
NADP	nicotinamide adenine dinucleotide phosphate
NADPH	nicotinamide adenine dinucleotide phosphate, reduced
NE	niacin equivalent
NTX	n-telopeptide
PL	pyridoxal
PLP	pyridoxal 5′-phosphate
PM	pyridoxamine
PMP	pyridoxamine 5′-phosphate
PN	pyridoxine
PNP	pyridoxine 5′-phosphate
PTH	parathyroid hormone
RBC	red blood cell (erythrocyte)

RBP	retinol-binding protein
RDA	recommended dietary allowance
RE	retinol equivalent
TE	tocopherol equivalent
TEE	total energy expenditure
THF	tetrahydrofolate
TPN	total parenteral nutrition
TPP	thiamin pyrophosphate
U.S.	United States
UV	ultraviolet

Definitions

Dietary Reference Intakes (DRIs): The DRIs are developed by the Institute of Medicine (82, 174, 187, 251) of the National Academy of Sciences. They are reference values used for evaluating and planning nutrient intakes for healthy individuals, and include the Recommended Dietary Allowances (RDAs), Adequate Intakes (AIs), Estimated Average Requirements (EARs), and Tolerable Upper Intake Levels (ULs). The RDA provides age- and gender-specific recommendations for the average daily nutrient requirements for nearly all (97-98%) healthy individuals. When the scientific data available are insufficient to determine an RDA, AIs are set, and these provide the minimum amount needed to maintain adequate nutritional status for nearly all members of a specific group. The UL is the maximum daily intake that is not likely to engender adverse effects.

APPENDIX B. Requirements

1. The estimated energy requirements (EER) for space missions shall be based on total energy expenditure (TEE), using an activity factor of 1.25 (active) along with the individual's age, body mass (kg), and height (m) in the following calculations:

   EER for men 19 y and older
   EER = 622 – 9.53 x Age [y] + 1.25 x (15.9 x Mass [kg] + 539.6 x Ht [m])

   EER for women 19 y and older
   EER = 354 – 6.91 x Age [y] + 1.25 x (9.36 x Mass [kg] + 726 x Ht [m])

2. The dietary intake of protein shall be 0.8 g/kg per day and not exceed 35% of the total daily energy intake. Approximately 2/3 of the total amount of protein shall be provided in the form of animal protein and 1/3 in the form of vegetable protein.

3. The dietary intake of carbohydrate shall comprise 50–55% of the total daily energy intake.

4. The dietary intake of fat shall comprise 25–35% of the total daily energy intake. Dietary intake of n-6 and n-3 fatty acids shall be 14 grams/day and 1.1–1.6 grams/day, respectively. Consumption of saturated fat, trans fatty acids, and cholesterol will be as low as possible.

5. The dietary intake of fiber shall be 10–14 grams/1000 kcal.

6. The dietary intake of fluid shall be 1–1.5 mL/kcal, with a minimum intake of 2000 mL.

7. The dietary intake of vitamin A shall be 700–900 μg/day.

8. The dietary intake of vitamin D shall be 25 μg per day.

9. The dietary intake of vitamin K shall be 90 and 120 μg per day for women and men, respectively.

10. The dietary intake of vitamin E shall be 15 mg/day.

11. The dietary intake of vitamin C shall be 90 mg/day.

12. The dietary intake of Vitamin B_{12} shall be 2.4 μg/day.

13. The dietary intake of vitamin B_6 shall be 1.7 mg/day.

14. The dietary intake of thiamin shall be 1.1 and 1.2 μmol/day for women and men, respectively.

15. The dietary intake of riboflavin shall be 1.3 mg/day.

16. The dietary intake of folate shall be 400 μg/day.

17. Based on the current recommendations for Earth (230), the dietary intake of niacin shall be 16 mg NE/day.

18. The dietary intake of biotin shall be 30 μg/day.

19. The dietary intake of pantothenic acid shall be 30 mg/day.

20. The dietary intake of calcium shall be 1200–2000 mg/day.

21. The dietary intake of phosphorus shall be 700 mg/day, and shall not exceed 1.5 times the calcium intake.

22. The dietary intake of magnesium shall be 320 and 420 mg/day for women and men respectively. The upper limit for both genders is defined as 350 mg/d from supplements only (not from dietary sources).

23. The dietary intake of sodium shall be 1500–2300 mg/day for both women and men.

24. The dietary intake of potassium shall be 4.7 g/d.

25. The dietary intake of iron shall be 8–10 mg/day.

26. The dietary intake of copper shall be 0.5–9 mg/day.

27. The dietary intake of manganese shall be 1.8 and 2.3 mg/day for women and men respectively.

28. The dietary intake of fluoride shall be 3 and 4 mg/day for women and men respectively.

29. The dietary intake of zinc shall be 11 mg/day.

30. The dietary intake of selenium shall be 55–400 μg/day.

31. The dietary intake of iodine shall be 150 μg/d.

32. The dietary intake of chromium shall be 35 μg/day.

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