NAME: OKOR PRECIOUS EIKHOMUN

MATRIC NO: 17/MHS01/248

DEPARTMENT: PHARMACOLOGY

COURSE: BCH 204

The Tolerable Upper Intake Level (UL) specifies the highest average daily intake level of a nutrient, consumed on a habitual basis, that is likely to pose no risk of adverse health effects for nearly all apparently healthy individuals in a given Dietary Reference Intake (DRI) age, sex, and life-stage group. The potential for adverse health effects increases as intakes increase above the UL. The UL is intended to provide guidance on intake levels that are safe; it is not intended to serve as an intake goal. The *Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease* (*Guiding Principles Report*) recommended that the UL be retained in the expanded DRI model, but that it should characterize *toxicological* risk ([NASEM, 2017](https://www.ncbi.nlm.nih.gov/books/NBK545424/)). Although this conceptual revision narrows the scope of the UL, it allows for a more nuanced characterization of the different types of risk that can exist with intake of a nutrient or other food substance. This chapter presents the committee's review of the evidence on the toxicological effects of excessive potassium intake and its conclusion regarding establishing a potassium UL. For context, the committee's findings are preceded by a brief summary of the decision made regarding the potassium UL in the *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (*2005 DRI Report*)

A potassium UL was not established in the *2005 DRI Report*. Potential indicators reviewed included gastrointestinal discomfort from certain forms of potassium supplements and arrhythmia from hyperkalemia. Available evidence indicated that, in generally healthy individuals, excess potassium is excreted in the urine. Because they may have impaired potassium excretion, individuals with certain conditions (e.g., chronic kidney disease, end-stage renal disease, diabetes, severe heart failure, adrenal insufficiency) and individuals who use certain medications (e.g., angiotensin-converting enzyme inhibitors [ACE-Is] and angiotensin-receptor blockers [ARBs]) were identified as potentially vulnerable subpopulations in which potassium intakes at the AI may not be appropriate ([IOM, 2005](https://www.ncbi.nlm.nih.gov/books/NBK545424/))

**REVIEW OF POTENTIAL INDICATORS OF TOXICOLOGICAL ADVERSE EFFECTS OF EXCESSIVE POTASSIUM INTAKE**

Although dietary potassium intake can be increased through behavioral change, there is a self-limiting aspect to such changes that makes toxic adverse effects from increases in dietary potassium intake unlikely. Reports and studies evaluating potassium supplements were therefore considered most useful to determine whether a potassium intake level that could lead to toxicity could be quantified. For ethical reasons, trials cannot be designed to evaluate whether an intervention will increase the incidence of adverse effects. Consequently, adverse effect data in trials are almost always secondary outcomes. These data, particularly if systematically and carefully reported, can provide useful information for evaluating the likelihood of adverse effects. However, as secondary outcomes, these trials may not be adequately powered to identify a statistically significant occurrence of an adverse effect. These strengths and limitations need to be taken into account when using data from trials for evaluating the potential for adverse effects.

Guided by the first step of the DRI organizing framework, the committee sought to identify potential indicators of toxicological adverse effects from excessive potassium intake. The section that follows describes the evidence the committee reviewed to identify indicators that could potentially inform the derivation of the potassium UL.

**Evidence Reviewed to Identify Potential Toxicological Indicators**

The committee conducted a literature scan to identify potential indicators that may be informative for the potassium DRIs . Among the identified indicators were blood lipid concentrations and catecholamines. Based on the committee's supplemental literature search , a systematic review was identified that compiled evidence from randomized controlled trials on these measures . Meta-analyses of randomized controlled trial data found that increasing potassium intake did not increase blood lipids, plasma adrenaline, or plasma noradrenaline concentrations among adult . No other potential indicator of potassium toxicity was identified from the committee's literature scan.

Additional exploration of systematic reviews and case reports on toxicity, adverse effects, and poisonings from potassium intake were undertaken in an effort to identify potential toxicological adverse effects. From these efforts, the committee identified a collection of case reports on deaths and sublethal symptomology attributed to high levels of potassium intake. The committee also compiled reported adverse effects of the potassium trials included in the Agency for Healthcare Research and Quality systematic review, *Sodium and Potassium Intake: Effects on Chronic Disease Outcomes and Risks* (*AHRQ Systematic Review*), and the committee's supplemental literature searches. The committee notes that the doses used in trials are generally not high enough to cause serious adverse effects, as it would be unethical to randomize participants to such an exposure. The intent of these evidence searches was to identify specific indicators that could potentially inform the potassium UL

##  Calcium Deficiency & Toxicity

Because of the large amount of calcium in bones, deficiency is rare1. Hypocalcemia (low serum calcium levels in blood) can result in tetany (involuntary muscle contractions)2. In addition, calcium deficiency in children can lead to rickets, which is a vitamin D deficiency. While not a deficiency, low calcium intake can lead to decreased bone mineral density and the conditions osteopenia and osteoporosis. How these differ from osteomalacia and normal bone is illustrated and described below. There are two different bone components that we will consider to understand what is happening in the bone. Matrix is the scaffolding onto which mineral is deposited. Mineral is at it sounds, the mineral that is deposited on the matrix.

Osteomalacia – Bone mass is normal, but the matrix to mineral ratio is increased, meaning there is less mineral in bone.

Osteopenia – Bone mass is decreased, but the matrix to mineral ratio is not altered from normal bone. This condition is intermediate in between normal and osteoporosis.

Osteoporosis – Bone mass is further decreased from osteopenia, but the matrix to mineral ratio is not altered from normal bone3.

The National Osteoporosis Foundation estimates that “about 54 million Americans have osteoporosis and low bone mass, placing them at increased risk for osteoporosis. Studies suggest that approximately one in two women and up to one in four men age 50 and older will break a bone due to osteoporosis.” To prevent osteoporosis it is important to build peak bone mass, 90% of which is built in females by age 18 and age 20 in males, but can continue to increase until age 30. After that time, bone mass starts to decrease. For women after menopause, bone mass decreases dramatically because of the decrease in estrogen production, as shown in the link below5.

Combining the decrease after menopause along with the fact that women have lower bone mass to begin with, helps further explain why osteoporosis is more common in females. A measure of bone status is bone mineral density. As the name indicates, bone mineral density is a measure of the amount of mineral in bone. Dual energy X-ray absorptiometry (DEXA) accurately measures bone mineral density using a small amount of radiation.

There are other methods of measuring bone mineral density, such as peripheral DEXA and ultrasound. These typically are done on the wrist or heel, but are not as accurate because that one area might not reflect the bone mineral density in other parts of the body7.

Calcium toxicity is rare, occurring in those with hyperparathyroidism or high calcium supplementation levels. Like vitamin D, toxicity can lead to calcification of soft tissues7. In addition, a very high intake of calcium can lead to kidney stone formation.

Magnesium, an abundant mineral in the body, is naturally present in many foods, added to other food products, available as a dietary supplement, and present in some medicines (such as antacids and laxatives). Magnesium is a cofactor in more than 300 enzyme systems that regulate diverse biochemical reactions in the body, including protein synthesis, muscle and nerve function, blood glucose control, and blood pressure regulation [[1-3](https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#en1)]. Magnesium is required for energy production, oxidative phosphorylation, and glycolysis. It contributes to the structural development of bone and is required for the synthesis of DNA, RNA, and the antioxidant glutathione. Magnesium also plays a role in the active transport of calcium and potassium ions across cell membranes, a process that is important to nerve impulse conduction, muscle contraction, and normal heart rhythm [[3](https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#en3)]. An adult body contains approximately 25 g magnesium, with 50% to 60% present in the bones and most of the rest in soft tissues [[4](https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#en4)]. Less than 1% of total magnesium is in blood serum, and these levels are kept under tight control. Normal serum magnesium concentrations range between 0.75 and 0.95 millimoles (mmol)/L [[1](https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#en1),[5](https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#en5)]. Hypomagnesemia is defined as a serum magnesium level less than 0.75 mmol/L [[6](https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#en6)]. Magnesium homeostasis is largely controlled by the kidney, which typically excretes about 120 mg magnesium into the urine each day [[2](https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#en2)]. Urinary excretion is reduced when magnesium status is low [[1](https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#en1)].

Assessing magnesium status is difficult because most magnesium is inside cells or in bone [[3](https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#en3)]. The most commonly used and readily available method for assessing magnesium status is measurement of serum magnesium concentration, even though serum levels have little correlation with total body magnesium levels or concentrations in specific tissues [[6](https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#en6)]. Other methods for assessing magnesium status include measuring magnesium concentrations in erythrocytes, saliva, and urine; measuring ionized magnesium concentrations in blood, plasma, or serum; and conducting a magnesium-loading (or “tolerance”) test. No single method is considered satisfactory [[7](https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#en7)]. Some experts [[4](https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#en4)] but not others [[3](https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#en3)] consider the tolerance test (in which urinary magnesium is measured after parenteral infusion of a dose of magnesium) to be the best method to assess magnesium status in adults. To comprehensively evaluate magnesium status, both laboratory tests and a clinical assessment might be required [[6](https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#en6)].

## Recommended Intakes

Intake recommendations for magnesium and other nutrients are provided in the Dietary Reference Intakes (DRIs) developed by the Food and Nutrition Board (FNB) at the Institute of Medicine of the National Academies (formerly National Academy of Sciences) [[1](https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#en1)]. DRI is the general term for a set of reference values used to plan and assess nutrient intakes of healthy people. These values, which vary by age and sex, include:

* Recommended Dietary Allowance (RDA): Average daily level of intake sufficient to meet the nutrient requirements of nearly all (97%–98%) healthy individuals; often used to plan nutritionally adequate diets for individuals.
* Adequate Intake (AI): Intake at this level is assumed to ensure nutritional adequacy; established when evidence is insufficient to develop an RDA.
* Estimated Average Requirement (EAR): Average daily level of intake estimated to meet the requirements of 50% of healthy individuals; usually used to assess the nutrient intakes of groups of people and to plan nutritionally adequate diets for them; can also be used to assess the nutrient intakes of individuals.
* Tolerable Upper Intake Level (UL): Maximum daily intake unlikely to cause adverse health effects.

Table 1 lists the current RDAs for magnesium [[1](https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#en1)]. For infants from birth to 12 months, the FNB established an AI for magnesium that is equivalent to the mean intake of magnesium in healthy, breastfed infants, with added solid foods for ages 7–12 months.

| **Table 1: Recommended Dietary Allowances (RDAs) for Magnesium [**[**1**](https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#en1)**]** |
| --- |
| **Age** | **Male** | **Female** | **Pregnancy** | **Lactation** |
| Birth to 6 months | 30 mg\* | 30 mg\* |  |  |
| 7–12 months | 75 mg\* | 75 mg\* |  |  |
| 1–3 years | 80 mg | 80 mg |  |  |
| 4–8 years | 130 mg | 130 mg |  |  |
| 9–13 years | 240 mg | 240 mg |  |  |
| 14–18 years | 410 mg | 360 mg | 400 mg | 360 mg |
| 19–30 years | 400 mg | 310 mg | 350 mg | 310 mg |
| 31–50 years | 420 mg | 320 mg | 360 mg | 320 mg |
| 51+ years | 420 mg | 320 mg |  |  |

## Magnesium Deficiency

Symptomatic magnesium deficiency due to low dietary intake in otherwise-healthy people is uncommon because the kidneys limit urinary excretion of this mineral [[3](https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#en3)]. However, habitually low intakes or excessive losses of magnesium due to certain health conditions, chronic alcoholism, and/or the use of certain medications can lead to magnesium deficiency.

Early signs of magnesium deficiency include loss of appetite, nausea, vomiting, fatigue, and weakness. As magnesium deficiency worsens, numbness, tingling, muscle contractions and cramps, seizures, personality changes, abnormal heart rhythms, and coronary spasms can occur [[1](https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#en1),[2](https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#en2)]. Severe magnesium deficiency can result in hypocalcemia or hypokalemia (low serum calcium or potassium levels, respectively) because mineral homeostasis is disrupted [[2](https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#en2)].

**Chlorine deficiency**, condition in which [chlorine](https://www.britannica.com/science/chlorine) is insufficient or is not utilized properly. Chlorine is a component of all body secretions and excretions resulting from processes of building ([anabolism](https://www.britannica.com/science/anabolism)) and breaking down ([catabolism](https://www.britannica.com/science/catabolism)) body tissues. Levels of chlorine closely parallel levels of [sodium](https://www.britannica.com/science/sodium) intake and output, since a primary source of both is sodium chloride, or common table [salt](https://www.britannica.com/science/salt). Chlorine is stored to a limited extent in the skin, subcutaneous tissues, andskeleton and [constitutes](https://www.merriam-webster.com/dictionary/constitutes) two-thirds of the negatively charged ions (anions) in the [blood](https://www.britannica.com/science/human-blood). [Chlorides](https://www.britannica.com/science/chloride) (chlorine compounds) play an essential role in the electrical neutrality and pressure of extracellular fluids and in the acid-base balance of the body. Gastric secretion is composed of chlorides in the form of [hydrochloric acid](https://www.britannica.com/science/hydrochloric-acid) and salts. Chlorine is readily absorbed during digestion, and similarly its rate of excretion through sweat, kidney excretion, and intestinal expulsion is high. The body’s supplies of chlorine are rapidly depleted during hot weather, when excessive perspiration reduces the fluid content of the body. Also, stored chlorides may become dangerously low in periods of severe [vomiting](https://www.britannica.com/science/vomiting) and [diarrhea](https://www.britannica.com/science/diarrhea) and in diseases that produce severe [alkalosis](https://www.britannica.com/science/alkalosis), an accumulation  of base or loss of acid in the body. Treatment of chlorine deficiency is directed towards the underlying cause.

# Iron: Deficiency and toxicity

Iron is an essential nutrient that is vital to the processes by which cells generate energy. Iron also can be damaging when it accumulates in the body. In fact, iron is a problem nutrient for millions of people. Some people simply don’t eat enough iron-containing foods to support their health optimally while others have so much iron that it threatens their well-being. The principle that too little or too much of a nutrient is harmful seems particularly apropos for iron. Iron has a knack of switching back and forth between two ionic states. In the reduced state, iron has lost two electrons and therefore has a net positive charge of two. Iron in the reduced state is known as ferrous iron. In the oxidized state, iron has lost a third electron, has a net positive charge of three and is known as ferric iron. Because iron can exist in different ionic states, iron can serve as a co-factor to enzymes involved in oxidation-reduction reactions. In every cell, iron works with several of the electron-transport chain proteins that perform the final steps of the energy yielding pathways. These proteins transfer hydrogens and electrons from energy- yielding nutrients to oxygen, forming water and, in the process, make ATP for the cells’ use. If you recall from my previous article on this website, ATP is adenosine triphosphate, the cellular energy currency of the body. A direct precursor to this substance is nicotinamide adenine dinucleotide (NADH).

**Iron deficiency:**

If absorption cannot compensate for losses or low dietary intakes, and body stores are used up, then iron deficiency sets in. Because so much of the body’s iron is in the blood, iron losses are greatest whenever blood is lost. Bleeding from any site incurs iron losses. Active bleeding ulcers, menstruation and injury result in iron losses.

Women are especially prone to iron deficiency during their reproductive years because of repeated blood losses during menstruation. Pregnancy places iron demands on women as well because iron is needed to support the added blood volume, the growth of the fetus and blood loss during childbirth. Infants and young children receive little iron from their high milk diets, yet extra iron is needed to support their rapid growth. The rapid growth of adolescence, especially for males, and the menstrual losses of teen females demand extra iron that a typical teen diet may not provide.

|  |
| --- |
|  |