

Sodium: How and How Not to Set a Nutrient Intake Recommendation

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Several months ago, in commenting on vitamin D, I remarked that more ink had been spilled on the issue of the vitamin D requirement than for any other nutrient, with the exception of sodium.¹ The issue of sodium intake continues to be a major focus of nutrition policymakers and regulators. Emerging evidence indicating that low sodium intakes might actually be harmful²⁻⁹ caused the Institute of Medicine (IOM) to convene an expert panel to reevaluate the 2005 Dietary Reference Intakes (DRIs) for sodium.¹⁰ That reevaluation, just recently released,¹¹ cautiously backs away from the stringent restrictions of the 2005 DRIs for sodium, noting that the evidence “does not support reduction in sodium intake to below 2,300 mg/day.” The one thing that seems clear in the discussions and controversy swirling around this issue is that there is no policy consensus concerning what may be optimal sodium intake or what may be the balance of harm and benefit as a result of reducing sodium intake below the current US average (3,400–3,600 mg/day).

Primarily to refresh our collective memories about how nutrient requirements and nutrient intake recommendations are to be formulated, it may be worth briefly reviewing the DRI process. The general guidelines for formulating DRIs are set forth in the IOM's

introductory volume to the DRI series¹² and have been applied to most nutrients following the formulation of the current approach in the mid-1990s. The reference intakes that are to be developed, where possible, are the estimated average requirement (EAR), the recommended dietary allowance (RDA), the no observed adverse effect level, the tolerable upper intake level, and the lowest observed adverse effect level. When data are deemed insufficient to define an EAR, the Food and Nutrition Board selects what it terms an “adequate intake” (AI). The latter is somewhat roughly defined as the approximate intake found in apparently healthy populations.¹²

Even brief acquaintance with the process as it has played out for the full array of nutrients reveals considerable inconsistency and even contradiction in the development of the corresponding DRIs. For example, in practice the AI has been used more often for nutrients with abundant data, whereas those with a paucity of data are nevertheless assigned EARs and RDAs. Both calcium and sodium have a vast literature relating intake to health outcomes, yet the Food and Nutrition Board assigns both only an AI. Magnesium, by contrast, suffers from an extreme shortage of relevant data, yet it is assigned both an EAR and an RDA.¹³

With sodium, in particular, the AI assigned by the IOM in 2005 corresponded with no actual intake found in the populations of any first world nation, where the average intake of apparently healthy adults is approximately 3,500 mg/day.¹¹ By contrast the IOM's 2005 AI is 1,500 mg/d up to age 50 years, 1,300 mg/d for ages 50–70 years, and 1,200 mg/d for ages >70 years, none of which is even remotely close to what the DRI process prescribes, and, given available foods, these levels have been found to be difficult if not impossible to

achieve in a diet otherwise adequate in total nutrients.^{14,15}

In defining these DRIs, the process consists first of the identification of harm associated with both too little and too much of the nutrient concerned. This approach is explicitly formulated on page 12 of “Dietary Reference Intakes” in the form of a generalized U-shaped graph (Figure 1), depicting increased risk of harm at both extremes of intake.¹² Across the full array of nutrients for which DRIs have been developed, this upwardly directed, concave curve seems to be universal. Sometimes it is J-shaped (forward or reverse), with risk at one extreme of intake rising to a greater extent than the other, but for most nutrients, risk of harm rises at both extremes and is lowest (or absent) near the center of the plausible intake range. For example, with vitamin D, it is well recognized that, among other systemic expressions, deficiency increases risk of rickets and osteomalacia, and excess produces vitamin D intoxication (i.e., hypercalcemia and renal calcinosis). Once the hazard is defined, the strength of the evidence relating to these various harms is evaluated, and an attempt is made to find an intake range over which risk is apparently absent (the high end of which is the no observed adverse effect level) or is at least countered by an offsetting benefit.

It is, in a sense, odd that the emphasis in this process should be placed on harm rather than benefit, for nutrition is, in the last analysis, about benefit. Nevertheless, the facts are that this is the approach that is taken officially. This same negative focus is expressed in diverse ways throughout the regulatory system, such as in the nutrition facts panel required on all manufactured foods, where the mandated, major emphasis is on nutrients whose intake is to be avoided, minimized, or concerned

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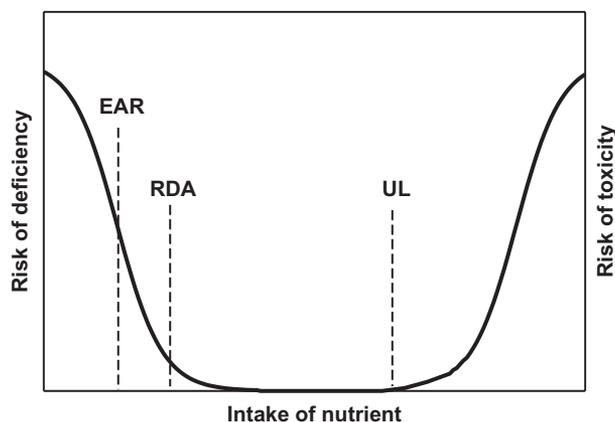


Figure 1. Relationship of risk and nutrient intake, showing the location of the 3 principal Dietary Reference Intakes. EAR, estimated average requirement; RDA, recommended dietary allowance; UL, tolerable upper intake level. Redrawn from Figure 1 in Dietary Reference Intakes.¹² Copyright Robert P. Heaney, MD, 2013. All rights reserved. Used with permission.

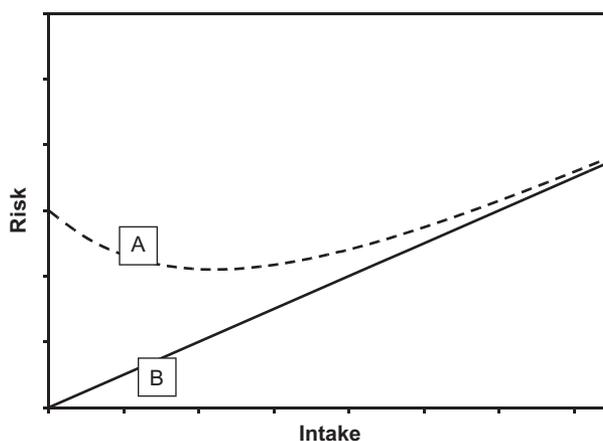


Figure 2. Contrast between a J-shaped curve and a linear curve of risk on intake. Curve A is the curve recently reported for sodium^{7,9} and generally accepted for most other nutrients; curve B is the curve implicitly employed in the setting of sodium Dietary Reference Intakes. Copyright Robert P. Heaney, MD, 2013. All rights reserved. Used with permission.

about. This attitude would seem to be a vestige of medicine's century-old, operative paradigm to the effect that disease is caused by external agents—microbial or toxic for the most part—hence the emphasis on nutrients as potentially harmful. Sodium, cholesterol, and saturated fat have for a long time been the poster children in this “usual list of suspects.”

In the case of sodium, the ultimate harm is generally considered to be cardiovascular disease and its associated morbidity and mortality.¹⁰ The proxy used for these outcomes has been blood pressure, which, in observational studies, is recognized to be associated with risk of cardiovascular disease, but which, in its recent reevaluation,¹¹ the IOM acknowledged as not tracking with health outcomes across the full range

of sodium intakes. It is generally recognized that lowering elevated blood pressure by pharmacologic means reduces risk, and it is assumed, in the case of sodium, that a reduction in blood pressure produced by a decrease in sodium intake would produce similar benefits. In such a calculus, it has generally been further assumed that there are no offsetting harmful effects of reducing sodium intake beyond a certain level. It is this assumption that has recently been called into question by studies^{3,7,9} reporting health outcomes after substantially reduced sodium intake.

In effect, the process actually used to develop sodium intake recommendations has implicitly used not a U-shaped or J-shaped model, standard for virtually all other nutrients, but an effectively linear model (Figure 2). In doing so it

would seem that the real benefit produced by lowering sodium intake from, e.g., 8 g/d to 6 g/d has been applied to a reduction from a basal sodium intake of, e.g., 3.5 g/d to 1.5 g/d. In short, all reductions of sodium intake, irrespective of starting point, were deemed to be beneficial. Indeed, some reduction in blood pressure is usually found with such changes. However, recent systematic reviews and population-based studies have shown risk curves that are quite consistent with that of other nutrients (i.e., with an upswing in risk of cardiovascular morbidity and mortality as one begins to approach the lower end of the plausible sodium intake continuum).^{7,9} In the studies concerned, the least risk of serious adverse outcomes has been found to fall in the intake range between 3.0 and 5.5 g sodium per day.

It is worth noting that, wherever that zone of minimum risk may be located, the data on which such conclusions are drawn consist of studies of adverse cardiac outcomes associated with, or produced by, particular sodium intakes. Such an approach is in keeping with the recent emphasis on “evidence-based” methods. Evidence-based medicine is of unquestioned value in the evaluation of medical interventions where randomized controlled trials alone provide evidence of efficacy. However, such approaches are not well suited to the evaluation of nutrients, where efficacy is not in question. All nutrients are, by definition, efficacious—otherwise they would not be nutrients. Rather it is quantity that is the critical variable, and randomized controlled trials are poorly suited to answer quantitative questions except in a very coarse way. There are many reasons for this, principal among which are two: (i) it is ethically problematic to test a hypothesis of harm in humans; and (ii) the approach to “normal” with nutrients is asymptotic. As a result, as intake approaches adequacy, the difference in outcomes becomes smaller and smaller, easily exceeding the sensitivity of a plausible randomized controlled trial to detect the difference.

For those reasons, nutritional science needs other means of approaching how much of a nutrient is adequate, optimal, and safe.¹⁶ One such, applicable to nutrients that are components of negative feedback control loops, is the assessment of the adaptive response produced by varying intakes, taking as “normal” an

intake that requires the least adaptation or compensation. Thus, at low calcium intakes parathyroid hormone secretion is elevated, and, assuming adequate vitamin D status, a calcium intake that minimizes (but not abolishes) parathyroid hormone response would arguably be the physiologically “normal” calcium intake. Thus, if we substitute “compensatory response” for “risk of deficiency” in Figure 1, we portray graphically how determination of the required intake might be approached. Moreover, doing so substitutes a directly measurable physiological variable for an indirect measure (i.e., risk). (Incidentally, this use of the afferent arm of the feedback loop is the standard approach in clinical endocrinology to regulate thyroid hormone replacement therapy.)

Something similar applies to sodium intake. Insufficient sodium intake evokes a response from the renin-angiotensin-aldosterone-system (RAAS), in the absence of which (as in Addison’s disease) blood pressure and extracellular fluid volume cannot be maintained at normal levels at low sodium intakes. “Insufficient” in this sense is defined precisely by the fact that it evokes a compensatory response to sustain homeostasis. The RAAS response, which, among other effects, conserves sodium in urine and sweat and constricts blood vessels, compensates for what would otherwise be a disabling reduction in blood volume and renal blood flow. It is worth noting that blood pressure does continue to decline (albeit slowly) as sodium intake falls in the intake region

over which RAAS is activated, just as, with reduced calcium intake, serum calcium falls slightly, despite compensatory parathyroid activity. This behavior is depicted diagrammatically in Figure 3, which proposes 4 zones of response to nutrient intake (or, in this case, sodium intake): zone T, at the highest intakes, with elevated blood pressure and its associated cardiovascular morbidity; zone N, “normal” intake, in which blood pressure is effectively constant irrespective of changes in sodium intake; zone C, a “deficient” intake over which blood pressure falls slightly despite compensation by RAAS; and zone F, a very low intake over which RAAS fails and blood pressure cannot be maintained.

Studies from Laragh’s laboratory >30 years ago¹⁷ showed that both plasma renin activity and aldosterone began to rise at sodium intakes <150 mmol/d and <120 mmol/d, respectively (Figure 3, zone C). Furthermore, studies published >20 years ago established that higher plasma renin activity was associated with a striking increase in risk of myocardial infarctions.^{18,19} These increases in risk are independent of salt intake, as elevated renin secretion can be produced in many ways. In the context of the sodium intake recommendation, however, it suffices simply to note that low salt intake is one, and perhaps the most common, cause of elevated plasma renin activity and aldosterone levels. Inescapably, therefore, compensatory responses to low sodium intake, although necessary and even life-saving in the short-term as responses to central

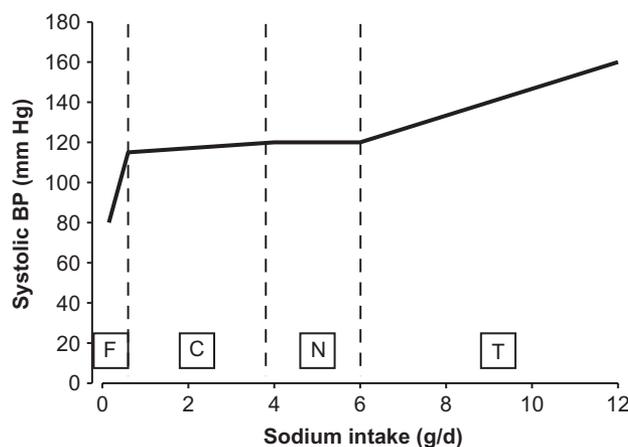


Figure 3. Diagrammatic representation of blood pressure over 4 zones of sodium intake. Zone F is severe deficiency; zone C is moderate deficiency; zone N is normal; and zone T is toxicity. Copyright Robert P. Heaney, MD, 2013. All rights reserved. Used with permission.

volume contraction, appear to incur risk of harm if the response is sustained.

Hence, it would seem that an intake that minimized RAAS response would be not only a measure of the “normal” sodium intake but also a guarantor of minimal cardiovascular disease risk. It may be argued that compensatory adjustments are a part of normal physiology, and, certainly, they are. Without them, homeostasis would be impossible. But a regimen that evokes and literally depends upon constant activation of a “rescue” mechanism seems distinctly unphysiological.

In closing, it is worth noting that the zone of minimal RAAS response is virtually identical to the zone of lowest risk found in clinical mortality and morbidity data. The convergence of these 2 very different approaches must be considered reassuring.

DISCLOSURE

The author declared no conflict of interest.

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