Tolerable upper intakes for dietary iron set by the US Food and Nutrition Board$^{1,2}$

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There is evidence for hepatic and pancreatic damage in sub-Saharan Africans caused by chronic intakes of 50–100 mg Fe/d from beer brewed at home in iron drums (Bantu siderosis; 1). These data, however, are compromised by the simultaneous intake of alcohol and by a possible genetic defect in iron metabolism in some of the affected individuals, both of which possibly contribute to the observed hepatic cirrhosis (2–4). In addition, Salonen et al (5) presented epidemiologic data from East Finland that suggest a causal relation between high body iron stores, as characterized by plasma ferritin values $>$ 200 µg/L, and the risk of acute myocardial infarction (AMI). This finding initiated a fierce controversy and stimulated substantial research at the epidemiologic and laboratory levels to either substantiate or reject the hypothesis. Although presently available data are not sufficient to definitely establish a causal relation between high dietary iron intake and increased risk of cardiovascular diseases, the evidence pointing to this hazard has become too strong to be ignored (eg, 5–13). Because of these uncertainties, the Panel on Micronutrients of the US Food and Nutrition Board did not base its assessment on these 2 hazards but chose to derive the tolerable upper intake level (UL) for dietary iron (45 mg/d) on the basis of the side effects of pharmaceutical iron preparations (14). A qualitative statement of caution was added to the “Risk Characterization” paragraph, stating that the possible cardiovascular and hepatic hazards make it “prudent to recommend that men and postmenopausal women avoid iron supplements and highly fortified foods.”

This approach avoids problems with the uncertain database for systemic iron-related health hazards. There is a clear cause-and-effect relation between the intake of oral iron preparations and reversible gastrointestinal distress, which is caused by direct irritation of the gastric and duodenal mucosa and depends on the available concentration of “free iron” in the gastrointestinal lumen (15). However, no free iron and, consequently, no gastrointestinal irritation is to be expected when the same quantity of iron is ingested with an iron-fortified diet. Therefore, producers of iron-fortified foods may have legitimate reasons to apply for permits to exceed a UL based on side effects of iron pills.

Moreover, gastrointestinal side effects of pharmaceutical iron preparations are minor and reversible. To build the UL on such a “proxy hazard” conveys the impression that the panel shifted its focus away from the controversial subject of a possible cardiovascular hazard related to moderately increased iron stores. This hazard has a much greater potential impact on public health than does temporary gastric discomfort after ingestion of iron pills. The panel’s report addresses the cardiovascular effects by quoting a meta-analysis of all epidemiologic studies done before 1997 (16). This analysis showed no convincing effect of increased iron stores on cardiovascular risk. The panel’s report states that on this basis “the relationship between iron intake and cardiovascular diseases was considered unclear at present time.”

Note that the evaluation by the panel failed to consider 2 large, prospective epidemiologic studies (6, 7) that were carefully controlled for inflammation as a potential cause of increased ferritin values. In addition, more than one variable was used to define iron stores, and cardiovascular risk was related to tertiles of plasma ferritin concentrations instead of a cutoff value of 200 µg ferritin/L as Salonen et al (5) used in their original study from 1992. Thus, these 2 studies were the first to present data for a response tailored to the criticism (8, 17, 18) of Salonen et al’s original study. The data from the Rotterdam Study (6), in fact, may well disqualify those data that defined body iron status by highly volatile variables such as plasma iron or transferrin saturation. This affects a major part of the database used in the meta-analysis on which the panel’s judgment on iron-related cardiovascular risk was based (16). Instead of feeding all available data into a meta-analysis, it would have been preferable to assess the quality of the data and to base the judgment mainly on the better-controlled studies. The data from the 2 large epidemiologic studies (6, 7) strengthen the concern about iron-related cardiovascular hazards that the panel expressed in its statement of caution.

Four studies concerning the cardiovascular risk of heterozygote carriers of hereditary hemochromatosis mutations were available to the panel. A comparatively small retrospective study found a higher AMI risk in control subjects than in heterozygotes for hereditary hemochromatosis (9). This study, however, selected cases according to preexisting atherosclerosis and thus was probably flawed by a survival bias. Another retrospective study found an increased risk of early-onset AMI related to high ferritin values that, however, was not significantly more frequent in heterozygotes (10). The 2 largest and best-controlled trials available at the time were prospective cohort studies that, indeed, showed an

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increased risk of AMI in heterozygotes (19, 20). In addition, recent data provide evidence for significantly increased concentrations of non-transferrin-bound iron in the serum of heterozygotes for hereditary hemochromatosis. Transferrin saturation was not higher in these patients than in control subjects (21), which may be explained by LDL peroxidation that is catalyzed by non-transferrin-bound iron. When the differences in study quality are included in the judgment, the risk of excess dietary iron intake becomes more evident, although, admittedly, a cause-and-effect relation between body iron stores and cardiovascular risk cannot be derived on the basis of epidemiologic cohort studies or retrospective evaluations. For this purpose an intervention trial is needed; however, none has been published.

Because the data from controlled epidemiologic trials are not definitive, a prudent and responsible approach should take into account the ample evidence supporting cause-and-effect relations between high free-iron concentrations and oxidative stress and between oxidative stress and cardiovascular risk. This evidence is based on fundamental biochemistry and on studies at the molecular and cellular level. The molecular interplay between the regulation of free-iron concentrations—ie, of iron that is so loosely ligated that it is available for Fenton chemistry—and oxidative stress is complex and potentially very hazardous, as can be observed, for example, during ischemia-reperfusion events such as AMI and stroke (11, 12). Evidence from several laboratories suggests that oxidative stress may trigger, at least temporarily, a further increase in free iron in cells and tissues, with the potential of setting in motion a vicious circle between these 2 variables (13, 22, 23). We cannot afford to ignore this body of evidence from the biochemical side of hazard assessment. If the iron effect is mediated by oxidative stress, it will be difficult to prove its impact in epidemiologic studies because there are an array of other influences on local oxidative stress that cannot be sufficiently controlled. To focus exclusively on iron may be too narrow an approach to understanding the complex pathophysiology of cardiovascular events. This problem may be partly responsible for the different outcomes of epidemiologic studies. Future trials may well remain contradictory, as long as their scope is focused on just one variable such as iron, although this variable may increase the cardiovascular risk in many situations.

On consideration of these issues and the available epidemiologic data, it hardly seems possible to quantify iron-related cardiovascular risk when setting a value for a UL. Likewise, because of alcohol intake and possible genetic defects, it does not seem possible to set a value on the basis of the risk of hepatic cirrhosis as the other systemic sequel of high dietary iron intake. Therefore, not to set any numeric UL for iron would be more honest than to base such a value on a reversible local effect that only occurs after ingestion of iron pills. In contrast, there is ample reason to suspect an iron-related cardiovascular hazard when the quality of epidemiologic data and the knowledge of underlying molecular and pathophysiological mechanisms are included in the analysis. It seems wise, on the basis of such evaluation, to have no UL but just a serious qualitative statement of caution and to recommend a dietary iron intake that satisfies dietary requirements but does not substantially exceed them. In any case, the attention of risk managers must explicitly be drawn to the large uncertainties inherent in the present UL for iron.

REFERENCES