A Review of Dietary Zinc Recommendations

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Abstract

Background. Large discrepancies exist among the dietary zinc recommendations set by expert groups.

Objective. To understand the basis for the differences in the dietary zinc recommendations set by the World Health Organization, the U.S. Institute of Medicine, the International Zinc Nutrition Consultative Group, and the European Food Safety Agency.

Methods. We compared the sources of the data, the concepts, and methods used by the four expert groups to set the physiological requirements for absorbed zinc, the dietary zinc requirements (termed estimated and/or average requirements), recommended dietary allowances (or recommended nutrient intakes or population reference intakes), and tolerable upper intake levels for selected age, sex, and life-stage groups.

Results. All four expert groups used the factorial approach to estimate the physiological requirements for zinc. These are based on the estimates of absorbed zinc required to offset all obligatory zinc losses plus any additional requirements for absorbed zinc for growth, pregnancy, or lactation. However, discrepancies exist in the reference body weights used, studies selected, approaches to estimate endogenous zinc losses, the adjustments applied to derive dietary zinc requirements that take into account zinc bioavailability in the habitual diets, number of dietary zinc recommendations set, and the nomenclature used to describe them.

Conclusions. Estimates for the physiological and dietary requirements varied across the four expert groups. The European Food Safety Agency was the only expert group that set dietary zinc recommendations at four different levels of dietary phytate for adults (but not for children) and as yet no tolerable upper intake level for any life-stage group.

Key words: Zinc, factorial approach, physiological requirements, dietary recommendations, expert groups

Background

The factorial approach was used by the World Health Organization (WHO) [1], the Institute of Medicine (IOM) [2], the International Zinc Nutrition Consultative Group (IZiNCG) [3] and the European Food Safety Agency (EFSA) [4] as the basis for the dietary zinc recommendations in view of the absence of specific and sensitive biomarkers of zinc status and the nonspecific nature of the clinical features of mild zinc deficiency. The factorial approach is based on the estimates of the amount of absorbed zinc required to offset all obligatory zinc losses plus any additional requirements for absorbed zinc for growth, pregnancy, or lactation. These physiological requirements for absorbed zinc are then adjusted to yield dietary zinc requirements by taking into account the bioavailability of zinc in the habitual diet. Four components of dietary zinc recommendations were compiled by WHO[1], IOM[2], and IZiNCG[3] for a particular life-stage and gender group: physiological requirements for absorbed zinc, dietary zinc requirements, recommended dietary allowances, and tolerable upper intake levels as shown below; EFSA[4] set the first three components, but has not yet set a tolerable upper intake level. The definitions used by the expert groups for each of the dietary zinc recommendations are similar, although there are some differences in the nomenclature as noted below.

The following steps are used to compile the dietary zinc recommendations: (1) Define the physiological requirement for absorbed zinc for a particular life-stage and gender group using the factorial approach. The physiological requirement is defined as the amount of zinc that must be absorbed to offset *total* endogenous losses plus any additional requirements for absorbed zinc for growth, pregnancy, and lactation, depending on the life-stage and gender group. (2) Convert the physiological requirement to the dietary zinc requirement. The latter is defined as the level that meets the dietary zinc requirement of 50% of healthy persons in a particular life-stage and gender group, and is termed “the Requirement” by WHO or the “Estimated Average Requirement” (EAR) by IOM and IZiNCG. EFSA use the term “Average Requirement” (AR). (3) Define the daily dietary intake level sufficient to meet the requirements of almost all (97–98%) of healthy persons in a particular life-stage and gender group. This is termed the Recommended Nutrient Intake (RNI) by WHO, and the Recommended Dietary Allowance (RDA) by both IOM and IZiNCG. These committees have calculated this value from the EAR+2SD $_{EAR}$. EFSA use the term Population Reference Intake (PRI) and have calculated the value from the AR for adults with a body weight at the 97.5th percentile for reference body weights for men and women based on European reference values. (4) Define the tolerable upper intake level. This level is defined as the highest intake likely to pose no risks of adverse health effects, and is termed the upper limit by WHO and the Tolerable Upper Intake Level (UL) by both IOM and IZiNCG. EFSA has not yet derived a UL.

Estimating the physiological zinc requirements for adults

The first step in deriving the dietary zinc recommendations is to define the physiological requirement for absorbed zinc for adults. The physiological requirement comprises both non-intestinal and intestinal endogenous losses, as shown in **Table 1**, measured initially by conventional balance studies, and later by radioactive or stable isotope studies of participants fed diets with a zinc bioavailability representative of their habitual diets. Non-intestinal endogenous losses include losses of zinc from urine, the integument (skin, hair, nails, and sweat), menstrual flow (in women of child-bearing age), and semen in men, all of which are assumed to be constant over the range of zinc intakes consumed in habitual diets (i.e., 4 to 25 mg Zn/day)[2]. In contrast, intestinal endogenous losses are not constant, and instead are *positively* correlated with the quantity of zinc absorbed over a wide range of zinc intakes and a major variable in the maintenance of zinc homeostasis. **Table 1** compares the adult estimates for the components of non-intestinal losses together with the intestinal endogenous losses derived by WHO, IOM, IZiNCG, and EFSA. The sources of the discrepancies in these estimates across expert groups are discussed in more detail below.

Intestinal endogenous losses

A major factor in the maintenance of zinc homeostasis is the excretion of intestinal endogenous zinc. In 1996 WHO based their estimates for total intestinal endogenous zinc losses for adult males and females on measurements from one study in men (n=8) [5] and another in women (n=5)[6], both consuming very low zinc intakes. Hence the values were subsequently inflated by 40% to account for the reduced excretion of zinc with very restricted zinc intakes [7]. IOM [2], however, adopted a different conceptual approach, later also adopted by IZiNCG, to estimate intestinal endogenous zinc losses. IOM [2] noted that the quantity of intestinal endogenous zinc is positively correlated with the quantity of absorbed zinc over a wide range of absorbed zinc (0.8 to 5.5 mg/d). As a consequence, the IOM[2] applied linear regression to analyze the relationship between intestinal (i.e., fecal) losses of endogenous zinc (EFZ) and total absorbed zinc (TAZ) using radio-active or stable-isotopic data generated from 10 whole-day diet studies conducted on men in Europe or North America. The relationship between intestinal endogenous zinc losses and total absorbed zinc was assumed to be similar for women by IOM in the absence of data. The relationship was then adjusted to yield total endogenous losses for males and females (i.e., their physiological requirements) by adding the constants for non-intestinal endogenous losses for adult males and females (shown to be independent of dietary zinc intakes) to the corresponding estimates for intestinal endogenous losses.

Although IZiNCG [3] applied a linear regression approach, similar to that of IOM, to estimate intestinal endogenous losses, they expanded the database to include an additional nine studies (i.e., 19 studies in total) of both men and women, irrespective of age and nationality, who consumed whole-day mixed diets based on common foods; studies using synthetic diets or zinc supplements were excluded. Hence IZiNCG were able to examine the relationship between total absorbed zinc and intestinal endogenous zinc losses for men and women separately, weighting by sample size to account for the expectation that larger samples would produce greater precision, a procedure not practiced by IOM. From this, IZiNCG calculated the minimum amount of zinc that must be absorbed to offset the total endogenous losses for men and women; calculated values are shown in **Table 1**. In the IZiNCG example displayed in **Fig.1**, the line of perfect agreement indicates where total endogenous zinc losses would be equal to the amount of absorbed zinc (i.e., the physiological requirement for absorbed zinc). The intercept between the line of perfect agreement and the gender-specific lines for total endogenous losses is then used to determine the minimum quantity of absorbed zinc required to replace *total* endogenous losses for men and women (i.e., their physiological requirements). In this example, the calculated average total minimal quantity of absorbed zinc and thus the physiological requirement is 2.69 mg Zn/d for men (i.e., 1.15 mg to match non-intestinal endogenous zinc losses and therefore 1.54 mg/d (2.69 – 1.15 mg) to match intestinal endogenous losses).The corresponding physiological requirement for women is 1.86 mg/d (0.80 to match non-intestinal zinc losses and therefore 1.06 mg (1.86 – 0.80 mg) to match intestinal endogenous losses).

A different approach was used by EFSA to estimate physiological requirements from the endogenous loss data presented in **Table 1**. EFSA used data from 10 stable isotope studies (either compartmental modeling or fecal isotope dilution) that included 85 participants (31 male and 54 female) to measure intestinal endogenous zinc (EFZ). All of the studies were undertaken in the USA, Europe, and China, with dietary zinc intakes ranging from 0.8 to 29 mg per day from both conventional foods and semi-purified diets. Multiple regression analysis was used to examine the relationship between TAZ and total endogenous losses. This revealed that the main predictor of TAZ was body size, expressed as weight, height, BMI and surface area, with R^2 values of 0.46, 0.42, 0.37 and 0.47 respectively. Differences in sex were accounted for by the body size covariate. The equation resulting from the least squares fit linking TAZ to body weight and total endogenous zinc losses was as follows:

$$\text{TAZ [mg/d]} = 0.642 + 0.038 \times \text{body wt [kg]} + 0.716 \times (\text{TAZ} - \text{total endogenous zinc losses [mg/d]})$$

The physiological requirement (PR) is equivalent to TAZ when the difference between absorbed zinc and total endogenous zinc losses equal zero at a given body weight. Therefore, the equation for estimating the PR is as follows:

$$\text{Physiological zinc requirement (PR) [mg/day]} = 0.642 + 0.038 \times \text{body weight [kg]}$$

Thus, PR for a man of reference weight 72.7 kg is 3.4 mg Zn/day and for women of reference weight 59.1 kg is 2.9 mg Zn/day, which differs slightly from the simple sum of the endogenous loss components shown in **Table 1**.

Urine

In 1996 WHO derived this estimate from data based on two balance studies performed in young adult men [5, 7] and one study in adult women [6] consuming diets very low in zinc (0.8 to 3.6 mg/d), and then inflated their original estimate by 40% to account for the reduced urinary excretion presumed to occur in response to very low zinc intakes. In 2001 IOM [2] based their estimate of urinary zinc losses on a larger number of studies in adult men (n=10) and women (n=10) with zinc intakes within the range in which urinary zinc excretion is constant (i.e., 4 to 25 mg/d), and hence likely to reflect more accurately the physiological requirement. These same estimates for urinary zinc losses for men and women were adopted by IZiNCG in 2004 [3]. EFSA [4] estimated urinary losses from the averages of 53 reported values (22 men and 31 women) from the 85 individuals in the included studies (T**able 1**).

Integument

WHO [8] based their estimate of surface losses on a single study of adult men (n=8) whose surface losses declined dramatically when receiving a dietary zinc intake that decreased from 8.3 to 3.6 mg

Zn/day. Presumably surface losses for women were derived by extrapolation from data for men adjusted for differences in body surface area, although this is not stated. In contrast, IOM [2] applied data from a later study of 11 adult males in which there was no evidence of a reduction in surface losses of zinc with dietary zinc intakes ranging from 1.4 to 10.3 mg Zn/d for 28 to 35 days [9]. Surface losses for women were based on the estimate for men adjusted for the different average body surface area of women. IZiNCG [3] used the same data [9] from the study of 11 adult males to estimate surface losses, although they chose to adjust the surface zinc losses in relation to body size for both men and women rather than body surface area, assuming the NCHS/CDC/WHO reference body weights of 65kg and 55kg for an adult man and women, respectively.

EFSA [4] used published studies to estimate integument and sweat losses from men [5, 9, 10]. The estimate for women was calculated by multiplying the value for men by the female to male ratio of sweat zinc losses and whole body sweat rates [11–16].

Semen and menstrual flow

These losses were not specifically considered by WHO [1, 8] in their calculation of the adult physiological requirements for absorbed zinc. In contrast, IOM, IZiNCG and EFSA included seminal zinc losses using data for seminal zinc from two studies of adult males [9, 17], one [9] being used to estimate surface losses. In this latter study there was no change in the concentrations of seminal zinc irrespective of zinc intake, although losses were lowest (0.09 mg/d) at the lowest dietary zinc intake level. IOM [2] chose to use a single figure of 0.1 mg Zn per day for seminal zinc based on a mean ejaculate volume of 2.8 mL and a weekly mean of 2.45 ejaculations [9,17]. IZiNCG [3] and EFSA [4] adopted the same value for daily seminal zinc loss in view of the absence of any additional data.

IOM [2] used 0. 1 mg/d to account for average menstrual losses based on data from one study that calculated the mean zinc content of menstrual fluid to be 2.8 µg Zn/g and an average menstrual flow excretion during a single period of 60 g [18]. However, this estimate was incorrect as the data of Hess et al. [18] yields a menstrual loss of 5.6 µg Zn/d (168 µg/Zn per period per month). IZiNCG recognized this error and concluded that the estimated loss of zinc from menstrual flow (i.e., 6 µg/d) was negligible and therefore could be ignored. ESFA [4] applied a figure of 10 µg/d to account for average daily menstrual zinc losses.

Estimating the physiological zinc requirements for infants, children, and pregnant or lactating women

The physiological requirements for absorbed zinc for these life-stage groups represent the summation of the total endogenous losses plus any additional requirements for absorbed zinc for growth, pregnancy, or lactation.

Normal birthweight infants aged 0 to 6 months

WHO applied the factorial approach to derive the physiological requirements for absorbed zinc for normal birthweight infants aged 0 to 6 months [1,8]. Their estimates were based on total endogenous losses, extrapolated from adult data based on a metabolic rate of 0.57 µg Zn/basal kcal, plus the additional amount of absorbed zinc that is incorporated into newly synthesized tissues for growth. Higher estimates for endogenous losses were applied by WHO/FAO/IAEA [8] for infants fed formula or mixed solid/liquid feeds compared to those fed exclusively breast milk (i.e., 40 µg Zn/kg body weight per day vs. 20 µg Zn/kg body weight per day) [19,20]. For newly synthesized lean and adipose tissue for infants 0 to 6 months WHO assumed a zinc concentration of 30 µg Zn/g [8]. The physiological requirements for absorbed zinc for breastfed infants aged 0 – 6 months set by WHO ranged from 0.7–1.3 mg/day, depending on age and gender.

In contrast, IOM [2], IZiNCG [3], and EFSA [4] did not set a physiological requirement for absorbed zinc for this age group in view of the paucity of data on zinc homeostasis. Instead IOM [2] set an “Adequate Intake” based on the *average* maternal zinc supply for exclusively breastfed normal birthweight infants in view of the evidence that breast milk zinc content appears adequate for full-term, normal-birthweight, exclusively breastfed infants until about 6 months of age [21]. The average maternal zinc supply was derived from data on the zinc concentrations in human milk during the first six months of lactation [22–25] together with the figure for the average volume of breast milk, assumed to be 0.78 L by IOM [2]. The latter proposed a single average value for the zinc transfer in breast milk (i.e., 2.0 mg Zn/d) for infants 0 to 5 months, even though breast milk zinc concentrations decline during the first few months post-partum. IZiNCG [3] and EFSA [26] adopted the same approach used by IOM for the majority of normal birthweight breast-fed infants aged 0 to 6 months, although EFSA assumed an average volume of breast milk of 0.80 L and a single average value of 2.5 mg Zn/L for the zinc transfer in breast milk [27]. For non-exclusively breast-fed infants, IZiNCG estimated the amount of absorbed zinc needed as 1.3 and 0.7 mg/d for infants aged 0 to 3 months and 3 to 5 months, respectively.

Infants 6 to 12 months and children 1 to 18 years

WHO, IOM, IZiNCG, and EFSA [1–4] all adopted the factorial approach to estimate the physiological requirements for absorbed zinc for older infants and during childhood. The estimates for total endogenous losses for these age groups were extrapolated from measured values from either adults (≥19 y) or younger infants, with the exception of intestinal endogenous losses for older infants, which the IOM, IZiNCG and EFSA [24] estimated from empirical data from breastfed infants aged 2 to 4 months [23]. WHO [8] adjusted the adult values based on metabolic rate, whereas the corresponding adjustments made by IOM, IZiNCG and EFSA [2–4] were based on reference body weights. For the latter, both WHO [1,8] and IZiNCG [3] adopted the NCHS/CDC/WHO reference body weights, whereas IOM [2] applied reference growth data adapted from the third US National Health and Nutrition Examination Survey. EFSA [4] applied reference body weights for infants and young children based on the more recent WHO Multicentre Growth Reference Study [27]. For older children, data from van Buuren et al. [28] were used.

There were also differences in the estimates for the amount of zinc required for synthesis of new tissue. IOM, IZiNCG, and EFSA [2–4] used 20 μg Zn/g for tissue accretion across the entire age range, irrespective of whether the gain was lean or adipose tissue because of the absence of more precise data on age-related changes in the body composition of infants and children. This estimate was based on data generated by Widdowson and Spray [29] that suggested that the concentration of zinc in the fat-free body tissue of whole fetuses of varying gestational ages was constant. In contrast, WHO [8] applied a figure of 30 μg Zn/g wet weight for new tissue for infants and children less than aged 10 y and 23 μg Zn/g wet weight for adolescents based on the assumption that there is an increase in fat tissue with a lower zinc content in older compared to younger children. The average amounts of new tissue gained were estimated to be 13 g/d, 6 g/d, 7 g/d and 10 g/d for older infants aged 7–12 mo, children aged 1–3 y, 4–8 years, and 9–18 y, respectively by both IOM [2] and IZiNCG [3]. EFSA [4] assumed a daily weight gain of 11.5 g per day for infants in the second half-year of life, which is based on observed weight increments of infants in the Euro-Growth Study [30]. For older infants and children, daily weight gains were also calculated from the same study, by subtracting the median weight at the lower boundary of the age group from that at the higher boundary of the age group and dividing this by the number of days in that age interval. As a result of these discrepancies, there were some differences in the physiological requirements for absorbed zinc for older infants and children among the four expert groups, as shown in **Table 2**.

Pregnant women

Estimates for the additional requirements for absorbed zinc during pregnancy differed across the four expert groups. WHO [1] provided an estimate for each trimester based on the calculated zinc retention of 100 mg throughout pregnancy [31]. No allowance was made by WHO for any adaptive response during pregnancy by increasing the efficiency of absorption or decreasing the endogenous loss of zinc. The source of the data used by IOM [2], IZiNCG [3], and EFSA [4] for the additional requirements for absorbed zinc imposed by the three trimesters of pregnancy [32] was the same as that used by WHO, although there were slight differences in the final additional requirements for absorbed zinc set by WHO and IOM across the three trimesters of pregnancy. In contrast, IZiNCG and EFSA set only one value to represent the additional needs throughout pregnancy. IZiNCG [3] used a value of 0.70 mg per day that reflected the additional needs during the third trimester, recognizing that this would be an overestimate of the average needs during the first and second trimester. EFSA [4] estimated an average daily rate of zinc accumulation over the four quarters of pregnancy that resulted in a value of 0.4 mg/day for the whole pregnancy. In all cases, the estimates for the additional requirements for absorbed zinc imposed by pregnancy were added to the total endogenous losses of absorbed zinc for adolescent girls or women, as appropriate to yield the physiological requirements, based on the assumption that intestinal endogenous losses are unchanged during pregnancy.

Lactating women

When deriving the additional physiological requirements imposed by lactation, each expert group took into account the decline in breast milk zinc concentrations which occurs irrespective of maternal dietary zinc intakes or status during lactation, as well as the redistribution of tissue zinc from the postpartum involution of uterine tissue and the decrease in blood volume that occurs during the first month. Data from three studies were used by WHO for estimates of breast milk zinc concentrations at 4, 12, and 16 weeks lactation [20,32,33], whereas IOM [2] and IZiNCG [3] used data from twelve studies for their age-specific estimates at 4, 8, 12, and 24 weeks lactation. EFSA [4] used data collated in a comprehensive review [34], which included 63 studies undertaken globally. The estimates of breast milk volume differed across the expert groups. IOM [2] based their average value of 0.78 L/day on test-weigh data derived from full-term infants of US women during the first year post-partum.. In contrast, IZiNCG [3] used breast milk volume for women from low income countries compiled in a review by Brown et al. [35] in view of their longer duration of breastfeeding compared to US women and the changes in breast milk volume with child's age. The physiological requirements for absorbed zinc were then based on the summation of the additional requirements imposed by lactation and the total endogenous losses for either adolescent girls or adult women. WHO[1] provided three physiological requirement estimates for absorbed zinc from 0–3 mo, 3–6 mo, and 6–12 mo lactation whereas IOM, IZiNCG, and EFSA [2–4] derived a single average value for throughout lactation, as shown in **Table 2.**

Conversion of physiological to dietary Zn requirements

The estimated average requirement (EAR), termed the 'Requirement' by WHO [1] and average requirement (AR) by EFSA [4], was defined by all expert groups as the level of dietary zinc that meets the requirement of 50% of healthy persons in a particular life-stage and gender group. To convert the physiological requirements to the dietary zinc requirements it is necessary to account for the proportion of dietary zinc that is absorbed by the intestine (i.e., fractional zinc absorption, FAZ), a step that is dependent on both the characteristics of the habitual diet and the physiological state (e.g., lactation). To achieve this conversion, the mean amount of absorbed zinc was regressed against total zinc intakes from diet types that differed in their composition. All expert groups used zinc absorption data from available published studies of radioactive or stable-isotopes of zinc.

The source of these data was not identified by WHO [1,8], although for the diet types considered to represent a relatively high level of zinc absorption, 12 sets of studies based on *whole-day diets* containing no known sources of zinc inhibitors were used. For the diet types corresponding to those of moderate and low zinc absorption, however, a combination of isotopically labeled single-meals, individual foods, as well as whole-day diet studies were used. This distinction is important because in the single meal studies an average correction factor for intestinal endogenous losses must be applied to yield an estimate of zinc absorption. Moreover, single meal studies may exaggerate the effect of absorption modifiers, as noted for non-heme iron [36]. The criteria used to classify the diets as having a high, moderate, or low level of zinc absorption were based on compositional data as well as evidence from studies on non-human species; more details are available in WHO [8].

In contrast only whole-day diet studies were selected by both IOM [2] and IZiNCG [3] to examine the relationship between the mean amount of absorbed zinc and the total zinc ingested from the diet being tested. IOM selected seven whole-day diet studies in only men consuming North American or European mixed or semi-purified formula diets (including the use of zinc supplements), whereas IZiNCG [3] selected whole-day diet studies (n=11) of both men and women from all nationalities; semi-purified formula diets or those using zinc supplements were excluded. IZiNCG [3] categorized the diets into mixed or refined vegetarian diets with phytate:Zn molar ratios 4–18 (n=10) and an unrefined vegetarian diet (n=1) with a phytate:Zn molar ratio > 18; further details justifying this classification are given in Brown et al.[3]. The amount of total dietary zinc for each diet type needed to provide an amount equivalent to the physiological requirement for zinc, was then derived by regression analysis. This amount of total dietary zinc represents the EAR for the respective diet type. Using the conceptual approach applied by IZiNCG [3] as an example, assuming the physiological requirement of absorbed zinc for an adult male = 2.69 mg/d absorbed zinc (based on factorial approach: see **Table 1**), then the total intake of dietary zinc (i.e., the EAR) likely to meet this requirement is 10.4 mg zinc/day for a diet with a phytate:Zn molar ratio of 24, and 15.0.mg zinc/day for a diet based on a phytate : Zn molar ratio of 24, as shown in **Fig 2**.

Fractional zinc absorption for each diet type was then calculated as the percentage of the physiological requirement relative to the total dietary zinc intake. The estimates for FAZ for the diet types examined by WHO [8], IOM [2], and IZiNCG [3] and calculated in this way are shown in **Table 3**, and also in **Fig. 2** for the IZiNCG two diet types for adult men. Note that WHO [8] assumed the FAZ of zinc from breast milk was 80% whereas both IOM [2] and IZiNCG [3] assumed a value of 50% [37]. For non-exclusively breastfed infants, WHO [8] proposed the use of 30%, unless infants were receiving phytate-rich vegetable protein formula or complementary foods based on non-fermented whole grain cereals, when a FAZ of 15% was recommended. IOM [2] assumed FAZ from complementary foods to be 30% and applied this same value to estimate the dietary zinc requirements (i.e., EARs) for all children 1–8 y, after which the adult figures were used. EFSA [4] assumed this same value for FAZ (i.e., 30%) from a mixed diet, but applied this figure for all children from aged 1–17 y. IZiNCG [3], however, applied their mean absorption figures generated for adults for each diet type (see **Table** 3) to all children aged 1–18 y, arguing that the figure used by IOM was only based on two single-meal studies in infants and young children [38, 39].

No allowance for an adaptive response to meet the additional physiological demands for zinc during pregnancy or lactation was made by WHO [8] in view of the paucity of data at that time. Subsequently, IOM [2], IZiNCG [3], and EFSA [4] adjusted the figure for FAZ during lactation (but not pregnancy~~)~~ based on more recent data [40–43]. As a consequence, FAZ for lactating women was estimated as 37% by IOM [2] (sum of 27% for non-lactating women plus 10% increase) and 45% by EFSA [4], whereas the figures set by IZiNCG [3] for FAZ in lactating women were 44% (34 % plus 10%) for women (≥19 y) consuming mixed or refined vegetarian diets and 35% (25% plus 10%) for those (≥19 y) consuming unrefined, cereal-based diets (see **Table 3**). For lactating women aged 14–

18 y, the corresponding estimates set by IZiNCG [3] were lower, 40% and 32% respectively, in view of their likely lower zinc intakes.

As phytate has been identified as the most important inhibitor of zinc absorption in adult human diets, EFSA used a trivariate model [44,45] to examine the relationship between TAZ, total dietary zinc (TDZ), and the phytate content (**Fig.3**). The relationship between TAZ and TDZ is most appropriately fitted with saturation response modeling (F**ig.4**), which was therefore used as the theoretical framework for the trivariate model (**Fig.3**). Data selected were extracted from whole-day isotope studies of true zinc absorption in healthy adults that reported measurements of TDZ and total dietary phytate. A total of 72 data points, reflecting 650 individual measurements, reported in 18 publications were used to generate predictions of TAZ as a function of TDZ at six different levels of dietary phytate, ranging from 0 to 3000 mg/d (**Fig. 4**). The amount of dietary zinc needed to meet the physiological requirement at the different phytate levels can then be determined in the same way as described above and illustrated in **Fig. 2**, for a physiological requirement of 3.4 and 2.9 for men and women respectively (**Table 2**).

Derivation of Recommended Dietary Allowances

The third step is to derive the daily dietary intake level sufficient to meet the requirements of almost all (97–98%) of healthy persons in a particular life-stage and gender group. By definition this level is defined as the EAR + 2 SD_{EAR} and is termed the RNI by WHO [1] and the RDA by both IOM [2] and IZiNCG [3], as noted earlier. Hence to calculate this level, an estimate of the individual variation in dietary zinc requirements for men and women is required. This was assumed to be 25% by WHO [1,8], 10% by IOM [2], and 12.5 % by IZiNCG [3]. The WHO estimate of 25% was based on the assumed variation in protein requirements (i.e., 12.5%) plus an additional 12.5% to include the estimated variation in requirements for absorbed zinc [8]. In contrast, the coefficient of variation

(CV) for zinc requirements of 10% chosen by IOM [2] was the figure adopted for all nutrients when no information on requirement distributions existed. IZiNCG [3] adopted a CV of 12.5% for men and women, arguing that any variation in protein digestibility was already covered by the WHO CV of 12.5%, making any additional 12.5% to account for variation in zinc absorption unjustified. Based on these differing CVs, the RNI for WHO is 150% of the EAR, whereas the RDA's for IOM and IZiNCG are 120% and 125% of the corresponding EARs, respectively. This level of the dietary zinc recommendations is used to evaluate the adequacy of the zinc intake of an individual within a particular life-stage and gender group.

EFSA [4] have adopted an alternative approach to derive the PRI for non-pregnant and non-lactating adults. Multiple regression analysis revealed that body weight was a strong determinant of the zinc requirement; therefore this committee has estimated the PRI as the zinc requirement of individuals with a body weight at the 97.5th percentile for reference body weights for men and for women [46]. This approach was considered to have less uncertainty than the mathematical application of a CV of between 10 and 20%, and is equivalent to CVs for the ARs of between 10 and 14%. For the additional requirement of zinc for pregnant and lactating women, and for the requirements for children, EFSA applied a CV for zinc requirements of 10% in view of the paucity of data on the variation in zinc requirements for these age and life-stage groups.

Derivation of Tolerable Upper Intake Levels

The tolerable upper intake level (UL) is defined by WHO [1], IOM [2], and IZiNCG [3] as the highest level of daily nutrient intake that is likely to pose no risks of adverse health effects for almost all individuals. The data used to derive the tolerable upper level were from studies reporting adverse effects of high doses of supplemental zinc (50 mg Zn/d) on copper status indices, notably reductions in the activity of erythrocyte copper-zinc superoxide dismutase (Cu-SOD) [47,48]. WHO [1] set an upper limit of intake of 45 mg/day for adults ≥19 y assuming a 20% variation in intake, and extrapolated this figure to other age groups based on differences in basal metabolic rates. This adjustment yielded upper limits for children ranging from 23 to 28 mg Zn/day. In contrast, IOM [2] based their UL on the Lowest Observed Adverse Effect Level (LOAEL), a figure of 60 mg Zn/d (50 mg Zn/d from supplement and 10 mg/d from diet) [48], and an uncertainty factor of 1.5 to account for individual variation in the response. This was extrapolated to a No Observed Adverse Effect Level (NOAEL) of 40 mg/d for the UL for male and female adults. For children, the IOM [2] estimates for the UL were based on one study in which no changes in copper status were found when infants were fed for six months a zinc-fortified infant formula containing 5.8 mg Zn/L or an unfortified formula with1.8 mg Zn/L. As a result, a NOAEL of 5.8 mg Zn/L was set for infants 0 to 6 months of age, which yielded a NOAEL of 4.5 mg Zn/d when an average breast milk intake of 0.78 L/day was assumed. Based on an uncertainty factor of 1.0, a UL of 4.0 mg/d was set for infants aged 0 through 6 months which was adjusted for older infants and children based on relative body weight (**Table 5**).

IZiNCG [3] adopted the IOM value for the UL for adults but did not set a UL for children in view of the paucity of data for this age group and the fact that US children often have zinc intakes greater than the IOM UL with no observed adverse effects as a result of their consumption of zinc fortified formulas and/or ready-to-eat breakfast cereals [498,50]. Instead, IZiNCG provided a NOAEL for young children as shown in **Table 5**, based on an Indonesian study in which infants aged 6 months were supplemented with 10 mg zinc or a placebo for 6 months, with no apparent change in plasma copper levels [51].

Conclusions and recommendations

Differences exist among the estimates for the dietary zinc recommendations set by WHO [1], IOM [2], IZiNCG [3] and EFSA [4]. The source of these differences include the data used for reference body weights, with WHO and IZiNCG using the NCHS/CDC/WHO reference body weight for children and adults; the IOM the most recent US reference growth data; and EFSA using the WHO Multicenter Growth Reference Study Group for children, and European reference body weight data for adults. There are also discrepancies across the four expert groups in the selection and application of the studies used to provide the empirical data for both the estimates of endogenous zinc losses and fractional zinc absorption from the differing habitual diets. The WHO estimates of endogenous zinc losses were based on extrapolation from limited balance study data on adults receiving very low zinc intakes. In contrast, both IOM and IZiNCG adopted a new conceptual approach to estimate intestinal endogenous zinc losses in view of their positive correlation with the quantity of absorbed zinc. They also considered a larger number of stable isotope studies based on whole-day diets and performed a back-calculation of absorbed zinc from the regression of endogenous zinc losses on TAZ. However, the statistical modeling used to examine this relationship differed: only IZiNCG applied the regression analysis with data weighted by sample size. EFSA examined the relationship between total endogenous zinc losses and TAZ using multiple regression analysis. As a result of these methodological differences, the estimates for the physiological requirements for zinc vary across the expert groups. In addition, the dietary requirements for zinc were not consistent across particular life-stage and gender groups, attributed largely to differences in the proportion of zinc absorbed from the habitual diets, which was governed mainly by their phytate content, at least among adults. Indeed EFSA set dietary zinc requirements for adults at four levels of dietary phytate intake. Unlike WHO and IOM, IZiNCG did not set a UL for young children but instead provided an estimate for the NOAEL on the basis that the UL set by IOM for this age group may be too low. EFSA has not yet derived a UL for any life-stage group

A dietary indicator based on the prevalence of inadequate intakes of dietary zinc has been recommended by WHO/UNICEF/IAEA/IZiNCG for assessing zinc status at the population level and evaluating nutrition interventions designed to combat zinc deficiency [52]. Clearly such prevalence estimates will depend in part on the dietary zinc recommendations applied, emphasizing the need to harmonize the dietary zinc recommendations for international use. We suggest that the factorial method should continue to be used as the basis for setting the dietary zinc recommendations. However, we recommend that the measurement of endogenous fecal zinc losses should be derived from stable isotope studies of men and women consuming whole-day diets based on conventional foods and semi-purified diets, irrespective of nationality. Further, the physiological requirements should be estimated from the endogenous losses using the approach adopted by EFSA whereby the covariate body weight is used in the regression equation describing the relationship between total absorbed zinc and total endogenous losses.

The marked impact of high-phytate plant-based diets on the level of dietary zinc needed to meet the zinc requirements for adults prompted EFSA to adopt the trivariate model of Miller et al. [44] to examine the relationship between total absorbed zinc, total dietary zinc, and the dietary phytate content. However, in many low-income countries, diets are plant-based diets with a very high phytate content. Hence, for international use, we recommend that more studies based on very high dietary phytate levels should be incorporated into the trivariate model so that dietary zinc requirements for adults with phytate intakes above 1200 mg/day can be developed. Moreover, because of the paucity of empirical data on the coefficients of variation in dietary zinc requirements coupled with the EFSA observation that body weight is a strong determinant of the dietary zinc requirement [4], we recommend that the zinc RDAs for non-pregnant and lactating adults correspond to the zinc requirements of individuals with a body weight at the 97.5th percentile for the NCHS/CDC/WHO reference body weights. Finally, to select the appropriate dietary zinc recommendation for calculating the prevalence of inadequate intakes among adult populations in low income countries, data on the phytate content of indigenous plant-based foods prepared with local food preparation and processing practices are urgently required.

To date, EFSA has not derived a UL for any life-stage group. However, new evidence supports the suggestion that the current UL for zinc for children needs to be re-examined based on the finding that sensitive biomarkers of copper status were unchanged by supplementation with 5, 10 or 15 mg zinc daily for 4 months in healthy boys in a double-blind, placebo-controlled randomized trial [53].

Author's contributions

RG, JK, and NL wrote the manuscript, and RG had responsibility for the final content. All authors read and approved the final manuscript.

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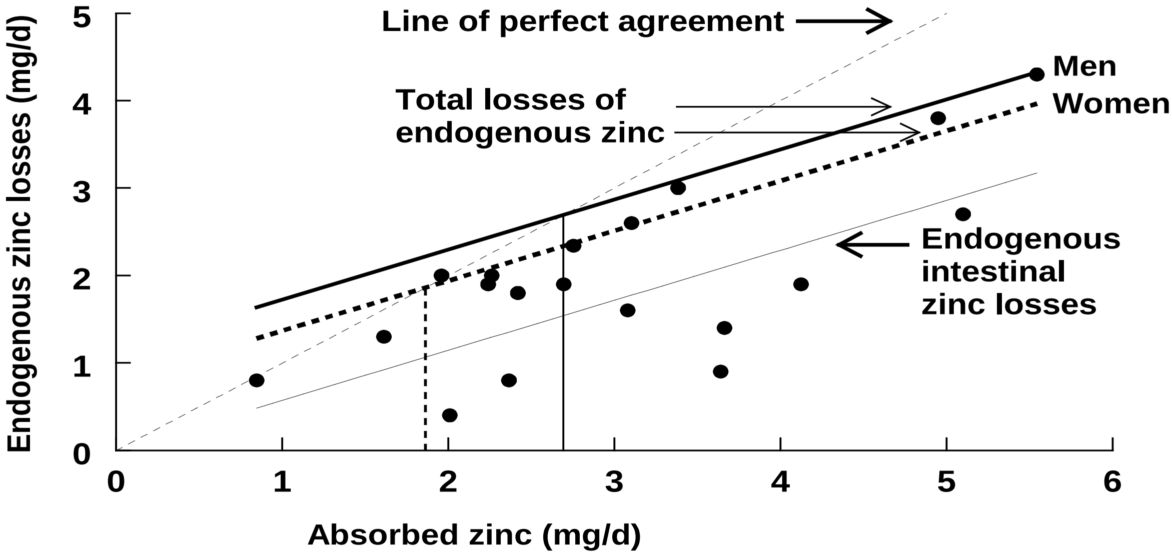

FIG 1. Graphical representation of the model used by IZiNCG to estimate intestinal endogenous zinc and total endogenous losses for men and women when the amount of absorbed zinc is sufficient to offset all zinc losses (i.e., physiological requirement). From [3]

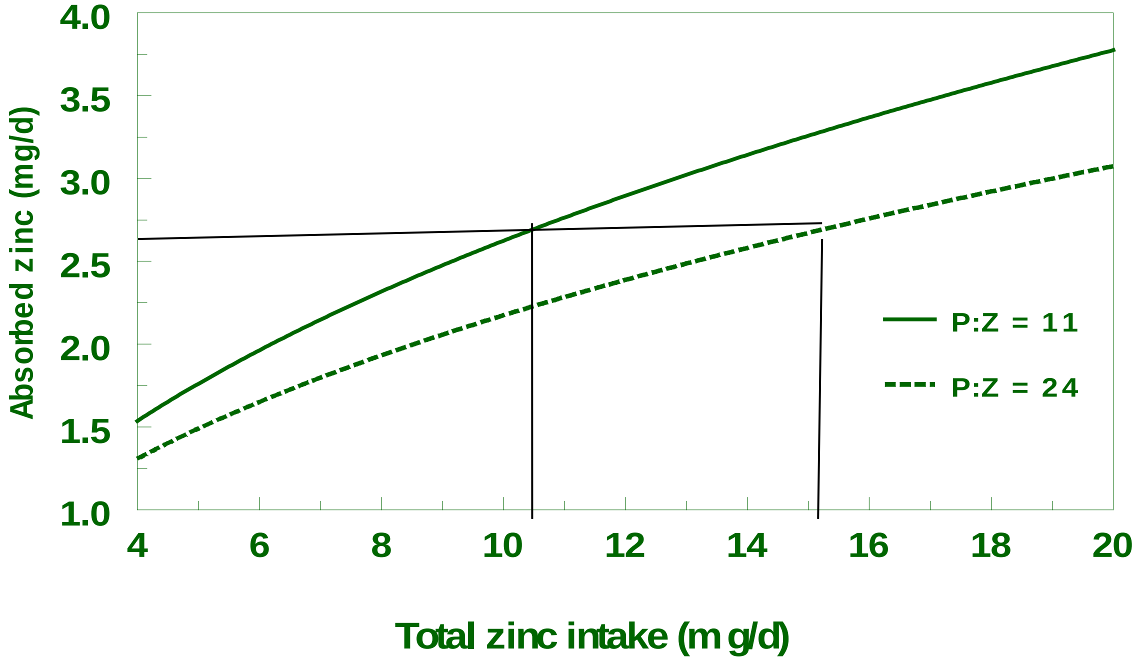

FIG 2. Derivation of the IZiNCG estimated average requirements for men and the critical level of zinc absorption for mixed/refined vegetarian diets (phytate:zinc (P:Z) molar ratios of 11) and unrefined cereal-based diets (phytate:zinc (P:Z) molar ratios of 24) based on the association between total zinc intake and absorbed zinc for each diet type and the physiologic requirements for men (2.69 mg Zn/d). From [3]

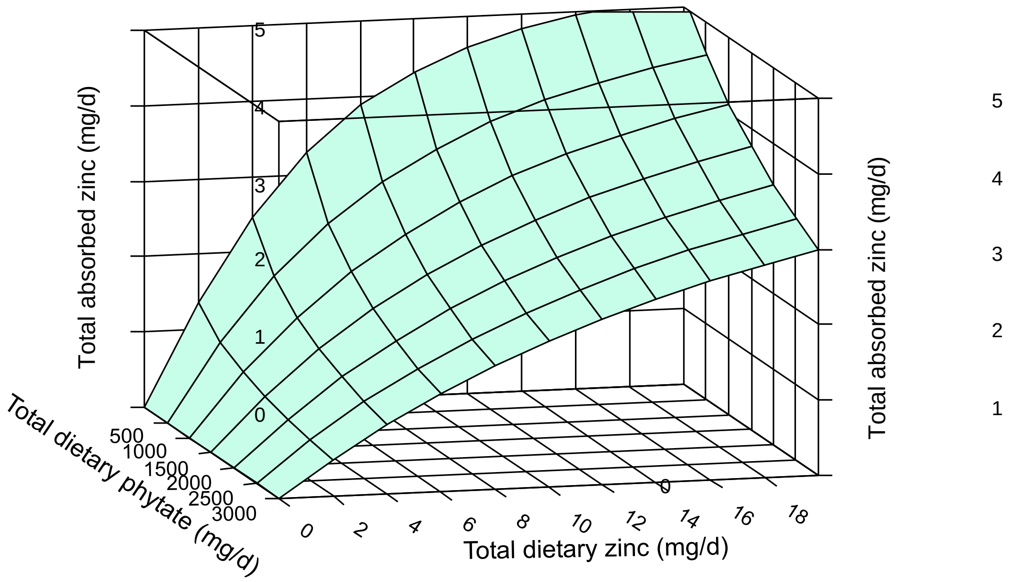

FIG.3. Three dimensional representation of the trivariate model describing the relationship between total absorbed zinc, dietary phytate and dietary zinc. From [4]

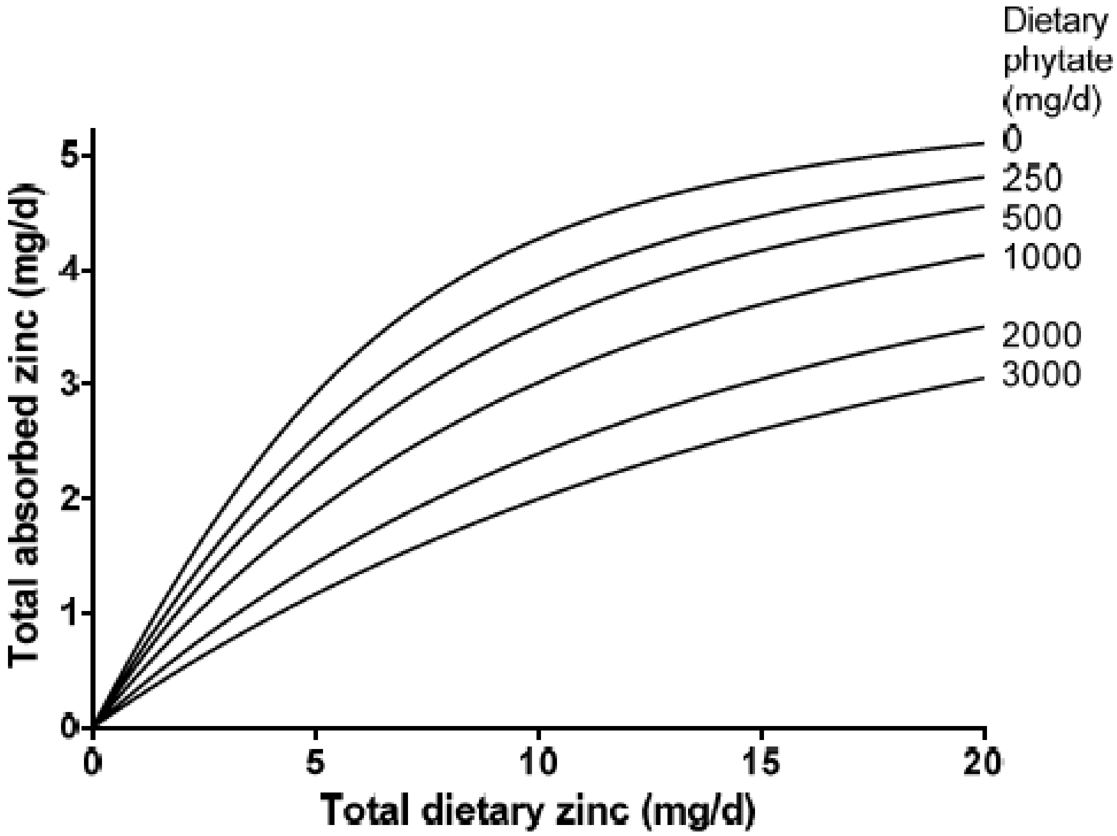

FIG.4. Saturation response model predictions of total absorbed zinc (TAZ) for selected levels of dietary phytate. From [4]

TABLE 1. Total endogenous losses (mg/day) in adult men and women as estimated by WHO, IOM, IZiNCG, and EFSA

Male	WHO [8]	IOM [2]	IZiNCG [3]	EFSA [4]
Reference body weight, kg	65	75	65	72.7
Urine, mg	0.30	0.63	0.63	0.54
Integument, mg	0.30	0.54	0.42	0.50
Semen, mg	-	0.10	0.10	0.10
Total non-intestinal losses, mg	0.60	1.27	1.15	1.14
Intestinal endogenous losses, mg	0.80	2.57	1.54	2.40
Total endogenous losses, mg	1.40	3.84	2.69	3.54
Female				
Reference body weight, kg	55	65	55	59.1
Urine, mg	0.30	0.44	0.44	0.32
Integument, mg	0.20	0.46	0.36	0.30
Menstrual flow, mg	--	0.10	0	0.01
Total non-intestinal losses, mg	0.50	1.00	0.80	0.63
Intestinal endogenous losses, mg	0.50	2.30	1.06	2.30
Total endogenous losses, mg	1.00	3.30	1.86	2.93

TABLE 2. Estimated physiologic requirements for absorbed zinc (mg/d) during childhood by age group and sex and during pregnancy and lactation by WHO, IOM, IZiNCG and EFSA

WHO [8]			IOM [2]			IZiNCG [3]			EFSA [4]		
Age, sex	Ref weight (kg)	Physiol. Req (mg/d)	Age, sex	Ref weight (kg)	Physiol. Req (mg/d)	Age, sex	Ref weight (kg)	Physiol. Req (mg/d)	Age, sex	Ref weight (kg)	Physiol. Req (mg/d)
6-12 mo	9	0.84	7-12 mo	9	0.84	6-11 mo	9	0.84	7-11 mo		
1-3 y	12	0.83	1-3 y	13	0.74	1-3 y	12	0.53	1-3 y	11.9	1.074
3-6 y	17	0.97	4-8 y	22	1.20	4-8 y	21	0.83	4-6 y	19.0	1.390
6-10 y	25	1.12							7-10 y	28.7	1.869
10-12 y, M	35	1.40	9-13y	40	2.12	9-13 y	38	1.53			
10-12 y, F	37	1.26									
12-15 y, M	48	1.82							11-14 y M	44.0	2.635
12-15 y, F	48	1.55							11-14 y F	45.1	2.663
15-18 y, M	64	1.97	14-18 y, M	64	3.37	14-18 y,M	64	2.52	15-17 y M	64.1	3.544
15-18 y, F	55	1.54	14-18 y, F	57	3.02	14-18 y, F	56	1.98	15-17 y F	56.4	2.969
Additional req for 1st,2nd, 3rd tri.	-	0.1, 0.3, 0.7	Additional req for 1st,2nd, 3rd tri.	-	0.16,0.39, 0.63	Additional req for pregnancy	-	0.70[a]	Additional req for pregnancy		0.40[a]
Additional lactation req 0-3, 3-6, 6-12 months	-	1.4, 0.8, 0.5	Additional req for lactation	-	1.35[b]	Additional req for lactation	-	1.0[b]	Additional req for lactation		1.1[b]

a. A single estimate for additional requirements is applied throughout pregnancy

b. A single estimate for additional requirements is applied throughout lactation

Adapted from [3] and [4].

TABLE 3. Estimates of fractional zinc absorption from selected diet types examined by WHO, IOM, and IZiNCG

	Diet categories	Phy:Zn molar ratio	Zn absorption (as %)
WHO [1]	Three categories: M+F	<5[a] 5-15[ab] >15 [abc]	50% 30% 15%
IOM [2]	One for M + F	Mixed diet[a] but not defined by phy:Zn molar ratios	41% M; 46% F
IZiNCG [3]	Two each for M & F	4-18: mixed or refined vegetarian diet[a] > 18: unrefined cereal-based diet[a]	26% M: 34% F 18% M; 25% F

a.whole day diets; *b*. single meals; *c*. Additional criteria used to define the three diet types are described in [1]
WHO, IOM, and IZiNCG: No adjustment for fractional zinc absorption for pregnancy
IOM: For women outside the reproductive cycle, fractional zinc absorption was assumed to be 27%
IOM and IZiNCG applied a 10 % increase in fractional zinc absorption during lactation.

TABLE 4. Estimated average requirements (EAR) for zinc (mg/d) by selected life-stage and diet types defined by WHO, IOM, IZiNCG and EFSA

WHO/FAO/IAEA [8]					IOM [2]			IZiNCG [3]				EFSA [4]		
Age, sex	Ref Wt (kg)	Requirement (mg/d) High[a]	Mod[b]	Low[c]	Age, sex	Ref Wt (kg)	EAR (mg/d)	Age, sex	Ref Wt (kg)	EAR Mixed	EAR unrefined	Age, sex	Ref Wt (kg)	Average requirement (mg/d)***
7-12 mo	9	0.6	0.6	0.6	7-12 mo	9	2.2	6-11 mo	9	3	4	7-11 mo		2.4
1-3 y	12	1.66	2.76	7.45	1-3 y	13	2.2	1-3 y	12	2	2	1-3 y	11.9	3.6
4-6 y	17	1.94	3.23	6.46	4-8 y	22	4.0	4-8 y	21	3	4	4-6 y	19.0	4.6
7-9 y	25	2.25	3.73	7.48								7-10 y	28.7	6.2
10-12 y, M	35	2.80	4.66	9.35	9-13y	40	7	9-13 y	38	5	7	11-14 y, M	44.0	8.9
10-12 y, F	37	2.38	3.96	7.95								11-14 y, F	45.1	8.9
12-15 y, M	48	3.65	6.05	12.14										
12-15 y, F	48	3.07	5.14	10.32										
15-18 y, M	64	3.90	6.53	13.12	14-18 y, M	64	8.5	14-18 y, M	64	8	11	15-17 y, M	64.1	11.8
15-18 y, F	55	3.08	5.12	10.29	14-18 y, F	57	7.5	14-18 y, F	56	7	9	15-17 y, F	56.4	9.9
Pregnancy	-	-	-	-	Pregnancy 14-18 y 19-50 y	 - -	 10.5 9.5	Pregnancy 14-18y ≥19 y	 - -	 9 8	 12 10	Pregnancy additional AR		1.3
Lactation	-	-	-	-	Lactation 14-18 y 19-50 y	 - -	 11.6 10.4	Lactation 14-18 y ≥19 y	 - -	 8 7	 9 8	Lactation additional AR		2.4

Ref Wt: Reference weight; EAR: Estimated Average Requirement
Calculated from average normative requirements for zinc (µg/kg/d) based on WHO reference body weight specified by WHO/FAO[1]
a. High bioavailability (50%); *b*. Moderate bioavailability (30%); *c*. Low bioavailability (15%)[1]
Assumes a fractional absorption of zinc of 0.3 in infants, children and pregnant women or 0.45 during lactation [4].

TABLE 5. Estimated Recommended Daily Allowances for zinc (mg/d) by life-stage and diet types defined by WHO, IOM, IZiNCG and EFSA

WHO/FAO [1]					IOM [2]			IZiNCG [3]				EFSA [4]		
Age, sex	Ref Wt (kg)	RNI (mg/d) High[a]	Mod[b]	Low[c]	Age, sex	Ref Wt (kg)	RDA (mg/d)	Age, sex	Ref Wt (kg)	RDA Mixed (mg/d)	RDA Unrefined (mg/d)	Age, sex	Ref Wt (kg)	PRI (mg/d)
7-12 mo	9	0.8[d]; 2.5[e]	4.1	8.4	7-12 mo	9	3.0	6-11 mo	9	4	5	7-11 mo		2.9
1-3 y	12	2.4	4.1	8.3	1-3 y	13	3.0	1-3 y	12	3	3	1-3 y	11.9	4.3
4-6 y	17	2.9	4.8	9.6	4-8 y	22	5.0	4-8 y	21	4	5	4-6 y	19.0	5.5
7-9 y	25	3.3	5.6	11.2								7-10 y	28.7	7.4
10-18 y, M	49	5.1	8.6	17.1	9-13 y M/F	40	8	9-13 y	38	6	9	11-14 y M/F	44.0/45.1	9.4
10-18 y, F	47	4.3	7.2	14.4	14-18 y, M	64	11	14-18 y, M	64	10	14	15-17 y, M	64.1	12.5
19-65 y, M	65	4.2	7.0	14.0	14-18 y, F	57	9	14-18 y, F	56	9	11	15-17 y, F	56.4	10.4
19-65 y, F	55	3.0	4.9	9.8										
65+y, M	65	4.2	7.0	14.0	≥19 y, M	76	11	≥19 y, M	65	13	19	≥ 18 y M 300 Level of 600 phytate 900 mg/day: , 1200	68.1	9.4, 11.7, 14.0, 16.3
65+y, F	55	3.0	4.9	9.8	≥19 y, F	61	8	≥19 y, F	55	8	9	≥ 18 y F 300 Level of 600 phytate 900 mg/day: , 1200	58.5	7.5, 9.3, 11.0, 12.7
Pregnancy 1st trimester 2nd trimester 3rd trimester		 3.4 4.2 6.0	 5.5 7,0 10.0	 11.0 14.0 20.0	Pregnancy 14-18 y 19-50 y	 - -	 13 11	Pregnancy 14-18y ≥19 y	 - -	 11 10	 15 13	Pregnancy		+ 1.6
Lactation 0-3 mos 3-6 mos 6-12 mos	-	 5.8 5.3 4.3	 9.5 8.8 7.2	 19.0 17.5 14.4	Lactation 14-18 y 19-50 y	 - -	 14 12	Lactation 14-18 y ≥19 y	 - -	 10 9	 11 10	Lactation		+ 2.9

a. High bioavailability (50%); *b*. Moderate bioavailability (30%); *c*. Low bioavailability (15%)
d. Exclusively breastfed infants: breast milk zinc bioavailability assumed to be 80%; *e*. Not applicable to exclusively breastfed infants

TABLE 6. Upper limits or no observed effects level (NOAEL)
for zinc intake by life-stage as defined by WHO, IOM and IZiNCG

WHO/FAO [1]		IOM [2]		IZiNCG [3]	
Age, sex	Upper limit (mg/d)	Age, sex	Upper limit (mg/d)	Age, sex	No observed effect level[a] (mg/d)
0-6 mo	-	0-6 mo	4	0-5 mo	-
7-12 mo	13	7-12 mo	5	6-11 mo	6[a]
1-3 y	23	1-3 y	7	1-3 y	8[a]
4-6 y	23	4-8 y	12	4-8 y	14[a]
7-9 y	28				
10-12 y, M	34	9-13y	23	9-13 y	26[a]
10-12 y, F	32				
12-15 y, M	40				
12-15 y, F	36				
15-18 y, M	48	14-18 y, M	34	14-18 y, M	44[a]
15-18 y, F	38	14-18 y, F	34	14-18 y, F	39[a]
18 – 60+ y, M	45	≥19y, M	40	≥19 y, M	40[b]
18-60+y,F	35	≥19 y, F	40	≥19 y, F.	40[b]

b.Represent upper limits.