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Protective role of dietary zinc on DNA damage, oxidative stress, and metal toxicity

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Dr. Bruce Ames illustrious career spanned many decades with far-reaching impacts both on our knowledge of DNA and in public health. In the 1990s he explored the connection between inadequate intake of micronutrients and single- and double-strand DNA breaks, genome instability due to oxidative damage, and increased susceptibility to cancer and other age-related diseases. In particular, zinc is an essential micronutrient required for many biological processes and is a key component of numerous proteins and enzymes involved in the defense against oxidative stress and DNA damage repair. Reduced zinc status due to inadequate dietary intake, reduced zinc absorption and increased excretion can lead to increased risks for infectious diseases, diabetes, cancer, and neurological disorders. Changes in zinc status can also positively or negatively modulate the outcome of exposure to toxic heavy metals including arsenic, cadmium, and lead. This mini review highlights the role of zinc in maintaining DNA integrity and antioxidant defense, the health consequences of inadequate zinc intake, and the impact of zinc status on the response to environmental exposure to toxic metals. Collectively, the work by Dr. Ames and others advances our understanding of how zinc status plays an integral role in health, and reaffirms the idea originally put forth by Dr. Ames that optimizing micronutrient intake to ensure adequate nutrition, including zinc intake, is essential in promoting health, longevity, and disease prevention.

KEYWORDS

zinc, zinc deficiency, DNA damage, oxidative stress, heavy metals toxicity

Introduction

Dr. Bruce Ames illustrious scientific contributions ranged from understanding the relationship between mutagenesis and carcinogenesis, to the role of oxidative stress and DNA damage plays in mitochondrial decay and aging (Ames, 2022). Early in his career, his research focused on the study of the genetic, enzymological, and regulatory aspects of the large and complicated histidine biosynthetic pathway in *Salmonella typhimurium* in the 1960s and ultimately led to the development of the Ames Test for mutagens. This test is widely used as a sensitive and cost-effective tool for identifying compounds with mutagenic potential from both synthetic and natural sources. In the 1990s he became interested in the connection between DNA damage and cancer, inflammation, and oxidative damage, which led to further ideas about poor quality diets and micronutrient deficiency being a major contributor to DNA damage and cancer.

Work by Dr. Ames and colleagues in the early 2000s indicated inadequate intake of micronutrients (including vitamins B12, B6, C, E, folate, niacin, iron and zinc) can

cause single- and double-strand DNA breaks, genome instability due to oxidative damage, and accelerate mitochondrial oxidative decay associated with aging (Ames, 1999; 2001; Ames et al., 2005). Dr. Ames published the Triage Theory in 2006 that postulates "DNA damage and late onset disease are consequences of a triage allocation response to micronutrient scarcity" and when micronutrients are limiting, processes that favor short-term and immediate survival are favored at the expense of systems that maintain long term health like antioxidant function and DNA repair mechanisms (Ames, 2006). The Triage Theory provides a causal link by which inadequate micronutrient intakes lead to DNA damage, loss of mitochondrial function, accelerated aging and age-associated chronic diseases. Moreover, ensuring adequate micronutrient intake through diet and supplementation may mitigate the triage process. Micronutrient inadequacies, defined as nutrient intake less than the Estimated Average Requirement (EAR), is pervasive worldwide and is a global public health concern (Passarelli et al., 2024). Dr. Ames' research brought attention to the importance of consuming optimal nutrients for achieving health, longevity, and disease prevention. He was a strong proponent in remedying micronutrient inadequacies via optimizing micronutrient intake (through diet and dietary supplements) to reduce the risks of age-related chronic diseases and promote healthy aging.

Among the various nutrients Dr. Ames studied, zinc is an essential micronutrient required for many biological functions including growth and development, cognitive function, reproduction, bone health, and immunity (Maywald and Rink, 2022). Zinc homeostasis is tightly regulated by zinc transporter family members, with zinc metabolism and signaling playing critical roles in many cellular processes (Hara et al., 2017; Chen et al., 2024). In particular, zinc is a key component of numerous proteins and enzymes involved in the defense against oxidative stress and DNA damage repair. In humans, decrease in zinc status can result from low dietary intake of zinc, inadequate zinc absorption, increased zinc excretion, or an increased need for zinc. While severe zinc deficiency caused by low dietary zinc intake is uncommon in high income countries, mild zinc deficiency is potentially prevalent worldwide (Lowe et al., 2024). In the United States, it is estimated that 15% of US adults have zinc intakes below the EAR, with select groups of individuals particularly at risk for zinc deficiency (e.g., children, pregnant or lactating women, adults ≥65 years of age, and individuals with certain chronic diseases) (Reider et al., 2020; NIH-ODS, 2022). Alteration in zinc status biomarkers (serum zinc concentrations) or zinc intake (dietary zinc intake or zinc supplementation) are associated with a variety of health outcomes (Li J. et al., 2022). For example, reduced zinc status is associated with increased risks for infectious diseases (Maywald and Rink, 2022), diabetes (Tamura, 2021), cancer (Sugimoto et al., 2024), and neurological disorders (Li Z. et al., 2022). At the same time, increased dietary zinc intake is associated with decreased risk for certain cancers, depression, and diabetes; while zinc supplementation improved depression symptoms, increased pregnancy rate, and decreased concentration of inflammatory markers (Li J. et al., 2022).

The work from Dr. Ames advanced our understanding of how maintaining adequate zinc status plays an integral role in health. In this mini review, we highlight and update the work by Dr Ames and colleagues since the proposal of the Triage Theory, with focus on the role of zinc in maintaining cellular antioxidant defense and DNA integrity. In the presence of low cellular zinc, due to the Triage Theory, the ability to adequately respond to stressors is impaired due to loss of antioxidant and DNA repair functions. We connect the impact of zinc status on environmental toxic metals exposure, as this highlights the interaction between micronutrient status and environmental factors that together influence health outcomes.

The Role of Zinc in Maintaining DNA Integrity and Antioxidant Defense

As proposed by Dr. Ames, the triage response to inadequate micronutrient intakes, including zinc, results in impaired antioxidant defense and oxidative DNA damage. Work by Dr. Ames and others has demonstrated the role of zinc in protecting cellular components from oxidative damage in a variety of cell lines and animal studies. Zinc has a well-established role in antioxidant defense and mediates its protective role against oxidative damage via multiple mechanisms. Zinc 1) serves as a cofactor for enzymes involved in the functioning of the antioxidant defense system; 2) affects cellular redox balance by inducing the synthesis of metallothionein and glutathione; 3) protects against protein sulfhydryl groups oxidation; and 4) inhibits the pro-oxidant enzyme NADPH-oxidase that generates reactive oxygen species (ROS) (Lee, 2018). Zinc also plays an important role in maintaining DNA integrity. It is required in the regulation of DNA replication via zinc finger proteins, affects chromatin accessibility and transcription factor binding to DNA, and is involved in DNA damage response and repair (Yan et al., 2008; Ocampo et al., 2024). Low intracellular zinc induces DNA damage in cells via a combination of increased oxidative DNA damage and disruption of zinc-dependent proteins involved in DNA-repair pathways, leading to impaired DNA repair and altered expression of DNA damage response genes, resulting in DNA strand breaks and genome instability (Ho and Ames, 2002; Ho et al., 2003; Yan et al., 2008; Sharif et al., 2012). In particular, zinc-dependent transcription factors such as p53, a critical gatekeeping factor in coordinating the response to DNA damage, was impacted with cellular zinc deficiency where loss of zinc in the DNA binding domain impaired DNA binding capacity and compromised function (Ho and Ames, 2002; Yan et al., 2008). Observations from cell culture models were supported by animal models, where severe zinc deficiency induced by dietary zinc restriction similarly caused oxidative stress, DNA damage, and impaired DNA repair and antioxidant defense responses (Oteiza et al., 1995; Bruno et al., 2007; Song et al., 2009b). In more recent animal studies zinc deficiency exacerbated age-related DNA damage by impairing the catalytic activity of 8-oxoguanine DNA glycosylase, an enzyme involved in the base excision repair pathway (Sharma et al., 2024). In other recent studies, zinc deficiency-mediated oxidative stress led to increased inflammation and fibrosis in the lung, induced inflammation and apoptosis in the kidney in zinc deficient animals, and exacerbated age-related chronic inflammation in old mice (Wong et al., 2021; Zhang et al., 2022; Xu et al., 2023).

To model inadequate zinc intake prevalent in human populations, both severe and marginal zinc deficient diets have been used in animal studies to examine various health outcomes, including the effects on DNA damage and integrity. While severe

zinc deficiency caused more damage, animals with marginal zinc deficiency similarly had increased oxidative stress, impaired DNA integrity and DNA repair functions, and increased DNA damage compared to animals in the zinc adequate group (Song et al., 2009b). Marginal zinc deficiency also sensitized animals to increased oxidative DNA damage after chronic exercise (Song et al., 2010a), altered zinc transporter expression and zinc homeostasis in the prostate (Song et al., 2010b), increased age-related chronic inflammation (Wong et al., 2021) and enhanced toxicity associated with exposure to heavy metals (see next section). Importantly, zinc repletion studies showed the deleterious effects of zinc deficiency on DNA integrity can be reversed via dietary intervention. The effects of dietary zinc depletion and repletion in rats showed the increase in DNA damage induced with low zinc intake can be normalized with zinc repletion that restored DNA integrity (Song et al., 2009b). Notably, similar observations were reported in human studies. In one human study, increased DNA strand breaks in peripheral blood cells associated with dietary zinc depletion were ameliorated by zinc repletion (Song et al., 2009a). In other human studies, a moderate increase in dietary zinc (Zyba et al., 2017) or daily oral zinc supplementation (Joray et al., 2015) resulted in a reduction in DNA strand breaks in leukocytes of individuals with improved zinc status. Collectively, these studies reaffirm Dr. Ames' Triage Theory, and showed dietary zinc deficiencies contribute to oxidative stress and DNA damage that can be reversed via dietary interventions. This underscores the role of zinc in maintaining DNA integrity and health, and the potential for disease prevention via increased zinc intake.

Zinc status and toxic metals exposure in the environment

Zinc deficiencies often occur in human populations in regions of the world that are also co-exposed to toxic heavy metal contaminants (Wong et al., 2019). In addition to direct health consequences (Triage response) attributed to inadequate micronutrient intake, an extension to the Triage Theory is that micronutrient deficiencies such as inadequate zinc can impair the cellular responses to environmental stresses, such as toxic metals exposure to exacerbate negative health outcomes. In this section, we discuss how zinc deficiency and zinc supplementation alter response to toxic metals exposure in cell culture, animals, and human studies.

Chronic environmental and occupational exposure to some heavy metals and metalloids cause diverse toxic effects in the body (Balali-Mood et al., 2021). According to the World Health Organization, lead, cadmium, mercury and arsenic are among the top 10 chemicals of major health concern (WHO, 2020). Data from 2007 to 2012 NHANES survey indicated that approximately 50% of the US population was exposed to a combination of three or more of these toxic metals (Shim et al., 2017). This has significant impact on public health as exposure to cadmium, lead, and arsenic can cause liver damage, injury to the central nervous system and lungs, and has been associated with gastrointestinal disorders, immune dysfunction, kidney dysfunction, cardiovascular dysfunction, degenerative bone disease, birth defects, cancer, and an increase in all-cause mortality (Balali-Mood et al., 2021; Guo et al., 2022). The toxic effects of exposure to heavy metals are complicated and dependent on the exposure route, form of the metal, and the dose and duration of exposure (Tchounwou et al., 2012). It is also notable that the effects of toxic metal exposure are dependent on the characteristics of the person exposed, with factors like age, gender, and nutritional status (e.g., zinc status) as determining factors if toxicity is observed (Tchounwou et al., 2012). Further, tissue accumulation of heavy metals and associated organ-specific toxicity can be modulated by the expression and activity of metal transporters, including zinc transporters (Dashner-Titus et al., 2023; Ferdigg et al., 2025).

The mechanisms by which metals cause damage and genotoxicity at the cellular level include: 1) Increasing ROS production and decreasing antioxidant defense, causing DNA, protein, and lipid damage; 2) displacing zinc from zinc finger proteins and disrupting DNA repair, cell division, and other zinc-dependent processes; 3) induction of endoplasmic reticulum stress and mitochondrial dysfunction; and 4) induction of inflammation and apoptosis (Banerjee et al., 2020; Balali-Mood et al., 2021; Koyama et al., 2024). Notably many of the cellular processes negatively affected by toxic metal exposure overlap significantly with zinc deficiency (Figure 1). This suggests potential interaction between zinc and toxic metal exposure, whereby changes in zinc status can positively or negatively modulate the outcome of metal toxicity (Hudson et al., 2025). In general, increased toxicity is observed from toxic metal exposure under the conditions of zinc deficiency, while zinc supplementation has been shown in some models to protect from heavy metal exposure (Wani et al., 2021; Hudson et al., 2025). The toxic metals that have been studied the most in the context of nutritional zinc status are cadmium, arsenic, and lead and are the focus of this review.

Zinc deficiency increases toxicity from cadmium, arsenic and lead exposures

The strongest evidence that zinc deficiency exacerbates metal-induced toxicities are from *in vitro* and animal studies. For example, in cell culture models zinc deficiency and arsenic co-exposure increased levels of ROS, DNA strands break, apoptosis, and inflammation, beyond what was observed with either condition alone (Cao et al., 2019; Wong et al., 2019). Further, zinc deficiency exacerbated lead-induced suppression of interleukin-2 production in immune cells (Trojan et al., 2024). Cellular zinc loss also enhanced the cytotoxicity of lead in neuronal cells by further reducing cell viability and increased the intracellular oxidant levels that led to activation of oxidant-responsive transcription factors, such as AP-1 that contributed to neuronal cell death (Aimo and Oteiza, 2006). In rats, dietary zinc deficiency increased lead and cadmium accumulations in various organs, resulting in impaired skeletal growth, increased neoplastic progression of testicular lesions and enhanced chronic progressive nephropathy (Bushnell and Levin, 1983; Waalkes, 1986; Waalkes et al., 1991; Jamieson et al., 2006). In mice, co-exposure of arsenic and zinc deficiency resulted in increased oxidative stress, DNA damage, and inflammation (Gaulke et al., 2018; Wong et al., 2019). Further, arsenic-induced perturbations in the gut microbiome was amplified with zinc

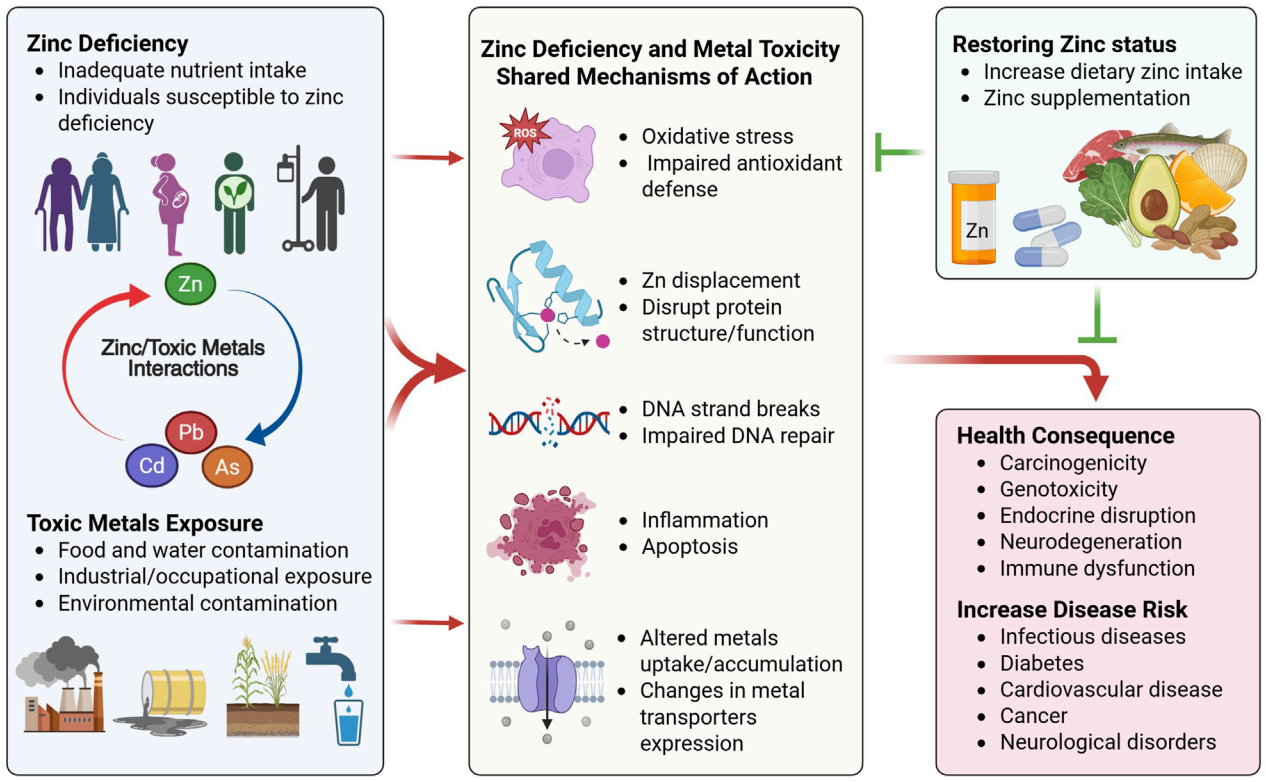

FIGURE 1
Interactions between zinc status and toxic metals exposure. Populations at risk for zinc deficiency and toxic metals exposure are susceptible to cellular and organ damage via common mechanisms. Zinc deficiency and toxic metals exposure both lead to increased oxidative stress and impaired antioxidant defense, resulting in impaired DNA repair, DNA strands breaks, inflammation and apoptosis. This is in part mediated via displacement of zinc and disruption of zinc finger protein structure and function, and dysregulated expression of metal transporters that alter zinc homeostasis and toxic metal uptake and accumulation. These common interactions between zinc deficiency and toxic metals exposure can exacerbate metal-induced toxicity when both conditions are present, resulting in further cellular damage, increased genotoxicity and carcinogenicity, disruption of cellular and organ functions, and increased risk for various chronic diseases. Improving zinc status via increased dietary zinc intake and/or zinc supplementation can ameliorate cellular damage and confer protection against toxic metals exposure. Created in BioRender. Wong, C. (2025) https://BioRender.com/mdjt9mx.

deficiency, likely increasing the microbiome's sensitivity to arsenic exposure and by altering the response of the microbiome to chemical exposure (Gaulke et al., 2018). In zebrafish, arsenic exposure significantly reduced the amount of zinc in the developing embryo, and zinc deficiency and arsenic co-exposure caused changes in the expression of genes that regulate zinc homeostasis, response to oxidative stress and insulin production, and decreased larval photomotor response, an assay used to assess neurotoxicological behavioral responses. The decline in larval behavior was significantly greater than what was observed with zinc deficiency or arsenic exposure alone (Beaver et al., 2017). Together these data suggest that zinc deficiency may sensitize cells and individuals to various toxic metal exposures.

Zinc supplementation protects against cadmium, arsenic and lead exposures

In vivo zinc supplementation studies demonstrated increasing zinc status protected against various metals toxicities (Wani et al., 2021; Yu et al., 2021; Banerjee et al., 2022; Hudson et al., 2025). One mechanism by which zinc mitigates metal toxicity is by reducing toxic metal accumulation. In mice chronically exposed to arsenic, zinc supplementation reduced the amount of arsenic detected in all tissues tested, in part by modulating the expression of metal transporters (Dashner-Titus et al., 2023). Similar reductions in heavy metal accumulation and toxicity was observed in animals exposed to cadmium (Pabis et al., 2018) and lead (Hietanen et al., 1982; Ugwuja et al., 2020; Butt et al., 2023). Reduced toxic metal tissue burden can be mediated by zinc's competition for metal cellular uptake, and its effect on the expression of metal transporters that affect metal absorption, accumulation, and excretion (Dashner-Titus et al., 2023; Ozoani et al., 2024). Another mechanism by which zinc reduces metal toxicity is via the induction of metallothionein expression and reduction of oxidative damage by upregulating and/or restoring antioxidant pathways. Metallothioneins are small proteins that function as antioxidants, scavengers of ROS, sequester toxic metals, and restore antioxidant capacity (Yang et al., 2024). In animal models, zinc supplementation reduced arsenic and lead toxicity by restoring antioxidant activity and increasing metallothionein expression (Ganger et al., 2016; Prastiya et al., 2023). Zinc supplementation also increased the activities of

antioxidant enzymes including superoxide dismutase, glutathione peroxidase, glutathione reductase, and catalase (Kumar et al., 2010), and restored function of other zinc-dependent proteins that were disrupted with arsenic exposure (Cooper et al., 2013; Banerjee et al., 2022; Bastick et al., 2022). Zinc supplementation also prevented cadmium and lead-mediated oxidative damage to the brain (Prasanthi et al., 2010; Brzoska et al., 2021). Among animal models of DNA damage, zinc supplementation reduced cadmium-induced DNA damage in zebrafish (Devarapogu and Asupatri, 2023), and reduced arsenite-enhanced DNA damage in response to ultraviolet radiation exposure in mice (Cooper et al., 2013).

Associations of zinc status, toxic metals exposure, and health in human studies

There are several lines of evidence in human population studies indicating zinc status and dietary zinc intake are inversely associated with metal toxicity (Talpur et al., 2018). For cadmium exposures, zinc intake is associated with lower cadmium burden in U.S. adults (Vance and Chun, 2015). In this study, increased levels of dietary and serum zinc were associated with a decrease in blood cadmium and an increase in urinary cadmium, suggesting zinc status influenced the absorption, accumulation, and excretion of cadmium. In other studies, dietary zinc intake/status modulated mortality risks associated with cadmium exposure (Kim et al., 2019), cadmium-induced risk of prostate cancer (Bede-Ojimadu et al., 2023), and renal damage (Chen et al., 2018). In children with autistic disorders, over 30% of the study population had zinc deficiency that correlated with high toxic metal burden including lead, cadmium, and arsenic (Yasuda and Tsutsui, 2022). High zinc levels in peripheral blood was associated with protection of workers against occupational exposure to lead, where zinc status inversely correlated with lead concentrations, DNA damage, oxidative stress and lead-induced blood cell membrane aberrations (Wani et al., 2017; Wani et al., 2019).

While human population studies demonstrated the association between zinc status and metal toxicities, to date there is only one intervention study that directly assesses individual toxic metal exposures and responses to zinc supplementation in individuals with chronic toxic metal exposures (NCT03908736, ClinicalTrials.gov). While some zinc supplementation intervention studies have been conducted in regions with populations at risk for toxic metal exposures, the relationship between zinc status and toxic metals exposure has not been examined. More intervention trials are needed to examine the efficacy of zinc supplementation in mitigating metal toxicity in at risk communities. Another ongoing challenge in human studies is the lack of reliable, specific and sensitive biomarkers to accurately identify and evaluate zinc status, particularly in individuals at risk for marginal zinc deficiency (Lowe et al., 2009).

The overall health consequence of toxic metal exposures can include dysfunction to multiple organ systems, resulting in persistent infections (Zheng et al., 2023; Zhang et al., 2024), increased risk for chronic and metabolic diseases (Planchart et al., 2018; Javaid et al., 2021; Pan et al., 2024), neurological disorders (Pamphlett and Bishop, 2023), and cancers (Khoshakhlagh et al., 2024). It is notable that zinc deficiency impacts similar organ systems and is associated with many of the same chronic diseases as toxic metals exposure. Many zinc supplementation studies have demonstrated the protective effects of zinc in similar diseases that are affected by metals toxicity (Li J. et al., 2022). In humans, zinc supplementation lowered the incidence, duration, symptoms, mortality and recovery times in infectious diseases encompassing viral, bacterial, and parasitic pathogens (Maywald and Rink, 2022; Ben Abdallah et al., 2023). In pre-diabetic and diabetic individuals, zinc supplementation improved glycemic control, insulin sensitivity, and reduced inflammatory biomarkers (Wang et al., 2019) and improved risk factors for cardiovascular diseases (Pompano and Boy, 2021). Other clinical studies showed zinc supplementation decreased clinical depression (da Silva et al., 2021; Yosaee et al., 2022), improved neurologic recovery in patients with traumatic brain injury (Young et al., 1996), and improved cognitive function in school children and overweight or obese women (de Moura et al., 2013; de Vargas et al., 2023). While these studies do not address toxic metals exposure, nevertheless accumulating evidence indicates improving zinc status via increased dietary intake or supplementation should confer protection to susceptible individuals, including populations at risk for toxic metal exposures.

Overall impact of zinc status on health

Work from Dr. Ames and others collectively establish zinc as one of the micronutrients essential for health, in particular via its role in cellular oxidant defense and maintaining DNA integrity. The consequence of zinc inadequacies has a significant impact on human health. Together this work highlights the importance of maintaining adequate micronutrient levels, like zinc in the body to preserve key biological functions and improve many aspects of human health. Large bodies of work from the past several decades underscores the idea originally put forth by Dr. Ames that adequate nutrition, including zinc intake, is essential for optimal health and promoting healthy aging.

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CW: Writing – original draft, Writing – review and editing. LB: Writing – original draft, Writing – review and editing. EH: Writing – original draft, Writing – review and editing.

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Conflict of interest

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