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Review

Toxic trace elements at gastrointestinal level

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ABSTRACT

Many trace elements are considered essential [iron (Fe), zinc (Zn), copper (Cu)], whereas others may be harmful [lead (Pb), cadmium (Cd), mercury (Hg), arsenic (As)], depending on their concentration and chemical form. In most cases, the diet is the main pathway by which they enter our organism. The presence of toxic trace elements in food has been known for a long time, and many of the food matrices that carry them have been identified. This has led to the appearance of legislation and recommendations concerning consumption. Given that the main route of exposure is oral, passage through the gastrointestinal tract plays a fundamental role in their entry into the organism, where they exert their toxic effect. Although the digestive system can be considered to be of crucial importance in their toxicity, in most cases we do not know the events that occur during the passage of these elements through the gastrointestinal tract and of ascertaining whether they may have some kind of toxic effect on it. The aim of this review is to summarize available information on this subject, concentrating on the toxic trace elements that are of greatest interest for organizations concerned with food safety and health: Pb, Cd, Hg and As.

Contents

Abbreviations: AECOSAN, Agencia Española de Consumo, Seguridad Alimentaria y Nutrición; AQP, Aquaglyceroporins; As(III), Arsenite; As(V), Arsenate; ATSDR, Agency for Toxic Substances and Disease Registry; bw, Body weight; CH_3Hg, Methylmercury; DMA(V), Dimethylarsinic acid; DMA(III), Dimethylarsinious acid; DMTA(V), Dimethylthioarsinic acid; DMDTA(V), Dimethyldithioarsinic acid; DMAA, Dimethylarsinoylacetic acid; DMT1, Divalent metal transporter 1; dw, Dry weight; EFSA, European Food Safety Authority; FSA, Food Standards Agency; fw, Fresh weight; GI, Gastrointestinal: Glut: Glucose permeases; Hg(II), Divalent inorganic mercury; IARC, International Agency for Research on Cancer; IL, Interleukin; JEFCA, FAO/WHO Expert Committee on Food Additives; LAT, Neutral amino acid transporters; MIP-2, Macrophage inflammatory protein-2; MMA(V), Monomethylarsonic acid; MMA(III), Monomethylarsonous acid; MMMTA(V), Monomethylmonothioarsonic acid; NaPi, Na-dependent phosphate transporters; NTP, National Toxicology Program; OATP, Organic anion transporting polypeptides; PTWI, Provisional tolerable daily intake; SHIME, Simulator of the Human Intestinal Microbial Ecosystem; TNFα, Tumor necrosis factor alpha; TMAO, Trimethylarsine oxide; TMAS, Trimethylarsine sulfide; TWI, Tolerable weekly intake; ZIP, Zrt/Irt-related protein; ZO-1, Zonula occludens 1.

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Toxic trace elements have aroused the interest of the scientific community and the organizations responsible for food safety in recent decades. Numerous reviews have been made of aspects related to the presence of these elements in food, and committees of experts such as the European Food Safety Authority (EFSA) or the FAO/WHO Expert Committee on Food Additives (JECFA) have published monographs in which toxicological reference values have been modified on the basis of new information. The aim of this review is to summarize the most important existing information on the processes that these contaminants may undergo during their transit through the gastrointestinal tract, and the toxic effect that this transit may have on the gastrointestinal epithelium. It must be borne in mind that the gastrointestinal epithelium is the first barrier that these elements encounter when they are ingested, and it limits their absorption ratio and subsequent entry into the systemic circulation. Moreover, the digestive tract cannot be considered to be a mere onlooker; a series of processes may take place in it which alter the form that the toxic element originally has in the food. The presence of food components and endogenous substances, the gastrointestinal epithelium, and the microbial flora are key factors not only in the process of digestion and absorption but also in processes of transformation that can produce important changes in the chemical form of these elements. The chemical changes are ultimately translated into modifications of the absorption and toxicity of these contaminants.

1. Food matrices in which the toxic trace elements of interest are found

As already mentioned, exposure to toxic trace elements is mainly due to ingestion of food and in some cases to consumption of water with high levels of the contaminant. This section provides a summary of existing information about toxic trace element contents and indicates the main dietary sources which contain them.

1.1. Dietary sources for lead

Lead (Pb) is mainly present in inorganic form in food products, although in recent decades, as a result of advances in analytical chemistry, organic forms have also been identified. Some wines from southern France show concentrations of trimethyl lead in a range of 8.1–112 ng/L (Lobinski et al., 1993). Chen et al. (2014) also found trimethyl lead chloride in oyster samples (0.23 mg Pb/kg dry weight, dw). Furthermore, Pb can coordinate with sulfhydryl or amino groups of various proteins or peptides in the food matrix (Srinivas et al., 2007).

EFSA examined 94,126 analytical data for Pb in food, collected during a nine-year period (EFSA, 2010); the highest amount of Pb was found in game meat (mean: 3.1 mg/kg), followed by edible offal from game animals (mean: 1.25 mg/kg) and alga-based supplements (mean: 1.02 mg/kg). High concentrations of Pb have also been reported for seafood products [crustaceans and mollusks (up to 6 mg/kg in mussels; Abi-Ghanem et al., 2014), and fish and fish products (up to 0.5 mg/kg; Olmedo et al., 2013)], sometimes exceeding the maximum levels established by EU legislation [(EC) No 1881/2006]. The highest contributors of Pb to the European diet are cereals, grains and grain-based products (14.3–16.3%), fish and shellfish (18%), fruits (14.4%), milk and dairy products (10.6%), non-alcoholic beverages (10.3%), vegetables and vegetable products (8.4–14.3%), drinking water (7–11%) and alcoholic beverages (6.7–14%) (EFSA, 2012a). The food groups contributing most to Pb dietary intake in Canada are beverages (e.g., beer, wine, coffee, tea, soft drinks), cereal-based foods and vegetables (Health Canada, 2011).

The EFSA Panel on Contaminants in the Food Chain established benchmark dose levels in adults of 1.50 μg/kg body weight (bw)/day and 0.63 μg/kg bw/day for cardiovascular and kidney effects, respectively (EFSA, 2010). A considerable reduction in exposure levels has been found in recent years as a result of the elimination of leaded gasoline and the use of lead-free utensils in the preparation of food. The latest EFSA report on Pb provides intakes for the various population groups in Europe. The data show that exposure was highest for toddlers and other children, with 1.32 and 1.03 μg/kg bw/day, respectively, while adult daily exposure was estimated at 0.50 μg/kg bw (EFSA, 2012a). One study made in Santiago de Chile showed a Pb exposure (3.03 μg/kg bw/day) much greater than the values reported for other countries (Muñoz et al., 2005).

1.2. Dietary sources for cadmium

The latest report on cadmium (Cd) produced by the European Food Safety Authority's panel on contaminants (EFSA, 2009a) shows that the main dietary sources of this element are cereals and cereal products, vegetables, nuts and pulses, starchy roots or potatoes, and meat and meat products. However, the highest concentrations are found in seaweed, seafood, chocolate, fungi, oilseeds and edible offal.

The existing studies on seaweed indicate that the highest Cd concentrations occur in certain species: *Porphyra* spp., *Undaria pinnatifida* and *Hizikia fusiforme* (Almela et al., 2006; Dawczynski et al., 2007). In seafood products, the highest values are found in shellfish, especially in bivalve mollusks (Amiard et al., 2008; Bendell, 2009), which sometimes exceed the limit established by the Commission Regulation (EU) N488/2014 (1 mg/kg). Mushrooms also have concentrations that exceed the legal values. Kalač and Svoboda (2000) report that the content in *Boletus aestivalis*, *Leccinum scabrum*, *Calocybe gambosa*, *Armillaria mellea* and *Russula cyanoxantha* growing in unpolluted areas can be up to 5 mg/kg dw; and that in species of the *Agaricus* genus the concentration can be as much as 50 mg/kg dw. Bearing in mind the maximum Cd concentration permitted by the European Union regulation in cultivated mushrooms other than *Agaricus bisporus*, *Pleurotus ostreatus*