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Toxic element contaminations of prenatal vitamins

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Abstract

The detrimental effects of gestational and lactational exposure to adverse chemical agents are gathering increasing attention. In our study, the presence of toxic heavy metals in several prenatal vitamins from six brands available in supermarkets and pharmacies was measured using ICP mass spectrometry. Several toxic heavy metals were detected, some at levels that could have potential toxicity to the fetus and the mother as well. Previous studies have also detected toxic heavy metals in prenatal and other vitamins. One of the reasons for toxic heavy metals in “natural vitamins” sold to consumers is that they are produced from naturally grown material and not synthesized. They are likely exposed to the heavy metals from the ground that they are grown in and there has not been any significant attempt to get rid of them before the vitamin pill was sold to consumers. Thus, this problem is not an isolated issue and regulatory agencies should be dealing more aggressively than they have been doing. In fact, several papers have already been published showing similar findings as we are reporting here. The vitamin pills we analyzed have elevated levels of boron, aluminum, molybdenum, barium, lead, titanium, nickel, arsenic, strontium, and cadmium. The levels of total chromium were also elevated but we did not separately determine Cr(III) and the much more hazardous Cr(VI), because of the tedious procedure required to separate these two forms of Cr.

Keywords

Prenatal vitamins; Heavy metals; Toxicities; Carcinogenesis

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Credit author statement

Zhuo Zhang is involved in data interpretation and analysis, discussion, and manuscript writing. Thomas Kruz is involved in experiment design, data generation and analysis, and discussion. Max Costa is responsible for overall experiment design and discussion.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.taap.2023.116670>.

1. Introduction

Prenatal vitamins are consumed daily during gestation and postnatally for up to 18–24 months. It is believed that supplementation achieves better birth outcomes. In the United States, over-the-counter prenatal vitamins do not require U.S. Food and Drug Administration (FDA) approval. Thus, the content and quality of prenatal vitamins vary.

Heavy metals are naturally occurring elements. Heavy metals, including arsenic (As), cadmium (Cd), chromium (Cr), mercury (Hg), lead (Pb), and nickel (Ni), are commonly contaminated in the soil. The persistent long-term heavy metal contamination in the soil threatens the environment and public health. During pregnancy, exposure to toxic metals, arsenic, cadmium, chromium, lead, and mercury caused adverse effects on the fetus (Needham et al., 2011; Quansah et al., 2015; ATSDR, 2008). The association between prenatal exposure to heavy metals and adverse birth outcomes has been studied previously. It has been reported that exposure to arsenic, cadmium, or lead during pregnancy caused short birth length, low birth weight, and small head circumference (ATSDR, 2008; Al-Saleh et al., 2014; IARC, 1999; U.S. EPA, 2006). It has also been reported that prenatal exposure to inorganic arsenic caused miscarriage and stillbirth (Quansah et al., 2015).

Pregnant women and their fetuses are vulnerable to adverse effects of exposure to toxic substances (Vahter, 2009; Zheng et al., 2014; Clark et al., 2022). These adverse effects can be extended into early childhood and later life (Gluckman et al., 2008). While the placenta, acting as a selective transporter, prevents the passage of potentially toxic substances to the developing fetus, some toxic substances can cross the placental barrier (Gluckman et al., 2008). Arsenic, cadmium, and lead, well-known toxic heavy metals, extend the health risk to the fetus at a low level through trans-placental circulation (Zheng et al., 2014; Caserta et al., 2013; Chen et al., 2014).

In this study, heavy metals were measured in several brands of prenatal vitamins sold in the national chain supermarkets and pharmacies.

2. Methods and materials

2.1. Collection of prenatal vitamins

The prenatal vitamins from six brands were purchased from national chain supermarkets, in New York, NY, USA. The six brands were selected because they are available in most retail stores and represent the three categories of pure natural sources, a mixture of natural and synthetic, and synthetic sources. One of the brands was purchased from three retail stores, representing different batches.

2.2. Sample preparation

Three types of vitamins including tablets, gummies, and gel caps (of which the internal contents were used) were studied. Vitamins were weighed. 8.5 mL of concentrated Optima grade nitric acid (Fischer Scientific) 1 mL of optima hydrogen peroxide, and 0.25 mL of hydrofluoric acid were added into each digestion vessel containing approximately 400 mg of the vitamin. Digestions were carried out using Perkin Elmer Titan MPS microwave at 170

°C for 10 min, and 200 °C for 45 min followed by a cooling period after which digestion mixtures were transferred into the Teflon beakers which were heated on the hot plate until approximately 1 mL of sample remained.

Digested Vitamin concentrates were adjusted into a total volume of 50 mL by adding Milli-Q water followed by three times dilution using 2% nitric acid. Internal standards were added to each sample prior to the measurements to control for variations in matrix composition among samples.

2.3. Instrumental analysis

All analyses were performed on a Nexion[®] 350D ICP-MS using both Standard and Kinetic Discrimination (KED-Helium gas) mode. The accuracy of the method was established by analyzing the certified reference material (NIST 1577 Liver Standard) in addition to sample spike recoveries. The percentages of recovery for major elements were listed in supplementary Table 1. The lowest detection limits were listed in supplementary Table 2. The instrumental conditions were provided in in Supplementary Table 3.

3. Results and discussions

A total of 32 elements from six brands (A-F) of prenatal vitamins were measured in this study. 17 elements that exert toxicity to humans were discussed in this paper. According to the process sources, we classified these prenatal vitamins into three categories, natural/organic, a mix of natural and synthetic, and synthetic (Table 1). Natural or organic vitamins are from whole foods, while synthetic vitamins are made in a laboratory. Brand C was labeled as organic by the manufacture but contained a small quantity that was synthetic. Brand E and B were classified as natural and synthetic vitamins because most ingredients are from natural and synthetic sources, respectively. Vitamins from brands A, D, and F were a combination of synthetic and natural materials. We noticed that both brands A and B contained a certain amount of fish oil, but not brands C, D, E, and F. The recommended doses by manufactures were also listed in Table 1.

3.1. Aluminum

Aluminum is the most abundant metal in the earth's crust. It is naturally occurring in air, soil, and water. Aluminum is a very reactive element and is found combined with other elements such as fluorine, oxygen, and silicon. These compounds can be found in clays, minerals, rocks, and soil. Aluminum compounds may be added during food processing. Aluminum is also found in over-the-counter medications, such as aspirin and antacids. While oral exposure to aluminum is not harmful, animal studies demonstrated that exposure to high levels of aluminum damaged the nervous system (Shaw and Tomljenovic, 2013). Bone disease caused by high levels of aluminum has been observed in children with kidney disease (Andreoli et al., 1985). An adult in the United States takes about 7–9 mg of aluminum daily in food. Based on taste, smell, or color, not on the levels that will affect humans, the EPA has recommended a Secondary Maximum Contaminant Level (SMCL) of 0.05–0.2 mg/L for aluminum in drinking water (<https://www.epa.gov/sdwa/drinking-water-regulations-and-contaminants>). The FDA has determined that aluminum is generally safe as

food additives and medicinals such as antacids. The FDA set a limit for aluminum in bottled water at 0.2 mg/L (<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=165.110>).

Aluminum products are listed as a “Group 1” human carcinogen by International Agency for Research on Cancer (IARC) in 2012 (Table 2).

Our results showed that the average aluminum weight in the prenatal vitamins from brand F was 309.9 µg per recommended dose, the highest one among all six vitamins (Table 3). It was 229.9 µg per recommended dose from brand D (Table 3). The aluminum weight was 3.3 µg in vitamins made synthetically in brand B (Table 3). It was 0.43 µg in brand E vitamins (Table 3). A value of 2 liters/day is generally applied as the daily drinking water intake for adults for exposure assessments conducted by many countries and international organizations. For example, a SMCL of 0.05–0.2 mg/L for aluminum in drinking water is equal to 0.1–0.4 mg per day for adults. None of these vitamins exceeded the limit (0.4 mg) by the FDA.

3.2. Antimony

Antimony can be found in the earth’s crust. Antimony metal is combined with other substances to form antimony compounds at very low levels. Antimony exists in two forms, trivalent or pentavalent. Trivalent antimony compounds are more toxic than pentavalent antimony compounds. Antimony has been used as a medicine to treat parasite infections. Short-term exposure to antimony in humans affected the skin and eyes (DHHS, 1993). Chronic exposure to antimony through inhalation caused lung inflammation of the lungs and bronchi (DHHS, 1993; ATSDR, 1992a). Animal studies have reported exposure to antimony prior to conception and throughout gestation in rats decreased the number of offspring (ATSDR, 1992a).

Lung tumors have been observed in rats exposed to antimony trioxide by inhalation (DHHS, 1993; ATSDR, 1992a; U.S. EPA, 1999). IARC has determined that antimony trioxide is possibly carcinogenic to humans (Table 2). The EPA has not classified antimony for carcinogenicity.

Our results showed that the highest weight of antimony was 0.2510 µg/recommended dose from vitamins by brand E followed by 0.1236 µg by brand C (Table 3), which are natural/organic vitamins. The antimony was not detectable in vitamins by brand A. They were 0.0011, 0.0172, and 0.0902 µg from vitamins by brands B, D, and F, respectively (Table 3).

3.3. Arsenic

Arsenic, a naturally occurring element, combines with either inorganic or organic substances to form various compounds. Inorganic arsenic compounds are found in soils, sediments, and groundwater. Inorganic arsenic is more toxic than organic arsenic. The exposure to inorganic arsenic for humans occurs through drinking water, foods such as rice and fruit juices, and by contact with contaminated soil or wood preserved with arsenic compounds. Short-term exposure to large doses of inorganic arsenic caused GI symptoms including nausea, vomiting, and diarrhea. Long-term exposure to high levels of inorganic arsenic in drinking

water and food has been linked to diabetes, cardiovascular diseases, and cancers. Arsenic exposure during pregnancy is also associated with infant mortality (U.S. EPA, 2006). Exposure in utero and in early childhood caused cancers, lung disease, heart attack, and kidney failure, resulting in increased mortality in young adults (Farzan et al., 2013). The EPA set the arsenic standard for drinking water at 10 ppb (<https://www.epa.gov/dwreginfo/chemical-contaminant-rules#:~:text=EPA%20set%20the%20arsenic%20standard,term%2C%20chronic%20exposure%20to%20arsenic>). The FDA issued guidance to the industry to not exceed inorganic arsenic levels of 100 ppb in infant rice cereal and on a level of 10 ppb of inorganic arsenic in ready-to-drink apple juices (U.S. FDA, 2020).

Arsenic has been associated with several cancers, including bladder, lungs, skin, kidney, nasal passages, liver, and prostate. IARC has classified arsenic and arsenic compounds as carcinogenic to humans and has stated that arsenic in drinking water is carcinogenic to humans (Table 2).

The results from Table 3 showed that arsenic weights among these six brands ranged from 0.064 to 8.012 μg per recommended dose. In general, synthetic vitamins contain less arsenic while natural vitamins have high arsenic weights. The arsenic weight was 0.064 μg per recommended dose from brand B which is synthesized vitamins (Table 3). The arsenic weights from three batches of brand F remained similar, which are 8.012, 7.617, and 6.495 $\mu\text{g}/\text{recommended dose}$ (Table 3). The arsenic weight was 4.532 $\mu\text{g}/\text{recommended dose}$ from the natural brand E (Table 3). Even though the levels of arsenic in these vitamins are below the standards of the EPA or FDA, the arsenic weight of 8.012 μg from brand F is a concern because pregnant women and fetuses are two of the most vulnerable groups in response to arsenic toxicity.

3.4. Barium-1

Barium, an odorless metal, is naturally found as water-insoluble compounds, barium sulfate or barium carbonate. Ingestion of large amounts of barium compounds may cause gastrointestinal symptoms, hypokalemia, and kidney damage (ATSDR, 2007). Chronic exposure to barium or soluble barium compounds causes adverse renal effects (ATSDR, 2007). OSHA PEL (permissible exposure limit) as an 8-h TWA concentration = 0.5 mg/m^3 for soluble barium compounds and 5 mg/m^3 for insoluble barium sulfate.

IARC has not assessed the carcinogenicity of barium. The EPA has concluded that barium is not likely to be carcinogenic to humans following oral exposure and its carcinogenic potential cannot be determined following inhalation exposure.

The results from Table 3 showed that the average barium weight from the three batches of brand F was 4.17 $\mu\text{g}/\text{recommended dose}$. The barium weight from brand E, natural vitamins, was 6.79 $\mu\text{g}/\text{recommended dose}$, higher than other brands of synthetic or a combination of synthetic and natural ones.

3.5. Beryllium

Beryllium is one of the lightest metals and is the 44th most abundant element in the Earth's crust. The major exposure route in humans is through airborne particles of beryllium metal, alloys, oxides, and ceramics (Kolanz, 2001). Inhalation of beryllium particles into the lungs and respiratory tract caused sensitization and chronic beryllium disease (CBD) (Deubner et al., 2001). The EPA set the maximum contaminant level of beryllium in drinking water as 0.004 mg/L (<https://www.epa.gov/ground-water-and-drinking-water/national-primary-drinking-water-regulations>).

The EPA has listed beryllium as a probable human carcinogen in the category of B1 for the inhalation route. However, beryllium is listed as a noncarcinogen for the oral exposure route. IARC has classified beryllium as Group 1 human carcinogen (Table 2).

Our results showed that the highest weight of beryllium from brand E was 0.192 µg/recommended dose (Table 3). The beryllium weight from prenatal vitamins made by brand C was 0. The beryllium weights from three batches of brand F were 0.0334, 0.0293, and 0.0291 µg/recommended dose (Table 3). The weights from synthetic vitamins of brand B were 0.0038 µg per recommended dose (Table 3). Overall, the beryllium weight is much lower in synthetic vitamins than in natural or a combination of natural and synthetic ones.

3.6. Boron

Boron is the 51st most common element in the earth's crust. Boron can be found in fruits, grains, nuts, and vegetables. It has been reported that the U.S. diet consumes an average of 1.5 mg of boron per day (Mastromatteo and Sullivan, 1994). The National Academy of Science Institute of Medicine categorizes boron as a possible trace mineral nutrient for humans. Both animal and human studies demonstrated that low intakes of boron affect cellular function and the activity of other nutrients (Pizzorno, 2015). Boron may interact with vitamin D and calcium, influence estrogen metabolism, and play a role in cognitive function (Nielsen, 2000; Miljkovic et al., 2009). Short-term exposure to high levels of boron caused stomach irritation and diarrhea (Litovitz et al., 1988). Long-term exposure to boron caused indigestion, dermatitis, loss of hair, and anorexia (Ulusik et al., 2018). WHO has derived a provisional guideline value of 0.5 mg/L in drinking water (WHO, 2003).

No data were found on the carcinogenicity of boron and compounds in humans.

Our results showed that the boron weights from three batches of brand F vitamin were 1594, 1509, and 1807 µg/recommended dose. It was 2.58 µg/recommended dose from synthetic vitamins by brand B. The boron weight was 121.91 µg/recommended dose from natural vitamins by brand E. The boron weight in synthetic vitamin brand B is much lower than that in natural vitamin brand E.

3.7. Cadmium

Cadmium, a widely dispersed element, is found naturally in the environment. Cadmium is used to produce batteries, alloys, coatings, plastic stabilizers, and pigments. In the United States, for nonsmokers, the primary exposure source to cadmium is the food supply. Leafy vegetables such as lettuce and spinach, potatoes, grains, peanuts, and soybeans contain high

levels of cadmium, approximately 0.05–0.12 mg cadmium/kg. Tobacco leaves accumulate high levels of cadmium from the soil. Ingestion with high cadmium levels through food or drinking water irritates the stomach, causing vomiting and diarrhea (ATSDR, 2012). Ingestion of lower levels of cadmium in the long term causes an accumulation of cadmium in the kidneys, resulting in kidney dysfunction (ATSDR, 2012). WHO set the cadmium standard in drinking water as 0.003 mg/L (WHO, 2011). It is 0.005 mg/L by the EPA (<https://www.epa.gov/ground-water-and-drinking-water/national-primary-drinking-water-regulations>).

IARC has determined that cadmium is a Group 1 human carcinogen (Table 2). The EPA has classified cadmium as a probable human carcinogen.

Our results showed that the highest cadmium weight among the six brands was 0.785 µg/recommended dose from brand E, the vitamins naturally made. Brand A, a combination of synthetic and natural vitamins, contained the least cadmium (Table 3). The average cadmium weight of three batches from brand F was 0.12 µg/recommended dose (Table 3). The cadmium weights from these prenatal vitamins are lower than U.S. EPA or WHO standards.

3.8. Chromium

Chromium is the sixth most abundant element in the Earth's crust. Naturally occurring chromium is present as trivalent Cr(III). Hexavalent Cr(VI) in the environment is derived from human activities, such as airborne emissions and effluents from chemical plants, contaminated landfill, tobacco smoke, and topsoil and rocks. Cr(III) is poorly absorbed, the toxicity of chromium is mainly attributable to the Cr(VI). Cr(VI) can be absorbed by the lung and gastrointestinal tract and intact skin. Most of the ingested Cr(VI) is converted to Cr(III) (Cohen et al., 1993). Exposure to Cr(VI) through inhalation causes respiratory tract irritants, airway obstruction, and lung, nasal, or sinus cancer. Ingestion of potassium dichromate experienced abdominal pain, vomiting, and intravascular hemolysis, even death (Kaufman et al., 1970; Sharma et al., 1978). Ingestion of sodium dichromate died of cardiopulmonary arrest (Ellis et al., 1982). The EPA set the chromium standard in drinking water as 100 ppb (<https://www.epa.gov/sdwa/chromium-drinking-water#standard>). The EPA and IARC have classified inhaled Cr(VI) as a known human carcinogen (U.S. EPA, 1998; IARC, 1990) (Table 2).

Our results showed that the highest chromium weight was 68.76 µg/recommended dose from brand C, organic vitamins. In brand E, naturally made vitamins, the chromium weight was 35.5 µg/recommended dose (Table 3). The average weight from three batches of brand F was 24.06 µg/recommended (Table 3). The chromium weight in synthetic vitamins brand B was 2.54 µg/recommended, and it is 0.89 µg/recommended in brand A, a combination of synthetic and natural vitamins, which are much lower than other brands (Table 3).

3.9. Copper

Copper is a reddish metal that occurs naturally in rock, soil, water, and air at low levels. Copper is an essential element for good health at low levels of intake. However, long-term exposure to copper irritates the nose, mouth, and eyes, causing headaches, dizziness, nausea, and diarrhea (ATSDR, 2022). High levels of copper can cause liver

(O'Donohue et al., 1993) and kidney damage (Chugh et al., 1975). The central nervous system is also a target of chronic copper toxicity (Owen Jr. et al., 1980; Hultgren et al., 1986). High concentrations of circulating copper cause hemolytic anemia (Brewer and Yuzbasiyan-Gurkan, 1992). The Food and Nutrition Board of the Institute of Medicine has developed recommended dietary allowances (RDAs) of 340 µg/day of copper for children aged 1–3 years, 440 µg/day for children aged 4–8 years, 700 µg/day for children aged 9–13 years, 890 µg/day for children aged 14–18 years, and 900 µg/day for adults (<https://ods.od.nih.gov/factsheets/Copper-HealthProfessional/>). The EPA has set that drinking water should not contain more than 1.3 mg/L (<https://www.epa.gov/ground-water-and-drinking-water/national-primary-drinking-water-regulations>).

The EPA does not classify copper as a human carcinogen.

Our results showed that the average weight of copper from three batches of brand F vitamins was 3334.89 µg, the highest weight among all six prenatal vitamins (Table 3). The second and third high weights were 2915.34 and 1394.64 µg from brands B and E, respectively (Table 3). They were less than 10 µg from vitamins of brands A, C, and D (Table 3).

3.10. Cobalt

Cobalt is a naturally occurring element found in air, rocks, soils, and water. Cobalt is widely used in industries, such as pigments and paints, colored glass, batteries, electroplating, and others. Cobalt is beneficial to human health at low levels but can be toxic in high concentrations. A small amount of cobalt in vitamin B12 as an essential trace element is important for good health. Food is a primary source of exposure to low levels of cobalt. The exposure routes of cobalt also include inhalation and drinking water. The EPA has not established a Reference Concentration (RfC) or a Reference Dose (RfD) for cobalt. The California Environmental Protection Agency 3 (CalEPA) set a chronic reference exposure level of 0.000005 mg/m³ for cobalt (California Environmental Protection Agency, 2020). ATSDR has established an intermediate inhalation minimal risk level (MRL) of 0.00003 mg/m³ (ATSDR, 2023).

Exposure to cobalt can damage the eyes, skin, heart, and lungs, depending on the dose and duration. Exposure to cobalt may cause cancer. The EPA has not classified cobalt for carcinogenicity. The IARC has classified cobalt and cobalt compounds as “probably” carcinogenic to humans (2A), indicating sufficient evidence that they cause cancer in animals, but inadequate evidence that they cause cancer in humans (Table 2).

Our results showed that the cobalt weight from the natural brand E was 2.06 µg (Table 3). The average weight from three batches of brand F vitamins was 1.96 µg (Table 3). Synthetic vitamins from brand B contain 0.19 µg of cobalt (Table 3), which was the lowest among all six vitamins.

3.11. Lead

Lead (Pb) is a naturally occurring element in the earth's crust. Lead and lead compounds have been used in a wide variety of products, including paint, ceramics, plumbing materials, batteries, cosmetics, and others. The common exposure sources to lead in the U.S. include

lead-based paint in older homes, contaminated soil, household dust, drinking water, and lead-glazed pottery. Exposure of a child to lead can be through touching, swallowing, or breathing in lead or lead dust. Lead exposure causes serious health issues for children, such as damage to the brain and nervous system, learning and behavior deficits, slowed growth and development, and hearing and speech disorders (ATSDR, 2006). The EPA has set drinking water standards as 15 ppb (U.S. EPA, 2023). The FDA has set several levels of concern for lead in various foods. For example, FDA has set a level of 0.5 µg/dL for lead in food products for use by infants and children and has banned the use of lead-soldered food cans (U.S. FDA, 2023).

Inorganic lead and lead compounds are probably carcinogenic to humans (Group 2 A) by IARC and EPA (Table 2).

The results from Table 3 showed that the highest lead weight was 0.45 µg per recommended dose from brand E, vitamins made naturally. The average weight of brand F from three batches was 0.12 µg/recommended dose (Table 3). The weight of brand B synthetically made vitamins, was 0.14 µg/recommended dose (Table 3).

3.12. Molybdenum

Molybdenum (Mo) is a naturally occurring trace element as an oxide or sulfide compound (Barceloux, 1999). It is used widely in industry, including high-temperature furnaces, tungsten filaments in incandescent light bulbs, and steel used in solar panels and wind turbines (Stiefel, 2002). Due to contamination near industrial operations, higher concentrations of molybdenum in air, soil, and water can be observed. The EPA set a health-based screening level of 40 µg/L molybdenum in drinking water (U.S. EPA, 2004).

Molybdenum is an essential nutrient and the nutritional requirement for adults is 0.64 µg/kg/day (NAS., 2001). Exposure to molybdenum trioxide at excess levels through inhalation decreased lung function and caused dyspnea and cough (Ott et al., 2004) and kidney damage (Murray et al., 2004). Oral exposure to molybdenum decreased in sperm count (Meeker et al., 2008). Studies have observed decreases in the number of live fetuses and fetal growth in rats administered 14 mg/kg as sodium molybdate (Pandey and Singh, 2002).

No increases in the risk of lung cancer were reported in workers who self-reported exposure to molybdenum (Droste et al., 1999). Exposure of mice to molybdenum trioxide for 2 years induced alveolar/bronchiolar adenomas or carcinomas (NTP, 1997). In rats, chronic exposure to airborne molybdenum trioxide caused alveolar/bronchiolar adenoma/carcinoma (NTP, 1997). The potential carcinogenicity of molybdenum in humans has not been evaluated by the EPA. The IARC has categorized molybdenum trioxide as Group 2B, possibly carcinogenic to humans (Table 2).

Our results showed that the average weight of molybdenum from three batches of Brand F was 89.5 µg, far higher than the other five vitamins which are 0.18, 0.13, 0.45, 1.07, and 71.2 µg/recommended dose from brands A, B, C, D, and E, respectively (Table 3). In consideration of intermediate duration (15–364 days) oral MRL of 0.06 mg Mo/kg/day for

molybdenum, none of the prenatal vitamins measured potentially exert any toxicity at the levels of molybdenum found in the vitamins.

3.13. Nickel

Nickel (Ni) is a natural element of the earth's crust. Low levels of nickel can be found in air, food, soil, and water. Food is the major source of nickel exposure with an average intake for adults estimated to be 100 to 300 µg/day. The common adverse effect of nickel in humans is an allergic reaction. The most serious harmful health effects from exposure to nickel include chronic bronchitis, reduced lung function, and cancer of the lung and nasal sinus (ATSDR, 2005). The EPA recommends that drinking water levels for nickel should not be more than 0.1 mg/L (<https://archive.epa.gov/water/archive/web/pdf/archived-technical-fact-sheet-on-nickel.pdf>).

IARC has determined that some nickel compounds are carcinogenic to humans and that metallic nickel may possibly be carcinogenic to humans (Table 2). The EPA has determined that nickel subsulfide is a human carcinogen (U.S. EPA, 2016).

Our results showed that the highest nickel weight was 11.06 µg/recommended dose from brand E, a naturally made brand (Table 3). The average weight of brand F from three batches was 9.21 µg/recommended dose (Table 3). It was 0.25 µg in brand A and 2.16 µg in brand B (Table 3). None of these vitamins' nickel weights exceeded the EPA standard.

3.14. Strontium

Strontium (Sr), a naturally occurring element, is found in coal, rocks, and soil. Strontium compounds are used to make ceramics and glass products, paint pigments, fluorescent lights, and medicines. Exposure to low levels of stable strontium has not been shown to affect adult health. However, it has been reported that exposure to high levels of stable strontium can result in impaired bone growth in children (ATSDR, 2004). In animals, exposure to radioactive strontium caused birth defects (ATSDR, 2004). The EPA has set a limit of 4 mg/L strontium in drinking water.

The EPA did not classify stable strontium for human carcinogenicity. IARC has assigned strontium chromate, along with other chromates, to Group 1, as a human carcinogen (IARC, 1990) (Table 2). The carcinogenicity of strontium chromate is attributed to the hexavalent chromium ion and not to strontium. No other stable strontium compound is listed by IARC.

Our results showed that the strontium weight from vitamins made by brand E was 2236.91 µg/recommended dose, the highest weight among all six vitamins (Table 3). The weights of the other five vitamins ranged from 8.81 to 141.22 µg (Table 3). None of those vitamins exceeded the standard by EPA.

3.15. Thallium

Thallium is widely distributed in the earth's crust. Exposure to thallium can be through air, water, and food. The levels of thallium in air and water are very low. The greatest exposure occurs through food, mostly homegrown fruits and green vegetables contaminated by thallium. Exposure to thallium at high levels in a short term damages the nervous

system, lungs, heart, liver, and kidneys, and even causes death (ATSDR, 1992b). Thallium compounds at as low as 0.7 mg/kg/day have been shown to cause testicular damage and reduced sperm motility in male rats (Formigli et al., 1986). Pregnant women orally exposed to high levels of thallium resulted in premature and low-birth-weight infants (Hoffman, 2000). The EPA set 13 ppb thallium in surrounding waters to protect humans from the harmful effects of drinking water and eating food (ATSDR, 1992b, 2015a).

The EPA has determined inadequate evidence for thallium exposure to cause human cancer.

The results from Table 3 showed that thallium weights from all six prenatal vitamins were very low, ranging from 0.0031 to 0.0205 µg/recommended dose.

3.16. Titanium

Titanium (Ti) is the 9th most abundant naturally occurring element in the earth's crust (Barksdale, 1968). Titanium consists of five isotopes, including ^{46}Ti , ^{47}Ti , ^{48}Ti , ^{49}Ti and ^{50}Ti with ^{48}Ti being the most abundant. Titanium is naturally exposed to oxygen to form titanium dioxide (TiO_2), which can be found in minerals, dust, sands, and soils (Peira et al., 2014). TiO_2 is widely used as microparticles and nanoparticles in cosmetics and foods, obtaining white color and ultraviolet light protection (Wiesenthal et al., 2011). Ti alloys and Ti have been also widely used as alternatives to other metals in invasive medicine, surgery, and dentistry (Bilhan et al., 2013). No reference dose (RfD) or reference concentration (RfC) for titanium is included on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2006).

IARC concluded that there was sufficient evidence of carcinogenicity in experimental animals and inadequate evidence of carcinogenicity in humans (Group 2B), "possibly carcinogenic to humans" (Table 2). Exposure of rats to TiO_2 showed adverse pulmonary responses, including persistent pulmonary inflammation and lung tumors (Lee et al., 1985). The National Institute of Occupational Safety and Health (NIOSH) concludes that TiO_2 is not a direct-acting carcinogen but acts through a secondary genotoxicity mechanism that is primarily related to particle size and surface area.

The weights of ^{48}Ti were measured in this study. The results from Table 3 showed that the highest titanium weight was 254.45 µg from brand D. They were 2.72, 64.42, 8.33, 132.28, and 68.69 µg from brands A, B, C, E, and the average of brand F, respectively.

3.17. Vanadium

Vanadium is widely distributed in the earth's crust at an average concentration of approximately 100 mg/kg. Industries using vanadium-rich fuel oil and coal cause releases of vanadium into the environment. Many foods contain low concentrations of vanadium. Seafood generally has higher concentrations of vanadium than meat from land animals. Daily intakes of vanadium from food ranging from 0.01 to 0.02 mg have been reported (ATSDR, 2015b). Average vanadium concentrations in tap water are approximately 0.001 mg/L. Vanadium also may be found in a variety of nutritional supplements and multivitamins in amounts ranging from 0.0004 to 12.5 mg. It should be noticed that consumption of vanadium-containing supplements may result in exceeding intakes of

vanadium in addition to food and water. Integrated Risk Information System (IRIS) has derived an oral reference dose (RfD) of 0.009 mg/kg/day for vanadium pentoxide (U.S. EPA, 1988). The EPA has not derived an inhalation reference concentration (RfC) for vanadium and vanadium compounds.

Lung cancer was observed in mice exposed to vanadium pentoxide. IARC has determined that vanadium is possibly carcinogenic to humans (Table 2).

The results from Table 3 showed that the highest vanadium weight was 18.42 µg per recommended dose from brand E, naturally made vitamins, and the lowest one is 0.096 µg per recommended dose from brand A, synthetic and natural combined vitamins. In brand B, synthetic vitamins, the vanadium weight was 0.39 µg per recommended dose while they were 3.26 and 3.03 from brands D and F, respectively. The weights of vanadium from all six vitamins are within the limits of IRIS.

4. Conclusions

Over-the-counter prenatal vitamins do not require FDA approval. Thus, the content and quality vary. What's on the label doesn't match in the bottle. Contamination of prenatal vitamins, particularly for those naturally or organic ones, is a concern. With the vulnerability of the developing fetus, attention to prenatal vitamins consumed in pregnancy is critical. In this study, to investigate metal contamination in prenatal vitamins, we measured the weight of a total of 32 elements that naturally occur in the earth's crust from six brands of prenatal vitamins sold in the market.

We observed that the weights of three metals, antimony, beryllium, and thallium were low. Consistent with a previous study (Schwalfenberg et al., 2018), our study observed that mercury weights in these prenatal vitamins were very low, among six brands of prenatal vitamins, in three of them the mercury was not detectable (data not shown).

In this study, all prenatal vitamins contain certain levels of aluminum, arsenic, cadmium, chromium, and nickel, which have been classified as Group 1 human carcinogens by IARC. Antimony, cobalt, lead, molybdenum, titanium, and vanadium, which have been classified as Group 2A or 2B human carcinogens, were detected at some levels in all six brands of prenatal vitamins.

The accumulative exposure to the fetus with daily maternal ingestion of adverse elements is concerning. Government regulators should consider how to address this concern to preserve pediatric health and public safety. To prevent teratogenic effects, manufacturers should be required to establish vigorous regulation to monitor health products, particularly for prenatal vitamins which are consumed during gestational and lactational states.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Data availability

Data will be made available on request.

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Table 1

Classification of prenatal vitamins and recommended dosage.

Brands	A	B	C	D	E	F
Processing Sources	Natural and synthetic	Synthetic	Organic	Natural and synthetic	Natural	Natural and synthetic
Recommended dose (tablets/day)	4	1	4	1	3	3

A total of eight prenatal vitamins from six different brands were purchased from retailers. Three bottles of prenatal vitamins of brand F were purchased from different retailers. According to the process source, these vitamins were classified into three categories, natural/organic, synthetic, and a combination of natural and synthetic.

Table 2

Elements classified as human carcinogens by the IARC.

Elements	Group	Year
Aluminum product	1	2012
Pentavalent antimony	3	2023
Trivalent antimony	2A	2023
Arsenic and inorganic arsenic compounds	1	2012
Beryllium and beryllium compounds	1	2012
Cadmium and cadmium compounds	1	2012
Chromium (VI) compounds	1	2012
Cobalt metal, soluble cobalt (II)	2A	2023
Lead compounds, inorganic	2A	2006
Lead	2B	1987
Molybdenum trioxide	2B	2018
Nickel compounds	1	2012
Titanium dioxide	2B	2010
Vanadium pentoxide	2B	2006

Among the total of 32 elements, 13 were determined as human carcinogens by IARC. Group 1, carcinogenic to humans; Group 2A, probably carcinogenic to humans; Group 2B, possibly carcinogenic to humans; Group 3, not classifiable as to its carcinogenicity to humans.

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Table 3

Element weight of prenatal vitamins.

Prenatal vitamins									
Elements	A	B	C	D	E	F-1	F-2	F-3	
Aluminum	30.7504 ± 4.2242	3.3490 ± 1.3902	48.8245 ± 28.1550	229.8961 ± 8.9886	0.4274 ± 0.6044	328.0840 ± 26.6783	312.7432 ± 12.2829	288.7501 ± 15.8380	
Antimony	0.0000 ± 0.0000	0.0011 ± 0.0008	0.1236 ± 0.1747	0.0172 ± 0.0006	0.2510 ± 0.0084	0.0858 ± 0.0086	0.0978 ± 0.0132	0.0869 ± 0.0117	
Arsenic	0.0775 ± 0.0708	0.0643 ± 0.0071	0.1460 ± 0.0438	0.6154 ± 0.0526	4.5318 ± 0.0479	8.0118 ± 0.5523	7.6170 ± 0.2730	7.4952 ± 0.6874	
Barium	1.4422 ± 0.0496	0.2393 ± 0.0010	5.5349 ± 0.1418	3.4131 ± 0.0562	6.7929 ± 0.1930	4.4682 ± 0.4920	4.0109 ± 0.2364	4.0235 ± 0.2809	
Beryllium	0.0071 ± 0.0039	0.0038 ± 0.0002	0.0000 ± 0.0000	0.0176 ± 0.0006	0.1920 ± 0.0027	0.0334 ± 0.0024	0.0293 ± 0.0026	0.0291 ± 0.0033	
Boron	2.9695 ± 0.0254	2.5809 ± 0.1558	128.5208 ± 3.7060	64.3377 ± 3.7731	121.9065 ± 2.0753	1594.2808 ± 95.2688	1508.8610 ± 46.2563	1807.0843 ± 144.1816	
Cadmium	0.0099 ± 0.0140	0.3629 ± 0.0012	0.0636 ± 0.0227	0.2374 ± 0.0222	0.7854 ± 0.0332	0.1122 ± 0.0098	0.1362 ± 0.0619	0.1070 ± 0.0080	
Chromium	0.8897 ± 0.6888	2.5435 ± 0.1317	68.7624 ± 1.2817	6.4695 ± 0.0610	35.4954 ± 0.1354	25.4749 ± 1.8123	23.4468 ± 1.6327	23.2522 ± 1.5805	
Cobalt	0.3434 ± 0.0136	0.1916 ± 0.0013	0.6567 ± 0.0124	2.8109 ± 0.0072	2.0587 ± 0.1219	1.9771 ± 0.0974	1.8116 ± 0.1748	2.1007 ± 0.2176	
Copper	1.1566 ± 0.1196	2915.3378 ± 79.0901	9.7794 ± 0.0617	0.4719 ± 0.0388	1394.6405 ± 111.0480	3469.4848 ± 330.0635	3190.4710 ± 261.9596	3344.7068 ± 492.6905	
Lead	0.0814 ± 0.0057	0.1371 ± 0.0028	0.2868 ± 0.0165	0.2215 ± 0.0015	0.4521 ± 0.0282	0.1295 ± 0.0115	0.1367 ± 0.0634	0.0904 ± 0.0210	
Molybdenum	0.1815 ± 0.0373	0.1332 ± 0.0135	0.4535 ± 0.0090	1.0692 ± 0.0294	71.1842 ± 3.0715	102.7805 ± 7.5920	86.2560 ± 10.1686	79.4649 ± 3.3248	
Nickel	0.2539 ± 0.0233	2.1584 ± 0.6445	2.5353 ± 0.1083	1.7691 ± 0.0205	11.0503 ± 0.7490	9.6524 ± 0.7126	9.0076 ± 0.6023	8.9849 ± 0.6075	
Strontium	8.8141 ± 0.5712	37.3077 ± 0.4997	23.9294 ± 0.4286	56.9046 ± 1.1625	2236.9060 ± 64.5849	141.2188 ± 9.3079	130.0670 ± 8.9322	139.6985 ± 9.8459	
Thallium	0.0032 ± 0.0000	0.0205 ± 0.0005	0.0118 ± 0.0002	0.0140 ± 0.0000	0.0173 ± 0.0003	0.0037 ± 0.0002	0.0033 ± 0.0002	0.0070 ± 0.0006	
⁴⁸ Titanium	2.7169 ± 0.0380	64.4177 ± 0.6477	8.3320 ± 0.1156	254.4455 ± 3.4155	132.2817 ± 5.0708	73.2349 ± 4.7232	67.1689 ± 4.3387	65.6560 ± 3.7474	
Vanadium	0.0961 ± 0.0005	0.3920 ± 0.0093	0.2874 ± 0.0031	3.2598 ± 0.0804	18.4238 ± 1.2044	3.2338 ± 0.2639	2.9681 ± 0.2078	2.8966 ± 0.1975	

The elemental weight (per recommended dose) of prenatal vitamins were measured using ICP mass spectrum. The weight was recorded. Data represented the mean ± SD. The measurements either in duplicate or triplicate were repeated one time.