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# Lead in pharmaceutical products and dietary supplements

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**Abstract**

The objective of this study is to determine lead concentrations in a variety of widely used pharmaceutical products, and to assess the risk of lead exposure from using these products. Lead concentrations of 45 products were measured with inductively-coupled plasma mass spectrometry. Six products had lead concentrations greater than 100 parts per billion (ppb), and the highest measured concentration was 500 ppb. The average mass of lead delivered to consumers by all products examined in this study when taken as directed was 0.22 micrograms per day, which is expected to increase the blood lead level of an adult by less than 1%. Five products were found to deliver more than 1 μg of lead per day when used as directed. Current tolerable lead limits in pharmaceutical substances vary widely, and in some cases exceed 10,000 ppb. The products examined in this study have lead concentrations far below these levels. However, in light of recent research demonstrating adverse effects in both children and adults from low level lead exposure, current lead limits for pharmaceutical substances are unacceptably high. Uniform lead limits that reflect current manufacturing capabilities are needed to insure the lowest achievable exposure to lead from these products.


*Keywords:* ICP-MS; Lead toxicity; Lead exposure; Pharmaceutical products; Calcium supplements; Vitamins; cGMP; USP lead limits

## 1. Introduction

Lead is a toxic heavy metal with no known biologic function in humans (Royce et al., 2000). Recent National Health and Nutrition Survey data on lead exposure in the United States indicates that the average blood lead level (BLL) in the population is 1.6 μg/dL, and 1.9 μg/dL in children 1–5 years of age (Centers for Disease Control and Prevention, 2005)—a dramatic decline from the averages of 10–20 μg/dL measured in 1976–80 (Centers for Disease Control and Prevention, 2004). This decline is due to concerted public health efforts to control common environmental sources of lead exposure. At the same time, blood lead levels in young children once thought harmless (those below 10 μg/dL) have been associated with adverse neurocognitive effects (Bellinger et al., 2003; Bowers and Beck, 2006; Canfield et al., 2003a,b, 2004, 2005; Kordas et al., 2006; Lanphear et al., 2005). These observations warrant continued vigilance to identify sources of lead exposure and to reduce them where possible.

As the lead content in common environmental sources such as solder, house dust and soil declines, other sources of lead may measurably contribute to overall lead exposure in humans. Among pharmaceutical and nutritional products, lead contamination of calcium supplements has been well documented (Bourgoin and Evans, 1993; Kim et al.,

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2003; Ross et al., 2000; Scelfo and Flegal, 2000), and numerous studies have identified traditional medicines that contain high levels of lead and other toxic heavy metals (Bhatti et al., 2004; Caldas and Machado, 2004; Chuang et al., 2000; Ernst and Thompson Coon, 2001; Fung et al., 2003; Hasegawa et al., 1997; Moore and Adler, 2000; Prpic-Majic et al., 1996; Saper et al., 2004; Spriewald et al., 1999). Moreover, as foreign manufacturers (where lead contamination of drug ingredients may be higher) increase their production of pharmaceutical and nutritional products sold in the U.S., there is a possibility that these products may increase lead burdens in the U.S. populations.

Little is known about lead contamination in the U.S. pharmaceutical supply. We measured the lead content in a sample of widely used pharmaceutical products and dietary supplements and used these measurements to assess the potential for these products to contribute to the daily lead burden of consumers when used as directed in product labeling.

## 2. Methods

### 2.1. Product selection and sampling

This survey has been designed in a manner that is consistent with the FDA's current emphasis on risk-based quality assessment. Products were selected on the basis of the potential risk to the population if they were found to contain high lead levels. Commonly prescribed drugs and commonly sold nonprescription products from both generic and brand-name manufacturers were targeted for this study. The sample set was selected to include products marketed for children as well as products frequently used by older adults in several common dosage forms (solutions, syrups, tablets, capsules and gelcaps). Product selection was guided by product class sales volume, and high volume products used to treat chronic conditions were of particular interest. Calcium-containing products were also targeted, because lead is a common contaminant in natural calcium sources. Applying these criteria, 45 pharmaceutical products and dietary supplements were selected for lead analysis (Table 1). All samples were taken from a single lot of the product under study in order to maximize the number of products that were examined. Thus this study provides information on the levels of lead contamination across a variety of products, but does not provide information on lot-to-lot variation in lead contamination for individual products. In view of the current paucity of information on lead contamination in pharmaceutical products, a broad survey of lead contamination in high volume products was the deemed to be the most prudent course of action.

Prescription samples were obtained from pharmaceutical wholesalers. Over-the-counter preparations were obtained from well-known internet pharmacies, and one foreign-sourced nonprescription analgesic (Norflam) was purchased directly over the internet. All product containers remained sealed until sample preparation was initiated. We also examined 10 samples of ibuprofen active pharmaceutical ingredient (API) collected during routine FDA inspections of API manufacturing facilities in England and India to determine if drug components manufactured overseas and intended for use in products marketed in the U.S. had lead levels that posed a potential risk to U.S. consumers.

The lead concentration of each product was determined by inductively-coupled plasma mass spectrometry (ICP-MS) (Lewen et al., 2004; Siitonen and Thompson, 1994). When tablets, capsules and gelcaps were analyzed, nine dosage units were homogenized prior to analysis. Tablets were crushed to a fine powder and mixed, and the resulting powder was sampled. Capsule and gelcap dosage units were opened and spilled into a common container. Sampling of capsules and gelcaps included capsule material in proportion to its relative mass in the unit dosage form. Solid samples of approximately 0.2 g mass were taken for analysis. Fluid dosage forms (syrups and solutions) were shaken prior to sampling. Liquid samples (syrups, solutions and gelcaps) of approximately 1.0 g were taken for analysis. All samples were subjected to microwave digestion prior to analysis. All reagents used for digestion and sample preparation were trace metal grade, and samples were stored in metal free containers at all times.

### 2.2. Sample digestion

Microwave digestion of the samples was performed with a CEM Model MDS-2000-2 digester using 70% nitric acid as the digestion medium. The instrument digests 12 samples per run. Each digestion run included 1–3 vessel blanks to determine background lead levels as well as spiked samples and samples of standard reference materials to determine lead recoveries. Spiked samples and digestion of standard reference materials (NIST SRM 1567) indicated recoveries of 99–110% of the expected mass of lead from the digestion vessel.

After the digestion process was completed, the samples were diluted to a concentration appropriate for ICP-MS analysis, and a bismuth internal standard was added to each sample. All dilutions and additions were measured gravimetrically. Immediately before they were delivered to the mass spectrometer, the sample solutions were homogenized by agitation.

Product 4 in Table 1 contains bismuth. Bismuth is a commonly used internal standard for lead analysis by ICP-MS. The bismuth containing sample was digested by placing the sample in an acid-washed metal free centrifuge tube, adding 3 ml of 70% nitric acid, sealing the centrifuge tube and sonicating for approximately 1 h at 60 °C. This procedure was necessary to avoid contamination of the microwave digestion vessels with Bi. Several other samples were also digested by both microwave and sonication methods, and in these cases both methods were found to yield consistent results for each sample.

### 2.3. ICP-MS measurement

ICP-MS measurements were made with a VG Elemental PlasmaQuad 3 spectrometer. The samples were aspirated into the ICP-MS at a rate of approximately 100 microliters per minute. Lead calibration standards were prepared over the range of 0–1 ng of lead per gram of solution (part-per-billion, ppb), and each lead standard included a known concentration (approximately 10 ppb) of the bismuth internal standard. The signals at masses 206, 207 and 208 were measured to determine lead, and mass 209 was measured to determine the internal standard signal. The complete set of standards was run at the beginning of each ICP-MS run, and individual standards were then run intermittently throughout the course of the ICP-MS run. The initial run was used to generate independent calibration plots for masses 206, 207 and 208, and subsequent runs of standard solutions were used as quality control checks. A blank solution was used to rinse the inlet to the ICP between each sample measurement. The zero point standard, which contained ~10 ppb bismuth and 0 ppb lead, was measured 10 times to determine the limit of detection, which was found to be 0.0009 ppb with respect to the sample delivered to the instrument. Detection limits with respect to the original product masses were calculated individually for each sample using the known dilution factor of the sample, and were in the 0.05–0.5 ppb range.

### 2.4. Data analysis

Each standard and sample was measured five times at lead masses 206, 207 and 208, and the mass count rates were normalized to the internal standard count rate at mass 209. The normalized count rates for the three lead isotopes were added together to determine the total normalized lead signal for each measurement of each standard and sample. A linear calibration equation based on the sum of lead isotope signals of the standards was found to have a correlation coefficient of 0.9999. The sum of the abundance of these three isotopes accounts for 98.6% of all