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In vivo quantification of strontium in bone among adults using portable x-ray fluorescence

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ABSTRACT

Background and objective: Bone strontium (Sr) is a reliable biomarker for studying related bone health outcomes and the effectiveness of Sr supplements in osteoporosis disease treatment. In this study, we evaluated the sensitivity of portable x-ray fluorescence (XRF) technology for in vivo bone Sr quantification among adults.
Materials and methods: Sr-doped bone-equivalent phantoms were used for system calibration. Using the portable XRF, we measured bone Sr levels in vivo in mid-tibia bone in 76 adults, 38–95 years of age, living in Indiana, US; we also analyzed bone data of 29 adults, 53–82 years of age, living in Shanghai, China. The same portable XRF device and system settings were used in measuring their mid-tibia bone. We compared bone Sr concentrations by sex, age, and recruitment site. We also used multiple linear regression model to estimate the association of age with bone Sr concentration, adjusting for sex and recruitment site.
Results: The uncertainty of in vivo individual measurement increased with higher soft tissue thickness overlying bone, and it ranged from 1.0 ug/g dry bone (ppm) to 2.4 ppm with thickness ranging from 2 to 7 mm, with a measurement time of 5 min. Geometric mean (95% confidence interval (CI)) of the bone Sr concentration was 79.1 (70.1, 89.3) ppm. After adjustment for recruitment site and sex, an increase in five years of age was associated with a 8.9% (95% CI: 2.5%, 15.6%) increase in geometric mean bone Sr concentration.
Discussion and conclusion: Sr concentrations were consistently well above detection limits of the portable XRF, and exhibited an expected increase with age. These data suggest that the portable XRF can be a valuable technology to quantify Sr concentration in bone, and in the study of Sr-related health outcomes among adults, such as bone mineral density (BMD) and bone fracture risk.

1. Introduction

Strontium (Sr) is a non-essential element in humans. It is ubiquitously present in food and drinking water. Over 99% of total body Sr is deposited in bone and teeth [1]. Diet is the primary source of human Sr exposure; the average daily Sr intake is approximately 2–4 mg [2]. The concentration of Sr varies by food. For example, vegetables, grain, and seafood contain more Sr than meats [1], and cereal and vegetables are the dominant dietary sources of human Sr exposure [3]. Hence, the amount of dietary Sr intake and its accumulation in human tissue may vary by dietary composition.

Sr is a bone-seeking element. Excessive intake of Sr could disturb calcium metabolism [1,4] and cause bone abnormalities [4–6]. On the other hand, low-dose Sr supplement has been used to treat bone diseases [7–9]. A few in vivo studies and clinical trials have shown that the use of low-dose strontium ranelate, a therapeutic agent for treating osteoporosis, can increase bone formation and decrease bone resorption, reducing the incidence of fracture caused by osteoporosis [1,10,11], especially among postmenopausal women [12–14]. Increased risk of myocardial infarction, however, has been found in patients who took strontium ranelate [15,16]. In its recent benefit-risk reassessment, the European Medicines Agency (EMA) recommended strontium ranelate

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use only for persons with severe osteoporosis but without cardiovascular contraindications [17,18]. In addition, a recent study in China showed that there is a significant positive correlation between Sr concentration in drinking water and bone mineral density (BMD) in the elderly. The same study also reported a significant positive association between Sr concentration in drinking water and increased incidence of children's rickets [19].

To study the health effects that are associated with long-term Sr exposure, it is critical to have a practical technology that can measure body Sr stores in vivo. Urinary Sr has been used to study Sr exposure and health effects such as hypertension, infertility, and cancer [20–22], however, urinary Sr is expected to be a short-term exposure biomarker. The long-term retention of Sr in bones [23,24] makes bone Sr a good biomarker of long-term Sr exposure. In this study, we used the portable x-ray fluorescence technology (XRF) developed in our group [25–27] to non-invasively quantify the cumulative bone Sr concentration among adults and determine its sensitivity.

2. Materials and methods

2.1. Study population

We recruited participants from the general population at recruitment sites in the US and China. Seventy-six American adults were recruited from northwestern Indiana. This same population has been studied in a parallel project of bone lead with portable XRF [28]. Bone Sr concentrations from three participants were estimated with extremely high uncertainty, due to unusually thick skin overlying their tibia bones (>9 mm), leaving 73 participants from this site whose data were included in our analyses. We also recruited twenty-nine Chinese adults living in Shanghai, China. The data from the Chinese population was used in a parallel study of bone lead, with the data collected by the same portable XRF [29]. Thus, our study analyses involved data from a total of 102 participants. The Institutional Review Boards of Purdue University, Boston University, Harvard University, and Xinhua Hospital affiliated to Shanghai Jiaotong University have approved this study. All participants provided their informed consent forms before undergoing the study procedures.

2.2. Portable XRF system

The portable XRF used in this study was a customized device from Thermo Fisher Scientific (Thermo Niton XL3t GOLDD+, Billerica, MA). The silver x-ray tube has an energy span up to 50 kV and uses a thermoelectric-cooled silicon drift detector with 25 mm^2 area and 1 mm thickness. The x-ray tube was set up at a voltage of 50 kV and a current of 40 μA with a silver (Ag) and iron (Fe) combination filter. Three measurement times, 2 min, 3 min, and 5 min, were used to assess how measurement duration affects the system sensitivity. The effective radiation dose to the participants from the 3-minute measurement is about 2.4 μSv [30], and from the 2-minute and 5-minute measurements are about 1.6 μSv and 4.0 μSv, respectively.

The interactions between material and photons, as well as the principle of x-ray fluorescence are described in detail somewhere else [31]. For this project, Sr K-shell characteristic x-rays were generated in the measurements with energies of 14.17 keV (K_α) and 15.84 keV (K_β). Only the K_α peak was used for the bone Sr concentration calculation because it has lower background under the Sr peak region. The K_β peak only represents 14% of the total characteristics x-rays, which will thus only minimally contribute to the determination of total Sr concentration. An in-house peak fitting program written in MatLab was used to calculate bone Sr concentration and its uncertainty. We used peak fitting with least-squares algorithm to extract the net counts of Sr K_α, where a Gaussian function was used to fit the Sr K_α peak and an exponential function to fit the background level. The bone Sr concentration obtained from an indiviual measurement has a unit of μg/g dry bone (ppm).

2.3. System calibration

We calibrated the portable XRF system using a 274 ppm Sr-doped bone-equivalent phantom. This bone-equivalent phantom used Mowiol 4–88 and bone meal, and composition of the matrix was described by Mostafaei et al. [32]. The Sr K x-rays are attenuated by the soft tissue overlying bone. As the soft tissue thickness increases, the system detects fewer Sr K x-rays and more Compton scattering counts from the soft tissue. Thus, to simulate the soft tissue over bone, we placed Lucite plates of 0–8 mm, in increments of 1 mm, over the bone phantom, and determined the relation between the Sr K net counts and Compton scattering counts. This relation represented the system calibration line. The in vivo bone Sr concentration was calculated by relating an in vivo Sr K_α net count to a known count per concentration from the 274 ppm bone phantom, as shown in the following equation.

$$Sr_{in\ \ vivo}\ \ [ppm] = SrNetCounts_{in\ \ vivo} \times (274\ \ ppm\ \ / SrNetCounts_{274ppm}) \quad (1)$$

where, $Sr_{in\ vivo}$ is the bone Sr concentration of an in vivo measurement; $SrNetCounts_{in\ vivo}$ is the measured Sr K_α net counts; $SrNetCounts_{274ppm}$ is the Sr K_α net counts of the 274 ppm phantom calculated from the relation between the Sr net counts and Compton scattering counts, at the location where the Compton scattering counts was the same as that calculated from the in vivo measurement. This relation allowed us to use the Compton scattering counts from the in vivo measurements to correct for the attenuation of the Sr signal caused by overlying tissue.

From the portable XRF calibration data, we also determined the relation between Lucite thickness and Compton scattering counts and used it to estimate the overlying skin thickness for an individual participant. All the calibration data were collected with 3-minute measurements.

2.4. System detection limit

The detection limit (DL) of the portable XRF for in vivo bone Sr measurements was determined by Specht et al. [26]. Instead of using one bone phantom, a set of bone phantoms with different Sr concentrations of 74–274 ppm were used to determine the DL. Since the soft tissue thickness could influence the signal detection, Lucite plates of 0–9 mm were placed between the bone phantoms and detector to determine the DL for each Lucite thickness. As demonstrated in Specht et al. [26], the DL increased with thicker Lucite, varying from 1.3 ppm with a 0 mm Lucite to around 15 ppm with a 9 mm Lucite. However, the discrepancy between the human soft tissue and Lucite plates could result in inaccurate DL estimates for the phantom with Lucite, thus, the uncertainty of in vivo bone Sr measurement for each participant was used to estimate an empirical DL.

2.5. In vivo portable XRF bone Sr measurements

In the in vivo portable XRF bone Sr measurement, the participant sat on a chair and straightened one leg and rested it on another chair. Alcohol prep-swabs were used to clean the mid-tibia area before the measurement to eliminate any extraneous contamination. The portable XRF device was placed in contact with the participant's skin right above the center of the tibia bone area. A 2-minute measurement was performed on the twenty-nine Chinese participants. To investigate the effect of longer measurement time on system DL reduction, we took 3-minute measurements on sixty-two U.S. participants and 5-minute measurements on the other eleven U.S. participants.

2.6. Statistical analyses

The bone Sr concentrations were not normally distributed; thus, the geometric mean was calculated to describe the bone Sr concentrations in

the sample. We used the Kruskal-Wallis (KW) test to compare the bone Sr by recruitment site and sex. A Spearman correlation was computed to assess the correlation between bone Sr concentration and age. We also used adjusted linear regression models of natural log-transformed bone Sr concentration to estimate the percentage difference in bone Sr concentration (the exponentiated coefficient) with increasing age, adjusting for recruitment site (Shanghai, Indiana) and sex (female, male). We conducted these statistical analyses using SYSTAT (San Jose, CA) and Stata 16 (College Station, TX) software.

3. Results

3.1. Study population

The 102 participants ranged in age from 38 to 95 years (mean [standard deviation (SD)], 65.4 [11.2]; Table 1). Compared with participants recruited in Indiana (USA), participants recruited in Shanghai (China) were somewhat older and more likely to be female.

3.2. System calibration

We utilized the Compton scattering interactions with the soft tissue and bone originated from the incident x-rays to correct for soft tissue thickness. Fig. 1 shows the increase in Compton scattering counts with the increase of the Lucite plate thickness (coefficient of determination $R^2 = 0.995$). Using this relation, we estimated the overlying soft tissue thickness for an individual participant directly from the XRF spectrum of their portable XRF bone Sr measurement. These soft tissue thicknesses were also used to evaluate how tissue thickness affects the uncertainty of the bone Sr concentration in in vivo measurements. Fig. 2 shows that the Sr K_α net counts decrease with the increase of the Compton scattering counts due to the signal attenuation, measured from the 274 ppm bone Sr phantom ($R^2 = 0.998$). Through this relation, the count per concentration from the 274 ppm bone phantom was calculated in relation to the Compton scattering counts. The in vivo bone Sr concentration was then calculated by relating an in vivo Sr K_α net count to this known count per concentration ratio, as shown in Eq. (1).

3.3. System detection limit

A consequence of signal attenuation by soft tissue over the bone was that the system DL calculated from the phantom and Lucite plates increased with thicker Lucite plates. Likewise, the uncertainty of in vivo bone Sr measurements using portable XRF was higher with progressively thicker overlying soft tissue (Table 2). Extending the measurement time from 2 min to 3 min reduced the uncertainty by a factor of 1.2. Similarly, extending the measurement time from 3 min to 5 min further reduced the uncertainty by a factor of 1.3. The measured in vivo bone Sr concentration was greater than twice uncertainty for all the participants (N = 102) regardless of overlying soft tissue.

Table 1
Age, sex, and soft tissue thickness of participants by recruitment site.

Recruitment site	Indiana (USA)	Shanghai (China)	Overall
N of participants	73	29	102
Age (Mean ± SD, years)	63.3 ± 11.2	70.6 ± 9.2	65.4 ± 11.2
Male (N (%))	39 (53.4%)	14 (48.3%)	54 (52.9%)
Female (N (%))	34 (46.6%)	15 (51.7%)	48 (47.1%)
Soft tissue thickness (Mean ± SD, mm)	5.0 ± 1.7	5.1 ± 2.1	5.0 ± 1.8

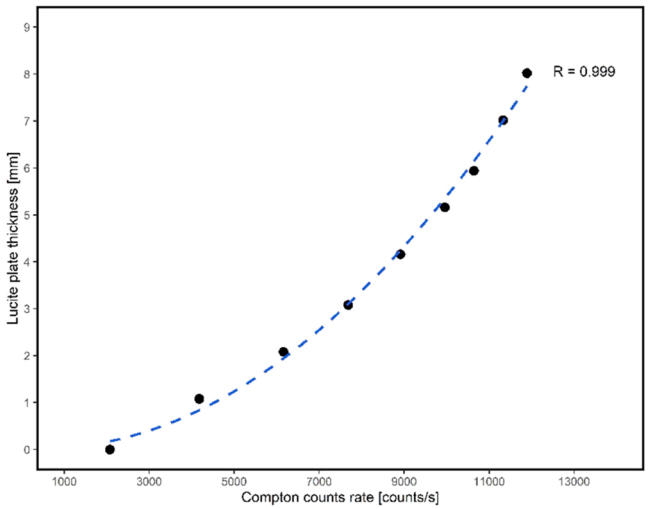

Fig. 1. Soft tissue thickness versus Compton scattering signal.

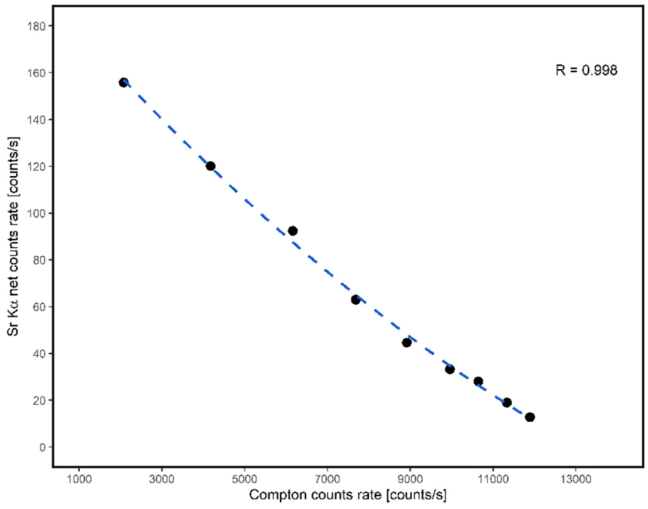

Fig. 2. Net count rate of Sr K_α versus Compton scattering signal measured from a 274 ppm Sr bone phantom.

3.4. In vivo bone Sr concentration by recruitment site, sex, and age

In unadjusted analyses, estimated bone Sr concentration did not discernibly vary by recruitment site (K-W *p*: 0.52) or sex (K-W *p*: 0.94) (Fig. 3; Table 3).

Spearman correlation analysis showed a positive correlation between bone Sr and age (Spearman's $\rho = 0.179$). From adjusted analyses of log-transformed bone Sr concentration, for each 5-year increment in age, bone Sr concentrations were about 8.9% higher (95% CI: 2.5–15.6%) (Table 4; Fig. 4).

4. Discussion

The results showed that bone Sr can be detected using the portable XRF for a general population. This is consistent with the conclusion made by Da Silva E. et al. in a previous study [33]. The DL increases with a corresponding increase in soft tissue thickness overlaying the bone. The DL for people with an average soft tissue thickness (~5 mm) was estimated to be about 5.2 ppm for a 2-min measurement, whereas the average bone Sr concentration for the study population was about 79.1 ppm. The measurement DL can be further reduced using a longer measurement time, as demonstrated by the 2-, 3-, and 5-minute

Table 2
Mean uncertainty[a] of in vivo bone Sr by overlying soft tissue thickness and measurement time using the portable XRF (N = 102).

Soft tissue thickness	< 5 mm	< 6 mm	< 7 mm	< 8 mm	< 9 mm
2-minute measurements (N = 29)					
N (% of study population)	14 (48%)	21 (72%)	23(79%)	25 (86%)	29 (100%)
Mean uncertainty, ppm	2.6	3.3	3.6	4.3	8.0
3-minute measurements (N = 62)					
N (% of study population)	33 (53%)	41 (66%)	52(84%)	61 (98%)	62 (100%)
Mean uncertainty, ppm	2.3	2.6	3.2	4.2	4.4
5-minute measurements (N = 11)					
N (% of study population)	7(64%)	10 (91%)	11 (100%)	–	–
Mean uncertainty, ppm	1.8	2.2	2.4	–	–

[a] The DL of the XRF systems is approximately twice the mean uncertainty.

measurements. The results also showed that bone Sr level was significantly and positively associated with age. Since Sr intake is highly related to diet and continuously accumulated in the bones, the increase of bone Sr with the increase of age is expected. There was no significant difference in bone Sr by sex in this population.

Although the method presented in the paper is rational, there are some underlying assumptions in calculating the bone Sr concentrations. The first assumption is that the Compton scattering from the soft tissue is the same as that from the Lucite. The assumption was shown to be valid in our previous studies: Monte Carlo (MC) simulations were performed and the results showed no significant difference in XRF spectra between bone-equivalent phantom with Lucite and bone with soft tissue [25]. The second assumption is that no conversion factor is needed to account for the difference between the dry bone in phantoms and the wet bone in in vivo measurements. We investigated this in our bone lead (Pb) study and found that the bone Pb concentrations obtained from the portable XRF have a better agreement with the concentrations obtained from the standard KXRF bone Pb concentrations without applying a correction factor for dry bone and wet bone [28]. There is a mass ratio of about 0.9 between the dry bone and wet bone, so this needs to be examined further. On the other hand, this does not affect the relative value of the bone Sr concentrations (i.e. it will only affect the absolute bone Sr concentrations).

Since over 95% of Sr in the human body deposits in bone and Sr can replace calcium in bone due to the chemical similarities between these two elements, Sr has been considered a significant element for bone health. As described in the introduction, the knowledge gaps on the effects of Sr in bone health include: the intake level with which Sr could

Table 3
In vivo bone Sr concentration of the participants by recruitment site, sex (N = 102).

Characteristic	N	Geometric mean [ppm] (95% confidence interval)
All participants	102	79.1 (70.1, 89.3)
Recruitment site		
Indiana, USA	73	78.9 (69.8, 89.3)
Shanghai, China	29	79.4 (58.4, 108.0)
Sex		
Male	54	76.8 (64.8, 90.9)
Female	48	81.8 (68.3, 97.8)

Table 4
In vivo bone Sr concentration of the participants by age (N = 102).

Characteristic	N	Geometric mean [ppm] (95% confidence interval)
All participants	102	79.1 (70.1, 89.3)
Age		
38–60 years	40	72.8 (57.4, 92.2)
61–70 years	28	78.2 (66.8, 91.6)
70–95 years	34	88.0 (71.3, 108.4)

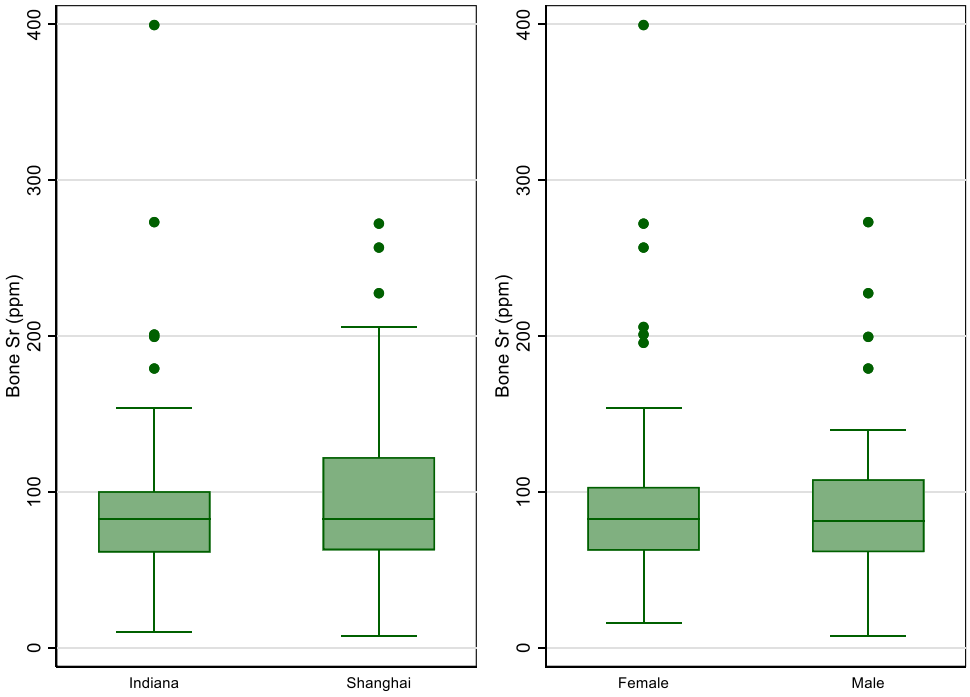

Fig. 3. Bone Sr concentrations measured by the portable XRF for the participants by recruitment site or sex.

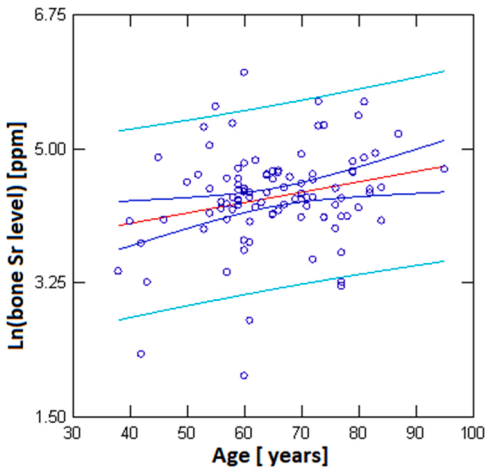

Fig. 4. Natural log-transformed bone Sr concentrations by age with fitted line.

bring beneficial effects, the association between bone Sr and bone health overall and among populations with different diet, and how bone Sr can be used as a biomarker to study Sr in bone health, among others. The bone Sr measurement technology developed in this project can be a valuable tool to fill these knowledge gaps.

5. Conclusion

We found that a brief, non-invasive measurement with a portable XRF can quantify Sr concentration in bone with excellent sensitivity. Although the uncertainty of in vivo individual measurement increased with higher soft tissue thickness, we were able to measure bone Sr in all of the 102 subjects. We also identified an expected association between age and bone Sr. These observations suggest that the portable XRF can be a valuable technology to explore health effects of Sr exposure not only on bone health, but other endpoints as well.

CRediT authorship contribution statement

Xinxin Zhang: Conceptualization, Methodology, Validation, Data analysis, Investigation, Data curation, Project administration, Writing – original draft, Writing – review & editing. **Ellen M. Wells**: Data analysis, Writing – review & editing. **Aaron J. Specht**: Methodology, Validation, Data analysis, Writing – review & editing. **Marc G. Weisskopf, Jennifer Weuve, Linda H. Nie**: Conceptualization, Supervision, Resources, Project administration, Methodology, Validation, Investigation, Writing – review & editing, Funding acquisition.

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.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jtemb.2022.127077.

References

[1.] W.E. Cabrera, I. Schrooten, M.E. De Broe, P.C. D'Haese, Strontium and bone, J. Bone Min. Res 14 (5) (1999) 661–668.
[2.] Agency for Toxic Substances and Disease Registry: Toxicological profile for Strontium. In. Edited by U.S. Department of Health and Human Services PHS. Atlanta, GA; 2004.
[3.] S. Pors Nielsen, The biological role of strontium, Bone 35 (3) (2004) 583–588.
[4.] T. Morohashi, T. Sano, S. Yamada, Effects of strontium on calcium metabolism in rats. I. A distinction between the pharmacological and toxic doses, Jpn J. Pharm. 64 (3) (1994) 155–162.
[5.] E.B. Neufeld, A.L. Boskey, Strontium alters the complexed acidic phospholipid content of mineralizing tissues, Bone 15 (4) (1994) 425–430.
[6.] S. Ozgur, H. Sumer, G. Kocoglu, Rickets and soil strontium, Arch. Dis. Child 75 (6) (1996) 524–526.
[7.] J.L. Omdahl, H.F. DeLuca, Rachitogenic activity of dietary strontium. I. Inhibition of intestinal calcium absorption and 1,25-dihydroxycholecalciferol synthesis, J. Biol. Chem. 247 (17) (1972) 5520–5526.
[8.] E. Canalis, M. Hott, P. Deloffre, Y. Tsouderos, P.J. Marie, The divalent strontium salt S12911 enhances bone cell replication and bone formation in vitro, Bone 18 (6) (1996) 517–523.
[9.] W. Querido, A.L. Rossi, M. Farina, The effects of strontium on bone mineral: A review on current knowledge and microanalytical approaches, Micron 80 (2016) 122–134.
[10.] D. Farlay, G. Boivin, G. Panczer, A. Lalande, P.J. Meunier, Long-term strontium ranelate administration in monkeys preserves characteristics of bone mineral crystals and degree of mineralization of bone, J. Bone Min. Res 20 (9) (2005) 1569–1578.
[11.] P.J. Marie, D. Felsenberg, M.L. Brandi, How strontium ranelate, via opposite effects on bone resorption and formation, prevents osteoporosis, Osteoporos. Int 22 (6) (2011) 1659–1667.
[12.] P.J. Meunier, C. Roux, E. Seeman, S. Ortolani, J.E. Badurski, T.D. Spector, J. Cannata, A. Balogh, E.M. Lemmel, S. Pors-Nielsen, et al., The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis, N. Engl. J. Med. 350 (5) (2004) 459–468.
[13.] P.J. Meunier, D.O. Slosman, P.D. Delmas, J.L. Sebert, M.L. Brandi, C. Albanese, R. Lorenc, S. Pors-Nielsen, M.C. De Vernejoul, A. Roces, et al., Strontium ranelate: dose-dependent effects in established postmenopausal vertebral osteoporosis–a 2-year randomized placebo controlled trial, J. Clin. Endocrinol. Metab. 87 (5) (2002) 2060–2066.
[14.] J.Y. Reginster, Strontium ranelate in osteoporosis, Curr. Pharm. Des. 8 (21) (2002) 1907–1916.
[15.] J.Y. Reginster, Cardiac concerns associated with strontium ranelate, Expert Opin. Drug Saf. 13 (9) (2014) 1209–1213.
[16.] J. Yu, J. Tang, Z. Li, S. Sajjan, C. O'Regan, A. Modi, V. Sazonov, History of cardiovascular events and cardiovascular risk factors among patients initiating strontium ranelate for treatment of osteoporosis, Int J. Women's. Health 7 (2015) 913–918.
[17.] J.Y. Reginster, M.L. Brandi, J. Cannata-Andia, C. Cooper, B. Cortet, J.M. Feron, H. Genant, S. Palacios, J.D. Ringe, R. Rizzoli, The position of strontium ranelate in today's management of osteoporosis, Osteoporos. Int 26 (6) (2015) 1667–1671.
[18.] Assessment report—periodic safety update report (EPAR - Protelos-H-C-560-PSU31) [⟨http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000560/WC500147168.pdf⟩].
[19.] H. Peng, F. Yao, S. Xiong, Z. Wu, G. Niu, T. Lu, Strontium in public drinking water and associated public health risks in Chinese cities, Environ. Sci. Pollut. Res Int 28 (18) (2021) 23048–23059.
[20.] Y. Tang, W. Xia, S.Q. Xu, H.X. Liu, Y.Y. Li, Association of urinary strontium levels with pregnancy-induced hypertension, Curr. Med Sci. 41 (3) (2021) 535–541.
[21.] Y. Miao, L. Liu, C. Liu, Y.L. Deng, P.P. Chen, Q. Luo, F.P. Cui, M. Zhang, W.Q. Lu, Q. Zeng, Urinary biomarker of strontium exposure is positively associated with semen quality among men from an infertility clinic, Ecotoxicol. Environ. Saf. 208 (2021), 111694.
[22.] L.J. Chen, L.Y. Tang, J.R. He, Y. Su, Y.L. Cen, D.D. Yu, B.H. Wu, Y. Lin, W.Q. Chen, E.W. Song, et al., Urinary strontium and the risk of breast cancer: a case-control study in Guangzhou, China, Environ. Res 112 (2012) 212–217.
[23.] H. Moise, D.R. Chettle, A. Pejovic-Milic, Monitoring bone strontium intake in osteoporotic females self-supplementing with strontium citrate with a novel in-vivo X-ray fluorescence based diagnostic tool, Bone 61 (2014) 48–54.
[24.] G.M. Blake, I. Fogelman, Long-term effect of strontium ranelate treatment on BMD, J. Bone Min. Res 20 (11) (2005) 1901–1904.
[25.] A.J. Specht, M. Weisskopf, L.H. Nie, Portable XRF technology to quantify Pb in bone in vivo, J. Biomark. 2014 (2014), 398032.
[26.] A.J. Specht, F. Mostafaei, Y. Lin, J. Xu, L.H. Nie, Measurements of Strontium Levels in Human Bone In Vivo Using Portable X-ray Fluorescence (XRF), Appl. Spectrosc. 71 (8) (2017) 1962–1968.
[27.] X. Zhang, A.J. Specht, M.G. Weisskopf, J. Weuve, L.H. Nie, Quantification of manganese and mercury in toenail in vivo using portable X-ray fluorescence (XRF), Biomark.: Biochem. Indic. Expo., Response, susceptibility Chem. 23 (2) (2018) 154–160.
[28.] X. Zhang, A.J. Specht, E. Wells, M.G. Weisskopf, J. Weuve, L.H. Nie, Evaluation of a portable XRF device for in vivo quantification of lead in bone among a US population, Sci. Total Environ. 753 (2021), 142351.

[29.] A.J. Specht, Y. Lin, J. Xu, M. Weisskopf, L.H. Nie, Bone lead levels in an environmentally exposed elderly population in shanghai, China, Sci. Total Environ. 626 (2018) 96–98.
[30.] A.J. Specht, X. Zhang, B.D. Goodman, E. Maher, M.G. Weisskopf, L.H. Nie, A. Dosimetry, Study of Portable X-ray Fluorescence in Vivo Metal Measurements, Health Phys. 116 (5) (2019) 590–598.
[31.] Cohen-Tannoudji C.D.-R.J., Grynberg G.: Atom-photon Interactions: Basic Processes and Applications: John Wiley & Sons Inc.; 1997.
[32.] F. Mostafaei, F.E. McNeill, D.R. Chettle, W.V. Prestwich, M. Inskip, Design of a phantom equivalent to measure bone-fluorine in a human's hand via delayed neutron activation analysis, Physiol. Meas. 34 (5) (2013) 503–512.
[33.] E.M.E. Da Silva, B. Kirkham, J. Groves, M. Gherase, D.E.B. Fleming, A. Pejović-Milić, Evaluation of portable X-ray fluorescence spectrometers for in vivo quantification of bone strontium and lead on the bases of the minimum detection limit: A phantom study, Adv. X-ray Anal. 61 (2018) 116–121.