

## **Strontium Myth and Reality: Efficacy and Safety Considerations for Consumers**

By Jarrow Formulas, Makers of Bone-Up®

Strontium (Sr) is a mineral with a reported effect on the reduction of bone fracture risk. Most of the data on strontium as a bone-building compound comes from its usage as a drug in Europe (as strontium ranelate). Strontium citrate, available as a dietary supplement in the US, is being marketed as a natural strontium source.

While data from Sr ranelate (and older Sr carbonate) studies have identified Sr as a potential bone-building treatment, it does have some potentially serious drawbacks of which consumers should be made aware. Sr supplements are not “supplementing” the diet, but providing levels of the metal that are orders of magnitude more than one could expect from any normal diet. Although these strontium supplements are being provided at pharmacological doses, they are not being surveilled by health practitioners as prescription Sr ranelate has been. The long-term safety and efficacy of high-dose Sr supplements has not been adequately determined.

What follows is a discussion of several statements that have been made concerning strontium.

### **Strontium citrate is a “natural” compound: Myth**

Strontium (Sr) occurs in nature as mineral deposits of celestine (strontium sulfate) and strontianite (strontium carbonate). Citric acid and citrate also occur in nature. However, the chelate strontium citrate (as provided in supplemental form) is NOT a natural compound. It is made synthetically from strontium minerals and citrate.

Strontium citrate marketed as “natural” is therefore not “naturally occurring” or “extracted from a natural source”, but rather “made synthetically from natural ingredients”. Some consumers may not be familiar with this marketing distinction.

### **Strontium naturally occurs in the diet and in the body: True** **Strontium is common in the diet and in the body: Myth**

Dietary strontium is estimated at 2-4 mg/day from vegetables and grains (Nielsen 2009 Bone 35(3) 583-8). The typical strontium supplement dosage (680 mg) is 170-340 times the naturally occurring strontium levels in the human diet per day. While some plants can take up relatively large amounts of strontium (spinach and kale have been reported to contain up to 70mg/kg), **few people eat the 21 lbs. of spinach each day** that would equal the recommended 680 mg dose of supplemental strontium.

The whole-body strontium content of an average (70 kg) human is estimated at **320 mg** (Emsley, John, *The Elements*, 3rd edition, Clarendon Press, Oxford, 1998). This means that by weight, naturally occurring strontium levels in the human body are about 0.0005%. The typical strontium supplement dosage (680 mg) supplies 2 times the human bodies **total** naturally occurring strontium content per day.

Strontium is not “common” in abundance, either in the body (0.0005% by weight) or in the earth (0.001% by weight; Morgan and Anders 1980, PNAS 77(12) pp. 6973-6977). One should be aware that “common” does not imply safety, efficacy, or utility. Lead and Rubidium are about as “common” in the human body as strontium

(0.0002% and 0.0005%, respectively), and like strontium, neither has an identified unique biological role.

### **Strontium is a nutrient: Depends on the definition**

The broader definitions of “nutrient” (“a nutritive substance or ingredient”; “Nourishing, affording nutriment”; “any substance that can be metabolized by an organism to give energy and build tissue”) can be applied to strontium. Note that many synthetic compounds or drugs could equally share these definitions.

More specific definitions (especially from scientific texts) describe nutrient(s) as:

*“stable elements that are vital to life”* (Krogh. 2007. A Brief Guide to Biology, Pearson/Prentice Hall).

*“a substance, element or compound necessary for the growth and development of plants and animals.”* (Glossary of Environment Statistics, Studies in Methods, Series F, No. 67, United Nations, New York, 1997.)

*“a chemical that an organism needs to live and grow”* (Whitney and Rolfes. 2005. Understanding Nutrition, 10th edition, Thomson-Wadsworth)

(Note the distinction between these definitions and the more precisely defined *essential nutrient*, which is vital or necessary for life and *must be obtained through the diet*. None of the above definitions preclude endogenously-produced compounds (e.g.. vitamin D) which could be considered nutrients when obtained exogenously)

The textbook definitions of nutrient, therefore, discuss them as being “vital” or “necessary” for living, and not simply as being “metabolized”. By this definition, strontium is not a nutrient in human nutrition. It is not vital for life. It has no unique role in human metabolism (e.g.. thus far, there are no strontium-specific binding proteins, no strontium-dependent enzymes, no strontium-catalyzed reactions in human metabolism).

The effect that strontium has on bone growth is because of its ability to substitute for calcium in bones and enzymes, which does not qualify it as a nutrient. In comparison, lead (Pb) is not a nutrient, but can also substitute for calcium in bones, and can also increase bone mineral density (Popovic, 2003, Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms. 213: 599-602). Incidentally, while the substitution of Sr for Ca in bones may have some desirable effects, substitutions elsewhere in the body may not. Recall that calcium is used not only in bone mineral, but also as an important cellular signal in neurotransmitter release, muscle contraction, and electrical conduction in the cardiac muscle. Substitution of strontium for calcium is routinely used to experimentally alter these processes (for example, to slow neurotransmitter release to study synaptic transmission; Xu-Friedman and Regehr, The Journal of Neuroscience, June 15, 2000, 20(12):4414-4422). Indeed, some of the serious potential adverse effects of strontium (see next section) may not be surprising considering its historical experimental usage.

In short, describing Sr as a nutrient may give the impression that this compound is somehow necessary for proper nutrition, but this has not been shown to be the case. It may reduce fracture risk reduction, but this a pharmacological (not nutritional) effect.

### **Strontium is natural, so it is completely safe: Myth**

Since strontium does not occur in the diet at levels which are being advised and provided for supplementation, it is difficult to determine its safety profile, especially long-term safety.

Metaanalysis of strontium studies (which are not simply “helpful reviews” or “types of surveys”, but widely regarded for their presentation and academic analysis of actual clinical data) reveal safety concerns for strontium (as strontium ranelate). The authors of the Cochrane metaanalysis (presumably experts in their field) conclude in their report “*Potential vascular and neurological side-effects need to be further explored*” (<http://mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD005326/frame.html>). While the metaanalysis only presented data from 4 studies (out of a potential 80 potential journal articles), the studies which were not included in the analysis were discarded because they had recognized methodology flaws (not randomized, blinded, or placebo controlled, included dropout data in the calculations, or were actually review articles). Between the 4 highest-quality studies in the metaanalysis, several thousand patients were included in the analysis.

The SOTI and TROPOS studies on the strontium drug Protelos®, reveal the largest potential safety concerns. Non-serious adverse events (headache, gastrointestinal issues) were no different between strontium ranelate and placebo in the trials. However, as the European Agency for the Evaluation of Medicinal Products (the European equivalent of the FDA) states in their report on strontium ranelate (Protelos®) (<http://www.emea.europa.eu/humandocs/PDFs/EPAR/protelos/121604en6.pdf>):

*“there was a worrying, increased reporting rate with strontium ranelate specifically for terms related to embolism and thrombosis”.*

Their surveillance of the drug during and following the trial revealed ~50% increase in annual risk of embolism and thrombosis in patients taking strontium ranelate. They also concluded that nervous system disorders are more frequent amongst strontium ranelate users:

*“Especially, reports of CNS effects such as mental impairment, disturbed consciousness, memory loss/amnesia and seizures create some concern”,*

and that there is

*“clear impact of treatment with strontium ranelate on skeletal muscle cell integrity”,*

although the clinical importance of this is unknown. The EMEA goes on to recommend that surveillance and a pharmacovigilance plan is needed for the drug (i.e.. the frequency and type of adverse events needs to be closely monitored to detect any

change in the safety profile of the drug). Based on this report, there is an increased risk of several types of serious adverse event associated with strontium (as ranelate) usage, and these possible adverse events are serious and significant enough for the EMEA to present in its report.

In short, strontium has only ever been extensively studied as an osteoporosis DRUG. Given by a doctor, under supervision, with risks and benefits clearly explained to the patient by the physician. In this context, it appears to reduce fracture risk (at least in the short term; see the comment by Alan Gaby in the Townsend Letter, November 2009). As a supplement, taken without any surveillance by a medical practitioner, it may present serious adverse events that at least bear mention on a product label.

### **Strontium leads to measured increases in bone mineral density (BMD): True\***

Strontium leads to increased BMD, having osteoblast stimulating activity and attenuating osteoclast activity. Strontium is able to substitute for calcium in hydroxyapatite (bone crystal).

### **Strontium artificially increases bone mineral density (BMD) measurements: True**

Strontium has a larger atomic weight than calcium ( $z=38$  vs.  $z=20$ ), which means that it attenuates X-rays more strongly than calcium. For every calcium atom that is replaced by strontium in bone, the density of the bone appears larger, although the same amount of mineral exists. In other words, strontium can artificially inflate the numbers of a DXA scan, yielding a misleading reading of greater density than is the case. **Comparisons of Ca hydroxyapatite (natural bone crystal) and Sr hydroxyapatite (Sr-substituted bone crystal) have revealed that for every 1% of strontium incorporated into bone crystal, BMD is overestimated by 10%** (Blake et al. 2007 J Clin Densitom. 10(3):259-65).

Now consider that when one starts a strontium regimen, much of the INCREASE in bone mineral content is coming from the addition of new STRONTIUM atoms to the skeleton. Since these Sr atoms have a higher apparent density by DXA, the new Sr in the bone contributes proportionally more to BMD than does calcium.

What does this mean? BMD **increases** from taking strontium are **overestimated by much more than 10%**. The SOTI and TROPOS studies on Protelos® used a correction factor of 50% (that is, **50% of the BMD increase is an artifact**). Blake and Fogelman (2006 JBMR 21(9) 1417-24) reanalyzed data from the SOTI study and determined that the correction factor is probably closer to 75%, that is, **75% of the BMD increase from strontium is an artifact**. Obviously, the total effect of Sr on density is still not entirely understood, and the only accurate way to determine bone Sr content (and thus an individual's correction factor) is by bone biopsy.

Since the primary endpoints of the SOTI and TROPOS studies were a decrease in fracture risk, the actual BMD increases in these studies were less important. In contrast, for a study or "challenge" that is **only** looking at bone mineral density increase, an accurate assessment of BMD is paramount, and BMD correction factors should be properly presented to a potential strontium consumer.

**Strontium can render BMD measurements inaccurate even after discontinuation of use: True**

Strontium also remains in bones after treatment is discontinued, sometimes for extended periods of time. Six months after discontinuation of Sr treatment, bone Sr retention was over 70% in patients who had undergone the longest treatment (8y). Power curves have estimated that at the longest treatment times (8 years, 1% total bone Sr), bone Sr content would not return to baseline levels for 25 years (Barenholdt et al. 2009 45(2) 200-6). Because of this relatively high Sr retention in bone, overestimation of BMD by DXA will continue at a variable rate for some time. One should be cautious when self-treating with strontium, as the most accepted measurements of BMD (DXA) will overestimate density, and this overestimation can potentially last for several years.