

Q&A

Since we introduced you to the health benefits of stable Strontium in *Advances* 2(3), we've been inundated with questions about this radical new bone health mineral. We're taking the opportunity to lay out the facts as we know them here.

Q The Strontium supplements I have found are either Strontium citrate or Strontium carbonate. But I keep hearing about Strontium ranelate in the news. Am I getting the wrong kind of Strontium?

A The reason for all the press stories on strontium ranelate is because a major international drug company is now moving this salt form of strontium through the clinical trial process in hopes of marketing it as a drug. So it should come as no surprise if the most recent, most lavishly-funded, and most well-publicized studies in recent years have been the ones performed using this form of Strontium. However, there is nothing "magical" about this particular strontium form. Independent studies have used many different forms of strontium, including strontium lactate,¹⁻³ gluconate,^{4,5} carbonate,^{5,6} chloride,⁷ acetate,⁸ and still other forms of the mineral. Guess what? They all work.

So why is the drug company using the ranelic acid salt? Some of the reasons are revealed in a review of the science on strontium written by Dr. Jean-Yves Reginster, an investigator with the World Health Organization (WHO) Collaborating Center for Public Health Aspects of Rheumatic Diseases, and with the Bone and Cartilage Metabolism Unit of the University of Liège.⁹ Dr. Reginster is the author of fourteen peer-reviewed scientific journal articles on the role of Strontium in bone health, and was a principal investigator on three of the largest and best-designed trials.^{10,11}

On the other hand, you can get an even higher elemental yield from some other forms of strontium. Strontium carbonate, for instance, has 593 mg of strontium per gram of the compound. But many of these forms of strontium have poor "gastric tolerance" - in other words, they're more likely to cause upset stomach or diarrhea. The ranelic acid salt has good gastric tolerance.⁹ They all work.

Independent studies have used many different forms of strontium.

Dr. Reginster also notes that strontium ranelic acid salt has good bioavailability - about 27%.⁹ However, this really doesn't make much of a difference in the case of strontium: all forms of strontium have bioavailabilities in the 25-30% range.⁷

But there is likely another reason why this particular pharmaceutical company is now pushing the ranelic acid salt form of strontium through the "drug" development pipeline: control. Strontium lactate, citrate, gluconate, and carbonate are all natural, unpatentable forms of strontium - whereas ranelic acid is a purely synthetic molecule that does not occur in nature. By using the ranelic acid salt, Big Pharma may be hoping to shore up its patent protection and regulatory exclusivity on the "drug" market for what is, fundamentally, a dietary supplement: strontium, a naturally-occurring trace mineral in the diet.

Certainly, the ranelic acid part of the strontium ranelate compound contributes nothing to the effects of strontium on your bones. When you swallow strontium bound to ranelic acid, the compound splits apart into two strontium ions and a molecule of ranelic acid. The two are then taken up into the body separately, and while the body absorbs 27% of the Strontium in a pill, it absorbs less than a tenth as much (2.5%) of the ranelic acid. Of the ranelic acid that is absorbed, 93% to 99% is excreted within 7 days without being metabolized by the body.⁹

Molecular and animal studies have also shown that the effects of the ranelic acid salt of strontium are due to the strontium. In a study on the use of strontium ranelate on bone formation in bone tissue culture, it was seen that strontium bound to ranelic acid enhanced the replication of pre-osteoblastic cells, but that "neither calcium ranelate nor sodium ranelate, at the same concentration, were able to induce similar effects".⁹ Again, many other mechanistic studies have used other forms of strontium, such as strontium carbonate and strontium chloride, and shown the same key effects on bone metabolism seen with strontium ranelate.⁷ Indeed, it's exactly the many animal studies and clinical trials using other forms of strontium that led to the interest by pharmaceutical companies in strontium for the bones.⁹

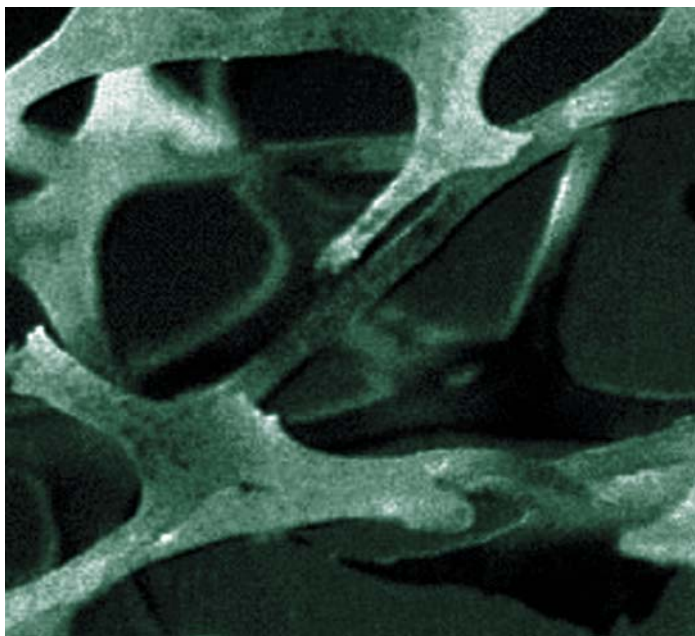
Strontium citrate enjoys the advantages of a relatively high elemental yield (about 300 milligrams elemental strontium per gram of strontium citrate), so you won't be popping fistfuls of pills to get your daily dose, and being very soluble, giving it good gastric tolerance and bioavailability compared to many other strontium forms (such as the carbonate). Citric acid is also a natural ligand, and is available as a dietary supplement.

Q What do you think about all these new supplements which contain a full day's dose of Strontium along with calcium, magnesium, and other key nutrients all in one convenient bottle?

A They're a disaster.

In his review, Dr. Reginster specifically notes (pg. 1914) that "The simultaneous intake of [strontium] and calcium remarkably reduces the bioavailability of [strontium]. This is probably due to competition at the sites of active absorption. Simultaneous food intake also has a negative influence on the bioavailability of [strontium]". Based on this critical factor, Dr. Reginster recommends that high-dose strontium should not be taken "concomitantly with a meal or a calcium intake."⁹

The simultaneous intake of strontium and calcium remarkably reduces the bioavailability of strontium.



The competition between strontium and calcium for absorption has long been known, and all of the trials successful strontium have carefully ensured that the supplement is taken on an empty stomach, away from calcium in food or in supplements.^{2,3,6,10-13} In the largest and best-designed trials,¹⁰⁻¹³ women have taken their strontium first thing in the morning, half an hour to an hour before breakfast, and/or three hours after dinner in the evening; they took their calcium supplements separately, with a meal. This is the protocol supported by pharmacology and by clinical trials, and it is the one that we recommend unless your doctor specifies otherwise. It is obviously impossible to

follow this protocol if you're taking a supplement that combines calcium and strontium in the same pill or powder! Such formulations are, therefore, not the "convenient," "inexpensive" deals they initially seem, but are ill-designed and likely ineffective "kitchen sink" hodgepodes. Persons taking these supplements will not reap the full benefits of strontium documented in the clinical trials. This is a major health issue, especially for people with advanced osteoporosis. If they and their physicians are taking these combination supplements instead of a reliable, separate supplement, or instead of an established drug therapy, the results could be ruinous.

Note that these problems do not hold if there is only a small, nutritional amount of strontium in a core bone health supplement- doses in the range of 500 micrograms to 5 milligrams, which are typical of human dietary intakes. Such doses are appropriate, as they preserve the ratio of calcium and strontium present naturally in whole-food diets. In fact, all natural calcium sources also have a small amount of strontium in them, because of the similar metabolism of the two nutrients in living beings. Calcium supplements with no strontium might be expected to upset this natural balance, leading to suppression of whatever strontium is in your diet, ultimately perturbing the natural balance of minerals in your bone.

Indeed, some evidence already exists that, over a lifetime, these low, nutritional doses of strontium do have a role to play in your health. For example, it was discovered in the 1960s that areas with more strontium in the water have a lower incidence of dental caries^{14,15} - a finding which was to be reinforced by at least eight more studies over the course of the next few decades.¹⁶

Some of these strontium-calcium combination products further shoot their users in the foot by using poor forms of key ingredients. Some, for instance, use poor forms of calcium, such as cheap calcium carbonate (which has low gastric tolerance and which reduces your absorption of other nutrients by neutralizing stomach acid) and synthetic calcium hydroxyapatite. The latter is an extremely poorly-absorbed synthetic calcium phosphate salt, not to be confused with ossein microcrystalline hydroxyapatite complex (MCHC), an extract of bone-health nutrients contained in an intact calcium crystalline matrix. Others use magnesium carbonate as a magnesium source; this is another antacid, and like calcium carbonate is poorly absorbed. Likewise, one of these products is even poaching the research on menatetrenone (MK-4) - the form of vitamin K2 used in all of the clinical trials - to sell another vitamin K2: the unproven, bacterial menaquinones.

Everyone concerned about their bone health needs a core calcium supplement, along with other key nutrients such as magnesium, vitamin D3, and menatetrenone. In such a supplement, a small, nutritional dose of strontium is a good balancing act, reflecting the trace levels of strontium naturally present in food. If you need the potent support of a "high dose" strontium supplement, it should absolutely not come in a combination with calcium. You need a separate strontium supplement, taken at a separate time.

Q The articles in *Advances* say that most trials have used dosages of strontium in the 600-700 milligram range. But I keep hearing stories about trials using one or two grams of strontium!

A This comes down to the question of elemental yield: the amount of strontium itself that is present in a given amount of a strontium compound. Strontium, like other minerals, does not come "naked," but as part of a compound - a salt or chelate form of the mineral. Different forms of the mineral are more or less mineral-dense. For instance, one gram (1000 mg) of calcium carbonate contains 400 mg of elemental calcium, while the same amount of calcium citrate contains just 210 mg of elemental calcium. Similarly, to get 420 mg of elemental magnesium takes 5600 mg of true, fully-reacted magnesium aspartate, because this superior form of the mineral is only 7.5% elemental magnesium by weight. By contrast, to get the same amount of elemental magnesium from cheap, dense, low-bioavailability magnesium oxide requires just 696 mg of the compound, because magnesium oxide is over 60% elemental magnesium by weight.

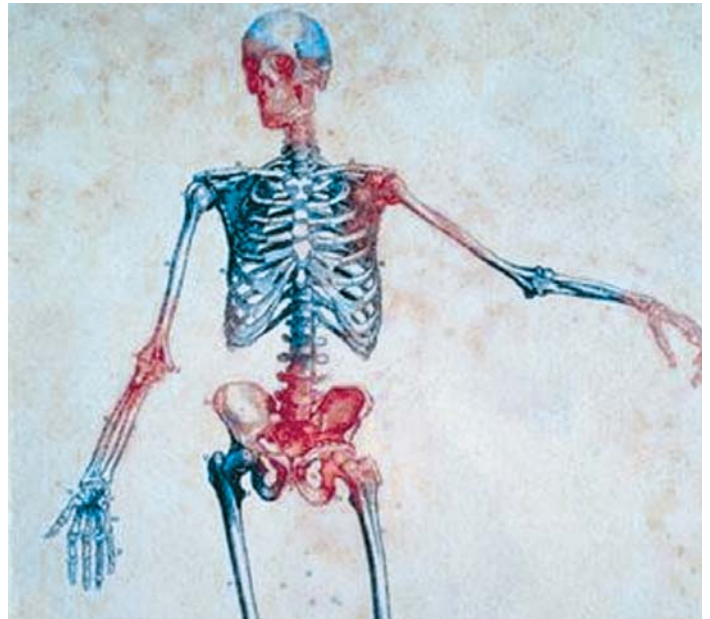
So when you hear that (for instance) some recent trials have used two grams (2000 mg) of strontium ranelate, they are telling you the amount of the compound they used - not the amount of elemental strontium. Two grams of strontium ranelate yield 680 mg of elemental strontium.

Q Can I take my entire daily intake of strontium at the same time?

A Yes, the blood levels of strontium remain fairly constant throughout the day. Strontium has a half life of 60 hours in the body, which means that it takes 60 hours for the strontium blood levels to drop by 50%. This means that there is no reason to divide your strontium intake.

Q How long do I have to wait before I can see results?

A Studies have shown that strontium reduced the incidence of fractures in as little as a year, and that increases in bone density are seen after two to three years of supplementation.¹⁷ Therefore, it is probably better to wait two years before reassessing your bone mineral density.



Q How long do I have to wait before eating?

A Food and dietary supplements can reduce the absorption of strontium by as much as 70%, which is why it is recommended to take strontium on an empty stomach, at least 2 hours before or after food or other supplements.¹⁸ The exception to this is vitamin D, which does not affect the bioavailability of strontium.

Q How long can I safely take strontium and should I stop taking it when my bone mineral density returns to normal?

A The recommendation to discontinue therapy for treatments aimed at increasing bone density comes from studies that have demonstrated that antiresorptive treatments can be associated with a rebound effect if the therapy is continued without interruption.¹⁹ Antiresorptive treatments slow down bone degradation which leads to a slow increase in bone density. When the treatment is stopped, there can be an acceleration in bone

breakdown which significantly reduces the efficacy of the therapy. This rebound effect is more pronounced when the therapy has been ongoing for several years and so, to prevent this problem, the treatment can be halted every few years.²⁰

Strontium is an anabolic agent and does not fall in this class of therapies. Strontium increases bone formation while reducing bone breakdown. Strontium does not produce a rebound effect and the follow-up studies have shown that the antifracture efficacy of strontium is maintained over time.

Q Can I combine strontium supplements with a bisphosphonate drug, such as alendronate (Fosamax®)?

A The quick answer is that the trials haven't been done, so we don't know.

There are two ways of addressing a decrease in bone mineral density. Therapies currently available fall in two categories: anticatabolic or anabolic agents. Anticatabolic agents prevent the breakdown of bone by inhibiting the activity of osteoclastic cells whereas anabolic agents stimulate the formation of new bone through their effect on osteoblasts.

At high doses, strontium is an anabolic agent with studies showing that it has the power to help your body create new bone. Bisphosphonates, in contrast, are anticatabolic and designed explicitly to treat a disease (osteoporosis). These drugs don't actually build bone - they work by slowing down the rate at which it is torn down (resorbed).

So the idea of combining a bone-building nutrient like Strontium with a bisphosphonate drug seems to offer a great way to get the best of both worlds. But does it actually work?

The problem is that bisphosphonates reduce both the osteoclastic and the osteoblastic activity in bones. Within weeks after you start taking a bisphosphonate, the drug begins to impair your body's formation of new bone.¹⁷ However, the rate at which old bone is torn down is reduced by much more than that of the bone-building activity, which means that the total mass of bone slowly increases. But by allowing old bone tissue to hang around longer without speeding its replacement, bisphosphonate use results in bone tissue that is, on average, older - and thus, of poorer quality.²¹⁻²³ The resulting bone is less prone to fracture, but is not the same as youthful, healthy bone.

Although no trials have been done to determine the combined effect of strontium and bisphosphonates, trials combining bisphosphonates with teriparatide (an anabolic drug) gave surprisingly disappointing results and showed that antiresorptive drugs, in the long term, wind up reducing the effectiveness of teriparatide.^{23,24} The studies showed that BMD was highest in the women taking the bone-building agent only, with no bisphosphonate drug.^{24,25} Based on those results, it is reasonable to assume that strontium supplementation may be less effective if it is combined with bisphosphonates. This does not mean that a person using strontium should never use a bisphosphonate - or vice-versa. You may decide - in consultation with your doctor - to adapt a protocol in which you take either strontium or a bisphosphonate drug for a period of time, and then switch over to the other. In fact, there is already such a protocol, where osteoporotic women take teriparatide for two years and then switch over to alendronate.²⁶

Although combining bisphosphonates with teriparatide or strontium may be ill advised, there may be a way to combine an anabolic with an anticatabolic agent. A protein called cystatin C, extracted from milk and contained in a registered product called Milk Basic Protein® (MBP), protects the collagen in bone from the action of cysteine protease, which is secreted by osteoclasts.²⁷ Cysteine protease is an enzyme responsible for digesting the collagen in the bone matrix. Since collagen constitutes the underlying structure of the bone matrix, cysteine protease inhibitors such as MBP inhibit the release of calcium from the bone matrix. Studies in women demonstrate that supplementation with MBP significantly increases bone mineral density in as little as 6 months.^{28,29}

What is particularly interesting about MBP is that it does not reduce osteoblastic activity like bisphosphonate drugs. Although trials are once again lacking, logic dictates that based on the mechanism of action behind MBP, the product is a good option for those looking for an addition to strontium. Indeed, given that strontium leads to new bone formation by increasing osteoblastic activity while reducing osteoclastic activity and that MBP reduces bone collagen breakdown, the two supplements should have an additive effect on BMD.

Q AOR emphasizes the importance of its use of calcium hydroxyapatite in its bone supplements. Why is AOR advocating the use of this source of calcium over other sources of calcium such as calcium citrate or carbonate?

A Many studies have confirmed that conventional calcium supplements - such as calcium gluconate, calcium citrate, calcium carbonate, and even calcium citrate-malate - can only slow menopausal bone loss, whether taken alone or with vitamin D.³⁰⁻⁴³ However, MCHC consistently halts, or even reverses, bone loss in controlled human clinical trials.⁴⁰⁻⁴⁶ When compared against other supplemental calcium forms, MCHC consistently trumps the conventional calcium supplement in its effects on parameters important to bone health.^{40-43,46-51}

It is also important (once again) to realize that "calcium hydroxyapatite" is not the same as ossein microcrystalline hydroxyapatite complex (MCHC) - the calcium source used in AOR's Ortho•Bone, and Bone Basics. "Calcium hydroxyapatite" - also known as "calcium orthophosphate" - is a synthetic calcium salt, whereas MCHC is a natural, calcium-containing bone nutrient complex, which contains a variety of growth factors, mucopolysaccharides, and peptides in addition to its calcium content. These nutrients are not found in calcium hydroxyapatite.

Importantly, studies show that neither calcium hydroxyapatite, nor heat-treated MCHC (which destroys its rich nutrient matrix), have the same effects on bone as true, intact lyophilized MCHC.⁴⁸⁻⁵¹ Therefore; it is hardly surprising that calcium hydroxyapatite would not deliver on MCHC's promises: it is in no way a comparable supplement.

MCHC remains, on the basis of the primary medical research, the best calcium supplement for bone health.

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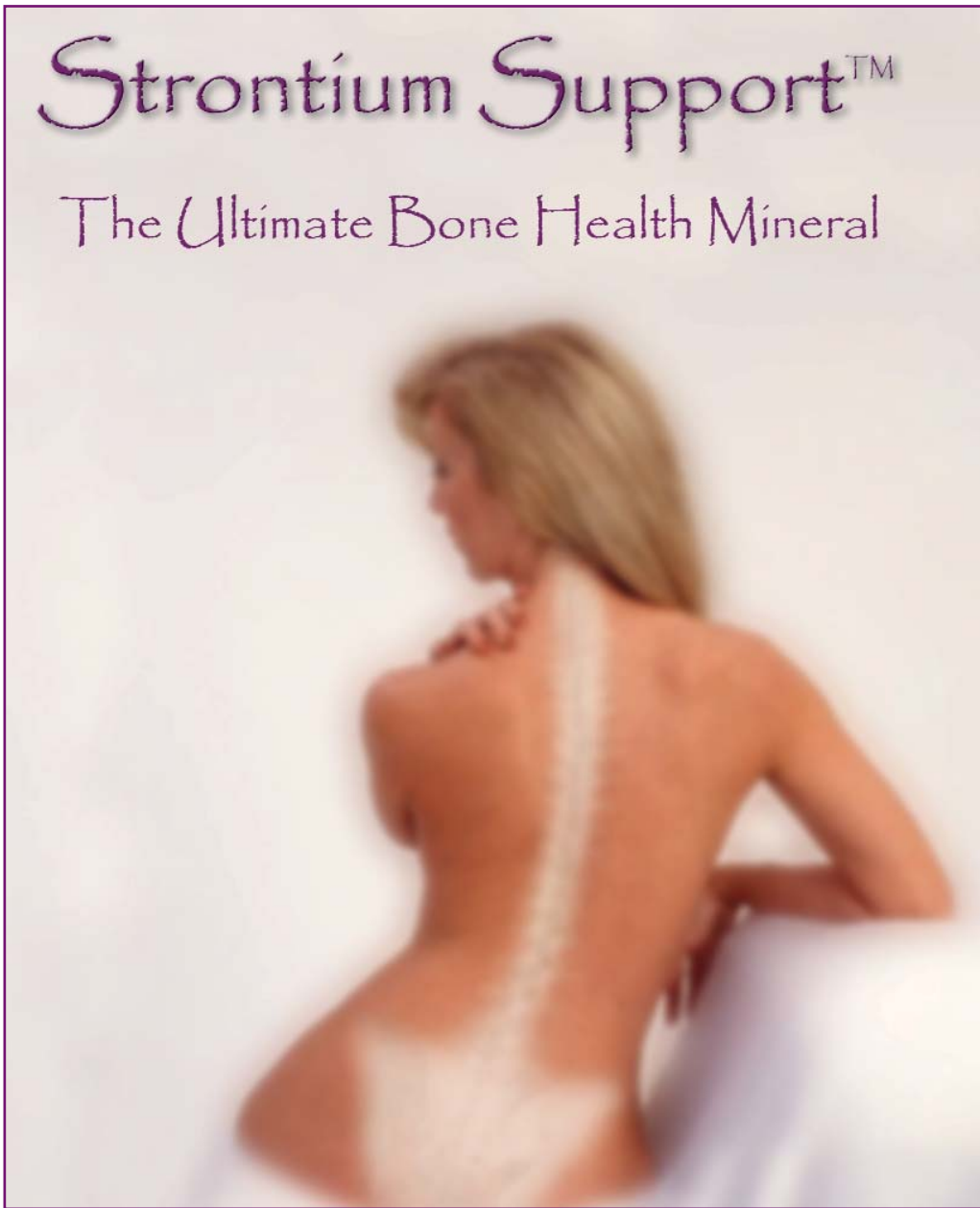
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