

# Thermodynamic Modeling of Integration of Strontium into Bone Tissue Hydroxyapatite

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*This study analyzes the  $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$  -  $\text{Sr}_{10}(\text{PO}_4)_6(\text{OH})_2$  binary system. In the system under study, individual compounds and solid solutions were synthesized by the solid-phase method. The resulting specimens were analyzed by X-ray powder diffraction. Theoretical prediction of thermodynamic functions of all system specimens was performed. Thermodynamic modeling of integration of strontium ions into the hydroxyapatite crystalline structure was conducted. Based on theoretical data, the possibility of existence of a superstructure in the polycrystalline specimen under study was determined.*

**Keywords:** *apatite; hydroxyapatite; thermodynamic modeling; solid solution.*

## Introduction

A generic, idealized formula of the apatite group compounds can be represented as follows:  $\text{M}_4^I\text{M}_6^II(\text{AO}_4)_6\text{L}_2$ , where M are mono-, di-, tri- and quadrivalent cations;  $\text{AO}_4$  anionic groups are represented by tetrahedral groupings of quadri-, penta- and hexavalent atoms of ( $\text{SiO}_4^{4-}$ ,  $\text{PO}_4^{3-}$ ,  $\text{AsO}_4^{4-}$ ,  $\text{SO}_4^{4-}$ ); the L position can be occupied by halogens, hydroxyl ions OH, etc. The apatite structural type allows for major iso- and heterovalent substitutions in both cation and anion positions [1-3].

Among other apatites, hydroxyapatite (HA)  $\text{Ca}_5(\text{PO}_4)_3\text{OH}$  is distinguished by its chemical and biological properties. Calcium phosphates are biocompatible, which can be useful in bone tissue regeneration processes. In medicine, synthetic HA and HA-based materials are used both as ceramics and composites to substitute for a part of the missing bone, and as implant coatings facilitating adhesion onto the bone tissue hydroxyapatite [4,5]. Depending on the bone type and specific features of the patient, orthopedic procedures may require materials containing HA with different properties.

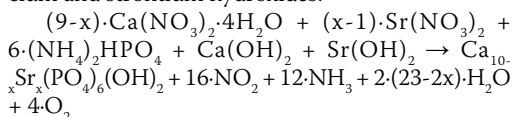
As strontium and calcium have similar crystallographic radius, chemical properties, they can be interchangeable in the crystalline lattice. In terms of physical and chemical properties, strontium is an equivalent of calcium, and its companion in geochemical processes [6].

Depending on the amount introduced in the body and the duration of exposure, stable strontium affects mineral metabolism: long-term introduction of high quantities of stable strontium can lead to severe salt metabolism disorders up to strontium-induced rickets in animals, as well as reduce weight gain and inhibit tibia lengthwise growth [7].

Thus, the objective of the study was to analyze the process of calcium replacement by strontium in the hydroxyapatite structure as advantageous for medical applications.

## Experimental

Polycrystalline specimens were synthesized by a solid-phase reaction between strontium and calcium nitrates, ammonium hydrophosphate, and calcium and strontium hydroxides:



The mixture of reacting agents in the required stoichiometric proportion was calcinated at 350°C for 4 hours, then at 650°C for 6 hours.

There are several approaches to generation of calcium hydroxyapatite and solid solutions on its base: solution [8], hydrothermal [9] and solid phase [10] methods. The advantage of the latter is better control over the end product stoichiometry and absence of potential side reactions in aqueous media used in the first two methods (introduction of water-dissolved carbon dioxide, hydrophosphate groups, etc.).

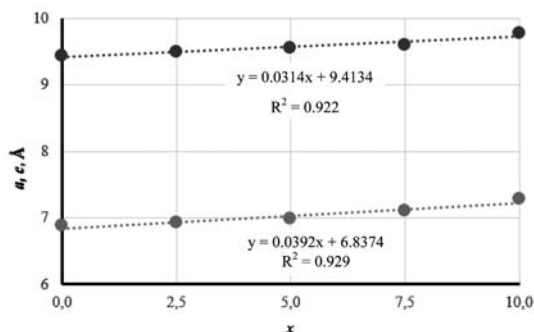
X-ray diffraction analysis of X-ray powder patterns (XRD 6000 Shimadzu X-ray diffractometer,  $\text{CuK}\alpha$  radiation at 0.02°) showed that target solid solutions and extreme members of the series were produced without admixtures of potential reaction by-products (calcium and strontium phosphates [11]).

Analytical indexing of X-ray powder patterns was used to determine elementary cell parameters (Table 1). It was assumed that the solid so-

Table 1

 Elementary cell parameters of  $\text{Ca}_{10-x}\text{Sr}_x(\text{PO}_4)_6(\text{OH})_2$  solid solutions depending on the composition

$x$	$a$ , Å	$c$ , Å	$V$ , Å <sup>3</sup>
0,0	9,430(1)	6,878(1)	529,7(1)
2,5	9,506(1)	6,922(1)	541,0(1)
5,0	9,550(1)	6,988(1)	551,9(1)
7,5	9,611(1)	7,102(1)	566,7(1)
10,0	9,773(1)	7,279(1)	602,1(1)



**Figure 1.** Dependency of elementary cell parameters of  $\text{Ca}_{10-x}\text{Sr}_x(\text{PO}_4)_6(\text{OH})_2$  solid solutions on the composition

lutions and extreme members of the series, calcium and strontium hydroxyapatites, had hexagonal symmetry and were crystallizable in space group  $P6_3/m$  [12, 13].

Based on the results, dependency of elementary cell parameters of  $\text{Ca}_{10-x}\text{Sr}_x(\text{PO}_4)_6(\text{OH})_2$  solid solutions on their composition was drawn up (**Figure 1**). As can be seen, there are no significant deviations of the dependency from linearity under Vegard's law. This is due to two factors. First, atoms are replaced in the same crystallographic positions of the apatite structure. Second, the proximity of the size of the replaced atoms: in this system, Goldschmidt's fundamental isomorphism rule on 15% difference of the replaced ion radii is fulfilled (11% for calcium and strontium [14]).

For further thermodynamic modeling of processes of integration of strontium ions into the bone tissue hydroxyapatite structure, theoretical calculation of thermodynamic functions of individual compounds and solid solutions within the system under study was performed (**Table 2**). Software Therm'AP was used [15,16]. This software allows to evaluate thermodynamic functions of phosphates with an apatite structure. The model used in Therm'AP is based on extensive experimental materials analyzed by the researcher. In the model, the energy contribution of each ion is in correlation with the respective binary compound, but with the use of correction factors determined for apatite chemical media. Due to this, the software can be used to evaluate thermodynamic functions not only of individual compounds, but of solid solutions with substitution in the cation sub-lattice as well. The relative error of the calculated values does not exceed 1% of the experimental values.

### Results and Discussion

Thermodynamic modeling of integration of strontium ions into the hydroxyapatite crystalline structure was performed using the GIBBS equilibrium complex method [17-19], which allowed to quantify the dissolution process taking place in the residue-solution system with different concentrations of strontium ions in the model solution. For computations, we used thermodynamic values of the tested substances, ions and complexes provided in **Table 2** and [20].

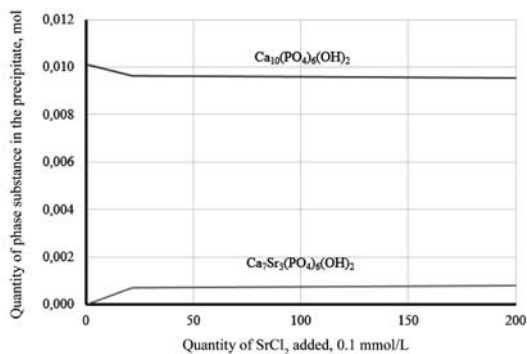
Table 2

 Assessment of thermodynamic functions of compounds in the  $\text{Ca}_{10-x}\text{Sr}_x(\text{PO}_4)_6(\text{OH})_2$  system using Therm'AP software

$x$	$\Delta H_f$ (kJ·mol <sup>-1</sup> )	$\Delta G_f$ (kJ·mol <sup>-1</sup> )	$\Delta S_f$ (J·mol <sup>-1</sup> ·K <sup>-1</sup> )	$S$ (J·mol <sup>-1</sup> ·K <sup>-1</sup> )
0	-12578	-13373	-2664	796
0,2	-12579	-13373	-2664	798
0,4	-12579	-13373	-2664	801
0,6	-12579	-13373	-2664	804
0,8	-12579	-13373	-2664	807

## Thermodynamic and thermophysical properties

x	$\Delta H_f$ (kJ·mol <sup>-1</sup> )	$\Delta G_f$ (kJ·mol <sup>-1</sup> )	$\Delta S_f$ (J·mol <sup>-1</sup> K <sup>-1</sup> )	S (J·mol <sup>-1</sup> K <sup>-1</sup> )
1,0	-12579	-13373	-2664	810
1,2	-12580	-13373	-2664	813
1,4	-12580	-13373	-2663	815
1,6	-12580	-13374	-2663	818
1,8	-12580	-13374	-2663	821
2,0	-12580	-13374	-2663	824
2,2	-12580	-13374	-2663	827
2,4	-12581	-13374	-2663	830
2,6	-12581	-13374	-2662	833
2,8	-12581	-13374	-2662	835
3,0	-12581	-13375	-2662	838
3,2	-12581	-13375	-2662	841
3,4	-12582	-13375	-2662	844
3,6	-12582	-13375	-2662	847
3,8	-12582	-13375	-2661	850
4,0	-12582	-13375	-2661	852
4,2	-12582	-13375	-2661	855
4,4	-12582	-13375	-2661	858
4,6	-12583	-13376	-2661	861
4,8	-12583	-13376	-2661	864
5,0	-12583	-13376	-2661	867
5,2	-12583	-13376	-2660	869
5,4	-12583	-13376	-2660	872
5,6	-12584	-13376	-2660	875
5,8	-12584	-13376	-2660	878
6,0	-12584	-13377	-2660	881
6,2	-12584	-13377	-2660	884
6,4	-12584	-13377	-2659	886
6,6	-12584	-13377	-2659	889
6,8	-12585	-13377	-2659	892
7,0	-12585	-13377	-2659	895
7,2	-12585	-13377	-2659	898
7,4	-12585	-13377	-2659	901
7,6	-12585	-13378	-2658	904
7,8	-12586	-13378	-2658	906
8,0	-12586	-13378	-2658	909
8,2	-12586	-13378	-2658	912
8,4	-12586	-13378	-2658	915
8,6	-12586	-13378	-2658	918
8,8	-12586	-13378	-2658	921
9,0	-12587	-13379	-2657	923
9,2	-12587	-13379	-2657	926
9,4	-12587	-13379	-2657	929
9,6	-12587	-13379	-2657	932
9,8	-12587	-13379	-2657	935
10,0	-12588	-13379	-2657	938



**Figure 2.** Composition of the solid phase in the “hydroxyapatite-model blood” system with a change in strontium ion concentration

To solve this task, a system consisting of the following components was selected as a model:

liquid water – 1 kg;

sodium ions – as dissolved sodium chloride in a concentration of 135 to 150 mmol/L;

potassium ions – as dissolved potassium chloride in a concentration of 3.9 mmol/L;

calcium ions – as dissolved calcium chloride in a concentration of 1.25 mmol/L;

$\text{NaH}_2\text{PO}_4$  and  $\text{Na}_2\text{HPO}_4$  phosphates which are buffer system components in the blood plasma, concentration of 1 mmol/L;

solid-phase hydroxyapatite – 0.01 mol;

strontium ions were added to the system at each calculation step in the amount of 0.1 mmol/L.

Thus, the system composition simulated the composition of blood plasma by concentrations and ions present [21].

As can be seen from **Figure 2**, calcium ions are integrated into the bone tissue hydroxyapatite in the system under study. Despite the calcium, strontium phosphates and solid solutions of other composition accounted for in the model, a single phase of  $\text{Ca}_7\text{Sr}_3(\text{PO}_4)_6(\text{OH})_2$  is produced. Approximately

up to the concentration of strontium ions of 2.2 to 2.4 mmol, the rate of formation of the solid solution is relatively high. Then a sharp reduction occurs accompanied by significant changes in the simulated blood composition.

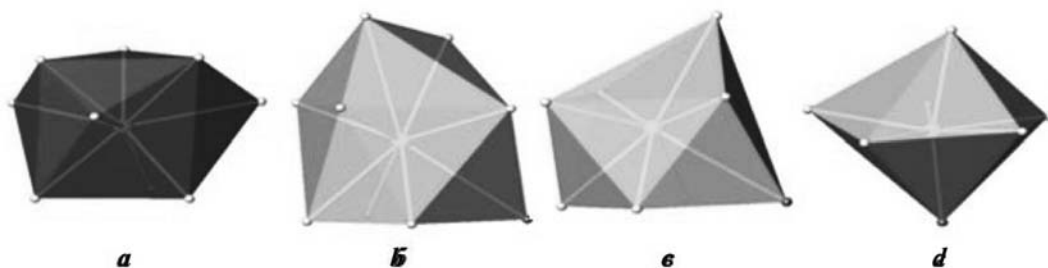
In terms of apatite crystalline structure, production of a stable compound of the specified stoichiometric composition appears uncommon.

The key peculiarity of apatite-structure compounds is the presence of two crystallographic cation positions in the elementary cell that are different from the resulting coordination polyhedra by local symmetry [11, 2]. Cations in the 4f position form tricapped trigonal prisms the columns of which are located along crystallographic axis *c* (**Figure 3a**). Cations in the 6h position can have coordination numbers from 7 to 9 and form coordination polyhedra as malformed pentagonal bipyramids, uncapped and bicapped trigonal prisms, respectively [22] (**Figure 3 b-d**).

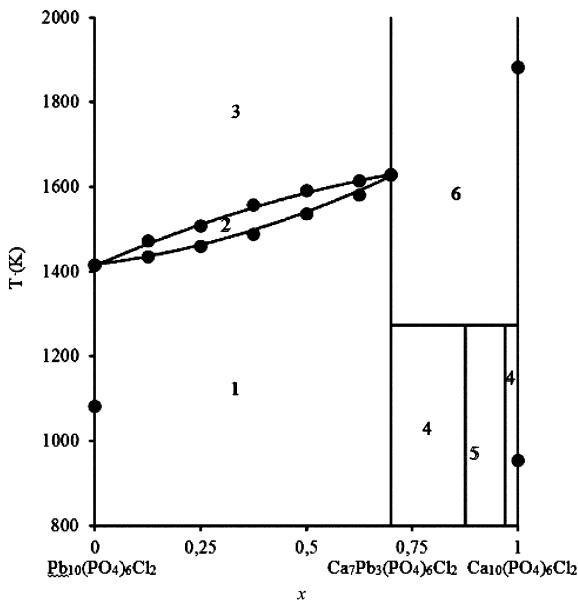
As per Wyckoff positions denomination, the proportion of the two types of cations in the elementary cell is 2:3. When mixed cation apatites (with two types of atoms in the M position) are formed, the 4f position is occupied by atoms with highest coordination numbers. Generally, these are compounds belonging to a separate mineralogical hedyphane group under the apatite supergroup mineral classification [23]:  $\text{Ca}_2\text{Pb}_3(\text{AsO}_4)\text{Cl}$ ,  $\text{Mn}_2\text{Ca}_3(\text{PO}_4)_3\text{Cl}$ ,  $\text{Ca}_2\text{Na}_3(\text{SO}_4)_3\text{Cl}$ , etc.

However, detailed study and thermodynamic modeling of the phase diagram of the  $\text{Ca}_{10}(\text{PO}_4)_6\text{Cl}_2$ - $\text{Pb}_{10}(\text{PO}_4)_6\text{Cl}_2$  binary system showed a stable individual compound of  $\text{Ca}_7\text{Pb}_3(\text{PO}_4)_6\text{Cl}_2$  to be formed in this system (**Figure 4**) [24].

Formation of this stable compound may be caused by the fact that a superstructure can be formed in apatite structure compounds [25]. Such effects occur if any atoms in the structure occupy several crystallographic positions, where population of these positions varies under the periodic law that can only be observed when several elementary cells are viewed simultaneously.



**Figure 3.** Types of  $\text{M}^{\text{II}}$  cation polyhedra in the apatite structure in position 4f (**a**) and 6h (**b – d**). Small white spheres are oxygen atoms, small dark spheres are L atoms.



**Figure 4.**  $\text{Ca}_{10}(\text{PO}_4)_6\text{Cl}_2$ - $\text{Pb}_{10}(\text{PO}_4)_6\text{Cl}_2$  system phase diagram. (1)  $\text{Pb}_{10}(\text{PO}_4)_6\text{Cl}_2$  -  $\text{Ca}_7\text{Pb}_3(\text{PO}_4)_6\text{Cl}_2$  system solid solutions, (2)  $\text{Pb}_{10}(\text{PO}_4)_6\text{Cl}_2$  -  $\text{Ca}_7\text{Pb}_3(\text{PO}_4)_6\text{Cl}_2$  + flux system solid solutions, (3) flux, (4)  $\text{Ca}_7\text{Pb}_3(\text{PO}_4)_6\text{Cl}_2$  -  $\text{Ca}_{10}(\text{PO}_4)_6\text{Cl}_2$  system solid solutions, (5)  $\text{Ca}_7\text{Pb}_3(\text{PO}_4)_6\text{Cl}_2$  -  $\text{Ca}_{10}(\text{PO}_4)_6\text{Cl}_2$  system solid solutions mixture, (6)  $\text{Ca}_7\text{Pb}_3(\text{PO}_4)_6\text{Cl}_2$  -  $\text{Ca}_{10}(\text{PO}_4)_6\text{Cl}_2$  system solid solutions degradation products.

Calcium hydroxyapatite is commonly known to have varying hydrogen atomic arrangement [26-28]. Moreover, variation of the arrangement of hydroxyl groups in the elementary cell at temperature rise is also often recorded as a polymorphic transition. And the transition temperature may vary significantly depending on the physical and chemical methods applied [29]. This could explain the presence of a superstructure in the compound under study.

### Conclusion

Thermodynamic modeling showed that integration of strontium into the hydroxyapatite structure creates only one solid solution:  $\text{Ca}_7\text{Sr}_3(\text{PO}_4)_6(\text{OH})_2$ . By studying mechanical properties of this solid solution, it would be possible to predict how the physical and mechanical characteristics of the bone tissue will change under the impact of radioactive strontium. Discrepancies between the X-ray diffraction analysis and thermodynamic modeling data could be due to the inadequate accuracy of determination of elementary cell parameters during

X-ray diffraction imaging. Further experimental research into the proposed binary system should be conducted by X-ray structural analysis of solid solutions with a smaller increment by composition.

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### References

1. D. McConnell. A structural investigation of the isomorphism of the apatite group // *American Mineralogist*. — 1938. — Vol. 23. — P. 1–19.
2. T.J. White, C. Ferraris, J. Kim, M. Srinivasan. Apatite — an adaptive framework structure // *Rev. Mineral. Geochem.* — 2005. — Vol. 57. — P. 307–402.
3. T.J. White, Z.-L. Dong. Structural derivation and crystal chemistry of apatites // *Acta Crystallographica B*. — 2003. — Vol. 59. — P. 1–16.
4. D. Tadic, M. Epple. A thorough physico-chemical characterisation of 14 calcium phosphate-based bone substitution materials in comparison to natural bone // *Biomaterials*. — 2004. — V. 25. — P. 987–994
5. V.M. Kashkarov, D.L. Goloshchapov, A.N. Rummyantseva, P.V. Seredin, E.P. Domashevskaya, I.A. Spivakova, B.R. Shumilovich. X-Ray Diffraction and IR Analyses of Nanocrystalline Synthesized and Biogenic Hydroxyapatite // *Surface. X-Ray, Synchrotron, and Neutron Research* — 2011. — № 12. — S. 1–7. (В.М. Кашкаров, Д.Л. Голощапov, А.Н. Румянцева, П.В. Середин, Э.П. Домашевская, И.А. Спивакова, Б.Р. Шумилович. РФА- и ИК-исследования нанокристаллического синтезированного и биогенного гидроксипатита // *Поверхность. Рентгеновские, синхротронные и нейтронные исследования*. — 2011. — № 12. — С. 1–7.)
6. Z.V. Dubrovina, I.A. Sarapultsev. On the Issue of Strontium and Calcium Exchange in Humans // *Hygiene and Sanitation* — 1967. — № 4. — S. 43–46. (З.В. Дубровина, И.А. Сарапульцев. К вопросу об обмене стронция и кальция у человека // *Гигиена и санитария*. — 1967. — №4. — С. 43–46.)
7. L.I. Levina. On Bernstein Nomographic Chart Extension for Pulmonary Artery Pressure Determination // *Medical Practice* — 1974. — № 8. — S. 19–22. (Л.И. Левина. О расширении номограммы Бернштейна для определения давления в легочной артерии // *Врач. Дело*. — 1974. — №8. — С. 19–22.)
8. R. B. Collin. Strontium-Calcium Hydroxyapatite Solid Solutions Precipitated from Basic, Aque-

ous Solutions // Journal of the American Chemical Society. — 1960. — V. 82. — P. 5067–5069.

9. B. Donazzon, G. Dechambre, J.L. Lacout. Calcium-strontium hydroxyapatite: hydrothermal preparation // Ann. Chim. Sci. Mat. — 1998. — V. 23. — P. 53–56

10. R.B. Collin. Strontium-Calcium Hydroxyapatite Solid Solutions: Preparation and Lattice Constant Measurements // Journal of the American Chemical Society. — 1959. — V. 81. — P. 5275–5278.

11. Bulanov E.N., Wang J., Knyazev A.V., White T., Manyakina M., Baikie T., Lapshin A.N., Dong Z. Structure and thermal expansion of calcium-thorium apatite,  $[\text{Ca}_4]\text{F}[\text{Ca}_2\text{Th}_4]\text{T}[(\text{SiO}_4)_6]\text{O}_2$  // Inorganic Chemistry. — 2015. — V. 54. — P. 11356–11361.

12. K. Sudarsanan, R.A. Young. Significant Precision in Crystal Structural Details: Holly Springs Hydroxyapatite // Acta Crystallographica. — 1969. — V. 25. — P. 1534–1543

13. K. Sudarsanan, R.A. Young. Structure of strontium hydroxide phosphate,  $\text{Sr}_5(\text{PO}_4)_3\text{OH}$  // Acta Crystallographica. — 1972. — V. 28. — P. 3668–3670

14. Database of Ionic Radii <http://abulafia.mt.ic.ac.uk/shannon/ptable.php>

15. C. Drouet. A Comprehensive Guide to Experimental and Predicted Thermodynamic Properties of Phosphate Apatite Minerals in view of Applicative Purposes // The Journal of Chemical Thermodynamics (JCT). — 2015. — V. 81. — P. 143–159.

16. C. Drouet. Applied predictive thermodynamics (ThermAP). Part 2. Apatites containing  $\text{Ni}^{2+}$ ,  $\text{Co}^{2+}$ ,  $\text{Mn}^{2+}$ , or  $\text{Fe}^{2+}$  ions // J. Chem. Thermodynamic. — 2015. <http://dx.doi.org/10.1016/j.jct.2015.06.016>.

17. M.V. Borisov. Geochemical and Thermodynamic Models of Hydrothermal Vein Ore Formation — Moscow : Nauchniy Mir, 200. — S. 360 (М.В. Борисов. Геохимические и термодинамические модели жильного гидротермального рудообразования — Москва : Научный мир, 200. — 360 с.)

18. M.V. Borisov, Yu.V. Shvarov. Thermodynamics of Geochemical Processes — Moscow : MSU Publishing House, 1992. — S. 256 (М.В. Борисов, Ю.В. Шваров. Термодинамика геохимических процессов. — Москва : Изд-во МГУ, 1992. — 256 с.)

19. Yu.V. Shvarov. Algorithmization of Numerical Equilibrium Modeling of Dynamic Geo-

chemical Processes // Geochemistry — 1999. — Vol. № 6. — S. 646–652. (Ю.В. Шваров. Алгоритмизация численного равновесного моделирования динамических геохимических процессов // Геохимия. — 1999. — Т. № 6. — С. 646–652.)

20. Thermal Constants of Substances / Edited by V.P. Glushko — Moscow : Publishing House of the Academy of Sciences of the USSR, 1965–1981. — Vol. I-X. (Термические константы веществ / Под ред. Глушко В.П. — Москва : Изд-во АН СССР, 1965–1981. — Т. I-X.)

21. <http://dendrit.ru/page/show/mnemonic/biohimiya-krovi-plazma-krovi-metabolizm/>

22. E.N. Bulanov. Synthesis and Physical-Chemical Study of Certain Apatites // Saarbrücken: LAP Lambert Academic Publishing, 2014. ISBN : 978-3-659-20303-9 (Буланов Е.Н. Синтез и физико-химическое исследование некоторых апатитов // Саарбрюккене : LAP Lambert Academic Publishing, 2014. ISBN : 978-3-659-20303-9)

23. M. Pasero, A.R. Kampf, C. Ferraris, I.V. Pekov, J. Rakovan, T.J. White. Nomenclature of the apatite supergroup minerals // Eur. J. Mineral. — 2010. — Vol. 22. — P. 163–179.

24. A.V. Knyazev, N.G. Chernorukov, E.N. Bulanov. Phase diagram of apatite system  $\text{Ca}_{10}(\text{PO}_4)_6\text{Cl}_2$ – $\text{Pb}_{10}(\text{PO}_4)_6\text{Cl}_2$  // Thermochimica Acta. — 2011. — V. 526. — P. 72–77.

25. P.A. Henning, S. Lidina, V. Petric. Iodo-oxyapatite, the first example from a new class of modulated apatites // Acta Cryst. — 1999. — V. 55. — P. 165–169

26. V.S. Urusov. Theoretical Crystal Chemistry // Moscow : MSU Publishing House — 1987. — 275 (Урусов В.С. Теоретическая кристаллохимия // М. : Изд. МГУ. — 1987. — 275)

27. J.M. Hughes, M. Cameron, K.D. Crowley. Structural variations in natural F, OH, and Cl apatites // American Mineralogist. — 1989. — V. 74. — P. 870–876.

28. Y. Suetsugu, T. Ikoma, J. Tanaka. Single crystal growth and structure analysis of monoclinic hydroxyapatite // Key Engineering Materials. — 2001. — V. 192. — P. 287–290.

29. A.V. Knyazev, N.G. Chernorukov, E.N. Bulanov. Apatite-structured compounds: synthesis and high-temperature investigation // Materials Chemistry and Physics. — 2012. — V. 132. — S.773–781.