CALCIUM

Diagnostic reagent for determination of Calcium concentration.
Liquid. Monoreagent. Store at +2/+8°C. For in Vitro Diagnostic Use (IVD). **Do not freeze.**

Ref No	Package	Ref No	Package	Ref No	Package	Ref No	Package
A2060N	500 mL	D2061	280 mL	L2060	500 mL	PL2060	240 mL
A2061N	200 mL	D2062	540 mL	L2061	240 mL	PL2061	150 mL
A2062N	100 mL	ER2060	112 mL	L2062	240 mL	RD2060	200 mL
A2064N	400 mL	ER2061	280 mL	L2063	240 mL	S2060	500 mL
A2066N	200 mL	HN060	400 mL	MD060	400 mL	S2061	200 mL
A2070N	400 mL	HN061	230 mL	MD061	200 mL	S2062	100 mL
BB040	160 mL	K2061	240 mL	M2060	500 mL	S2065	100 mL
BY2060	700 mL	LB060	200 mL	M2061	200 mL	TB2060	400 mL
BY2061	500 mL	LM060	160 mL	M3060	320 mL	TB2061	200 mL
BY2062	350 mL	LM061	240 mL	M3061	240 mL	8A2060	700 mL
BZ2040	300 mL	LM062	240 mL	M4060	500 mL	8A2061	500 mL
DM2060	333 mL	MH062	120 mL	M4061	200 mL	8A2062	350 mL

Changes made in the instructions for use are marked as grey.

INTENDED USE

The test is applied for the quantitative determination of Calcium in serum, plasma and urine.

GENERAL INFORMATION

Calcium is the fifth most abundant element in the body and the most common cation. An average human body of 70 kg contains approximately 1 kg (about 25 mol) of calcium. The skeletal system contains about 99% of the calcium in the body, mostly in the form of extracellular crystals of unknown structure and a composition close to hydroxyapatite [$Ca_{10}(P0_4)_6(OH)_2$]. Soft tissues and extracellular fluid contain about 1% of the calcium in the body.[1] Almost all calcium in the blood is found in plasma, with an average calcium concentration of 9.5 mg/dL (2.38 mmol/L). Calcium is present in plasma in three physicochemical states: 50% free (ionized), 40% bound to plasma proteins and 10% complexed with small diffusible inorganic and organic anions, including bicarbonate, lactate, phosphate and citrate.[2]

Calcium is essential for the mineralization of bone and is a key regulator of many body functions. The circulating concentration of calcium ions is kept constant under the control of parathyroid hormone (PTH) and vitamin D metabolites.[1]

Calcium is found in many foods, but is particularly found in dairy products and fish eaten whole (e.g. sardines, herring). Even with adequate dietary calcium intake, calcium absorption may be restricted by the presence of other dietary components that form insoluble complexes with calcium, such as oxalates and phytates, or by insufficient calcitriol, which stimulates the absorption of calcium ions. The recommended calcium intake is 1000 mg/day (25 mmol/day). Larger amounts are needed during pregnancy and lactation.

Adequate dietary calcium intake during childhood and adolescence is an important determinant of peak bone mass (typically reached at 20 to 25 years of age), which itself is a predictor of osteoporosis risk. Furthermore, plasma calcium concentration can be maintained over a wide range of dietary intake because homeostatic mechanisms can eliminate bone calcium if necessary to maintain extracellular fluid concentration, and excesses are usually readily excreted.[3]

Approximately 98% of calcium filtered through the renal glomeruli is reabsorbed from different parts of the renal tubules. Of this reabsorption, 60-70% occurs in the proximal tubules, 20% in the thick ascending loop of the henle, 10% in the distal convoluted tubule, and 5% in the collecting ducts. The distal nephrons are primarily responsible for calcium excretion, although they are responsible for a small proportion of reabsorption. The majority of calcium reabsorption from the proximal tubules occurs passively via the paracellular pathway, whereas a small proportion occurs actively via the transcellular pathway in which parathyroid hormone and calcitonin are involved as regulators.[4]

The free calcium fraction is biologically the active form. Deviations of the free (ionized) calcium concentration outside the very narrow reference range can cause morbidity and mortality. Its concentration in plasma is strictly regulated by the calcium regulatory molecules PTH and $1,25(OH)_2D$. PTH synthesis and secretion by the parathyroid glands is controlled through the calcium-sensing receptor (CaSR), a transmembrane receptor on the surface of parathyroid gland cells. A decrease in circulating free calcium is detected at the CaSR, and as a result the parathyroid gland master cells increase the secretion of PTH to increase free calcium via the kidneys (calcium reabsorption), intestine (calcium absorption) and skeletal system (bone resorption releases calcium).

When calcium is sufficiently increased, free calcium interacts with CaSR to initiate a classic reverse feedback loop that decreases PTH synthesis.[5] Approximately 80% of protein-bound calcium is associated with albumin and the remaining 20% with globulins.[1,5,6] Since calcium binds to negatively charged regions of proteins, its binding is pH dependent. Alkalosis leads to an increase in the negative charge of proteins and an increase in binding and thus a decrease in free calcium; conversely, acidosis leads to a decrease in the negative charge, a decrease in binding and an increase in free calcium. For every 0.1 unit change in pH in vitro, there is an inverse change of approximately 0.2 mg/dL (0.05 mmol/L) in serum free calcium concentration. Changes in the concentrations of calcium, protein and small anions, together with changes in pH or changes in the amounts of free calcium and total calcium in plasma, can redistribute acutely or chronically between the three physicochemical pools.[1]

Physiologically, calcium can be classified as intracellular and extracellular. Intracellular calcium plays a key role in many important physiological functions such as muscle contraction, hormone secretion, glycogen metabolism and cell division.[7] The intracellular calcium concentration in the cytosol of unstimulated cells is less than 1/20,000 of that in the extracellular fluid (≈ 0.1 /mmol/L).[1] Extracellular calcium provides calcium ions for the preservation of bone mineralization, blood coagulation and plasma membrane potential of intracellular calcium.

Calcium stabilizes plasma membranes and affects permeability and excitability. A decrease in the concentration of free calcium in plasma results in increased neuromuscular excitability and can lead to tetany; increased concentration decreases neuromuscular excitability.[1]

Low total plasma calcium (hypocalcemia) can be the result of a decrease in albumin-bound calcium, the free fraction of calcium, or both.[8] Hypoalbuminemia is the most common cause of marked hypocalcemia, especially in hospitalized patients, because 1 g/dL (1 g/L) of albumin binds approximately 0.8 mg/dL (0.02 mmol/L) of calcium. Common clinical conditions associated with low plasma albumin include chronic liver disease, nephrotic syndrome, congestive heart failure, malignancy, malnutrition, and volume replacement with saline or colloidal solutions after surgery. In these conditions, the free calcium concentration is typically maintained within the physiologic reference range.[1]

The most common causes of hypocalcemia are late-stage chronic kidney disease (CKD), hypoparathyroidism and hypomagnesemia. In CKD, hypoproteinemia, hyperphosphatemia, low plasma $1,25(OH)_2D$ (caused by reduced renal synthesis) and skeletal resistance to PTH may all contribute to hypocalcemia. Some medications (bisphosphonates, denosumab, imatinib, proton pump inhibitors, etc.), conditions associated with various malignancies (osteoblastic metastases, some hematologic cancer treatments, etc.), post-surgery (thyroidectomy, parathyroidectomy etc.) and some surgical procedures (gastric bypass surgery etc.), calcium deposition in damaged tissues (crush injuries, tumor lysis syndrome etc.), vitamin D deficiency, nutritional deficiencies and malabsorption may cause hypocalcemia.[8] Hypercalcemia usually occurs when there is excessive calcium entry into the extracellular fluid compartment from the skeleton, intestine or kidney, such as excessive resorption of bone mineral in malignancy. Hypercalciuria often develops in such cases. Hypercalcemia develops when the capacity of the kidney to excrete filtered calcium is exceeded, and hypocalciuria may be paradoxically present when renal failure is present and calcium excretion is reduced. Hypercalcemia may also be seen in many different conditions such as various malignancies, endocrine disorders (hyperparathyroidism, hypothyroidism, acromegaly, acute adrenal insufficiency etc.), loss of function mutations in CYP24A1 (25-Hydroxyvitamin D 24-Hydroxylase), infantile idiopathic hypercalcemia, granulomatous diseases, vitamin overdose (vit D and A), total parenteral nutrition, milk-alkali syndrome, some drug use (chlorothiazide diuretics, some vitD and analogues, calcium+vitD, lithium, growth hormone, PTH therapy, etc.), CKD and immobilization.[1]

Most stones formed in Western societies are composed of calcium, usually in combination with oxalate, although calcium phosphate and urate may also be present, either alone or in combination with calcium oxalate. As a result, the measurement of calcium in urine is of great importance. In general, calcium oxalate stones suggest hyperoxaluria as the main cause, whereas calcium phosphate stones suggest hypercalciuria and/or insufficient acidification of the urine.[9] There is considerable overlap in hypercalciuria between stone-forming and non-stone-forming causes, but a limit of 4 mg/kg body weight (0.1 mmol/kg) is useful. Excretion above this level occurs in common metabolic abnormalities that form calcium stones and is observed in up to 50% of patients. On the other hand, crystal formation is clearly dependent on the concentration of calcium as opposed to the rate of excretion.[10,11,41] The rate of urinary calcium (UCa) excretion provides information on calcium intake, intestinal absorption, skeletal resorption and renal tubular filtration and reabsorption.[2]

The link between calcium intake and cancer risk has been extensively studied. Although the results of these studies are not always consistent, they suggest that adherence to calcium intake may have some advantageous effect on the likelihood of developing colorectal cancer.[12] Moreover, there is also evidence linking high calcium intake with an increased risk of cardiovascular disease.[13]

TEST PRINCIPLE

Colorimetric (arsenazo) method

Total calcium is most commonly measured by spectrophotometry using metallochromic indicators or dyes. Arsenazo III, which causes a color change after selectively binding to calcium, is one of the most widely used metallochromic indicators.

Arsenazo III (1,8-dihydroxynaphthalene-3,6-disulfonic acid-2,7-bis[azo-2]-phenylarsonic acid) has a much higher affinity to calcium than to magnesium at slightly acidic pH[1] and forms an intense blue-violet complex by binding it. The absorbance of this complex is measured at 660 nm and is proportional to the calcium concentration in the sample.

Note 1: Methods used to quantify calcium in the blood may measure the free Ca^{+2} ion or the total calcium concentration and then provide a calculation of albumin-adjusted calcium. The term ionized calcium, although widely used, is a misnomer because all calcium in plasma or serum is ionized, regardless of whether it is free or associated with protein or small anions through ionic binding.[1]

Note 2: Since the spectral properties of arsenazo III are pH dependent, the solution should be well buffered. The binding of calcium to arsenazo III may be affected by buffer and sodium concentration.

Note 3: Several methods for measuring total calcium have been described. Currently, photometric, ion selective electrode (ISE) and sometimes atomic absorption spectrophotometry (AAS) methods are used in clinical laboratories to measure total calcium in serum and urine.

Total calcium adjusted for albumin (adjusted or corrected calcium): Large variations in the concentrations of calcium-binding compounds in the blood can occur, this variation will affect the measured total calcium concentration without changing the free calcium fraction. Various types of calculation have been proposed to "adjust" the measured calcium concentration. The aim is to find the answer to the question "What would be the adjusted result if the concentrations of all calcium-binding compounds were within their respective reference ranges?". In practice, only albumin-based adjustments are commonly used. The term adjusted calcium is preferable to corrected calcium, because "corrected" may give the impression that the result has been corrected due to an error.[14,15]

Corrected calcium is calculated using total calcium and albumin. A correction factor is calculated by first multiplying the deviation of plasma albumin from the mean of the reference interval by the slope of the regression of total calcium against albumin. The following two equations are often used for results expressed in mg/dL and mmol/L respectively:

Adjusted total calcium (mg/dL)
= Total calcium (mg/dL) + 0,8 [4 – Albumin (g/dL)]

Adjusted total calcium (mmol / L)
= Total calcium (mmol/L) + 0,02 [40 – Albumin (g/dL)]

Note 1: These are fairly simple calculations and in practice it is recommended that laboratories create equations specific to their reference populations that include linear regression from the different methods used to measure total calcium and albumin concentrations.

Note 2: Many factors influence the distribution of calcium between free, complex and protein-bound fractions. The reliability of serum albumin adjustment is impaired in patients with very low or high serum albumin concentrations, in patients with severe disease and multiple organ failure, which is common in intensive care units. It should be noted that equations developed for specific reference patient groups, such as hemodialysis patients[14-16] or patients with liver disease, may be better than no adjustment in this patient group.[1]

Note 3: The accuracy of the adjusted calcium equation in outpatients can be improved by deriving a population-specific equation when applied in a specific care setting.[17,18]

REAGENT COMPONENTS

Arsenazo (III)	: ≤ 0.2 mmol/L
Good's buffer	: ≤ 50 mmol/L
Stabilizers.	

REAGENT PREPARATION

Reagent is ready for use.

REAGENT STABILITY AND STORAGE

Reagents are stable at +2/+8°C till the expiration date stated on the label which is only for closed vials.

Once opened vials are stable for 30 days at +2/+8°C in optimum conditions. On board stability is strongly related to auto analyzers' cooling specification and carry-over values.

Reagent stability and storage data have been verified by using Clinical and Laboratory Standards Institute (CLSI) EP25-A protocol.[19]

SAMPLE REQUIREMENTS

Serum, plasma and urine can be used and are collected according to the standard procedures. For plasma, sample collection tubes with Li heparin and Na heparin should be preferred. Multiple sample freezing and thawing should be avoided. In order to prevent precipitation of the calcium salt in random urine samples (samples collected in less than 24 hours and evaluated instantly), collect them in a bottle containing 1 or 2 mL 6mol/L HCl. To prevent precipitation of calcium salt in 24-hour urine samples, collect them in a bottle containing 20 or 30 mL HCl.[43]

The stability of Calcium in serum/plasma:[42]

7 days at +20/+25ºC
3 weeks at +2/+8ºC
8 months at -20°C

The stability of Calcium in urine:[42]

2 days at +20/+25ºC
4 days at +2/+8ºC
3 weeks at -20°C

Note 1: Posture alters serum calcium concentration. Changing from upright to horizontal posture causes a decrease of about 4% (range 2% to 7%).[20]

Note 2: In addition to serum, heparinized plasma may be preferred. Citrate, oxalate and ethylenediaminetetetraacetic acid (EDTA) anticoagulants should not be used in spectrophotometric methods as they complex with calcium and cause interference.[1]

Note 3: Although calcium has been reported to precipitate with fibrin (e.g. heparinized plasma) or lipids during storage or freezing, total calcium measurements are little affected by storage, provided that water loss associated with long-term refrigerated or freezer storage is avoided (by using tight-fitting containers designed for such storage). Calcium can be adsorbed from dilute solutions during storage in plastic and glass.[1]

Note 4: Calcium salts such as calcium oxalate precipitate during and after collection of urine samples. To prevent precipitation of calcium salts, samples can be collected in a container with acid. The commonly used acid is HCl at 6 mol/L and 10 to 30 mL is added to the container for a 24-hour collection (1 to 2 mL for random samples).[1,20,21]

CALIBRATION AND QUALITY CONTROL

Calibration: The assay requires the use of an Arcal Auto Calibrator or Calcium Calibrator.

Arcal Auto Calibrator (Lyophilized)
Ref.No: A39052
Ref.No: A39054
Ref.No: A39055 (For Olympus AU Series.)

Calibration stability is 15 days.Calibration stability depends on the application characteristics and cooling capacity of the autoanalyzer used.

Serum traceability is provided with SRM 956d material.

Control: Commercially available control material with established values determined by this method can be used. We recommend:

Arcon N Level 1 Control (Lyophilized)
Ref.No: A3910
Ref.No: A3912 (For Olympus AU Series.)
Ref.No: A3913 (For BS Series.)
Ref.No: A3914 (For Erba.)

Arcon P Level 2 Control (Lyophilized)
Ref.No: A3920
Ref.No: A3922(For Olympus AU Series.)
Ref.No: A3923 (For BS Series.)
Ref.No: A3924 (For Erba.)

At least two level controls must be run once in every 24 hours. Each laboratory should determine its own quality control scheme and procedures. If quality control results are not within acceptable limits, calibration is required.

REFERENCE INTERVALS / MEDICAL DECISION LEVELS

Serum/Plasma	:	8.5 - 10.5 mg/dL
Random urine (Male)[10]	:	0.9 - 37.9 mg/dL
Rastgele idrar (Female)[10]	:	0.5 - 35.7 mg/dL
Urine[10]	:	100 - 300 mg/24 hour

Detailed pediatric reference interval values can be found in the results of CALIPER study: https://caliper.research.sickkids.ca/#/

To convert results from mg/dL to mg/day (24-hour urinary excretion);
24-hour excretion = [(V × c) ÷ 100] mg/day
Formula
V = 24-hour urine volume (mL)
c = analyte concentration (mg/dL)

Critical values: Critical values indicating the likelihood of morbidity are values less than 6.0 mg/dL (1.5 mmol/L) and greater than 14.0 mg/dL (3.5 mmol/L).[20]

Note 1: Plasma calcium concentration has been reported to vary with age, gender, season, during pregnancy and over a 24-hour period.[22,23]

However, in an outpatient group of healthy men and women living in the Southwestern United States, no age-related decline or sex-related difference in total or free calcium values was found.[24] During pregnancy, total calcium and corrected calcium decrease in parallel with plasma albumin.[25,26] The fetal circulation is relatively hypercalcemic[24,27] evidenced by higher total and free calcium in cord blood than in maternal plasma. In healthy term newborns, calcium concentrations decrease in the first few days after birth, but soon rise to concentrations slightly higher than those observed in adults.[28]

Note 2: According to the literature, healthy men and women excrete up to 300 mg (7.5 mmol) calcium per day on a calcium-unrestricted diet and up to 200 mg (< 5 mmol) calcium per day on a calcium-restricted diet. Reference data for UCa globally are not well established and it may be preferable to use 4 mg/kg body weight (0.1 mmol/kg) as an upper reference limit in an individual patient.[1]

Note 3: The UCa reference range for spot fasting following an overnight fast or for samples collected over a specified time interval is less than 0.16 mg/100 mL (<0.04 mmol/L) glomerular filtrate (GF) as calculated by the following equation:

UCa (mg / 100 mL GF)
= [UCa (mg/dL)] x [Serum creatinine (mg/dL)] / Urine creatinine (mg/dL)

Fasting calcium excretion (mg/100 mL [mmol/L] GF) is used to assess the skeletal component. A value higher than 0.16 mg/100 mL (0.04 mmol/L) GF usually indicates an increase in osteoclastic bone resorption. This test is used in the evaluation of kidney stone disease and high cycle osteoporosis.[1]

Alternatively, the ratio of urinary calcium to urinary creatinine can be calculated. Reference intervals for the ratio depend on age and sex.[1]

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary, determine its own reference range.

Reference interval has been verified by using CLSI EP28-A3c protocol.[29]

Unit Conversion:
mg/dL x 0.2495 = mmol/L

PERFORMANCE CHARACTERISTICS

Measuring Interval

According to CLSI EP34-ED1:2018, "Measuring Interval" refers to the interval where the analyte concentration is measured with intended accuracy in terms of medical and laboratory requirements without dilution, concentrating or any kind of pre-treatment that is between the analyte's lower limit of quantitation (LLoQ) and upper limit of quantitation (ULoQ).[30]

The determined analytic measuring interval for Calcium is 1.5 – 20 mg/dL.

Detection Capability

Limit of Detection (LoD): 0.5 mg/dL

Limit of Quantitation (LoQ): 1.5 mg/dL

Note: LoQ values are based on Coefficient of Variation Percentage (CV) ≤ 20%.

LoD and LoQ values have been verified by using CLSI EP17-A2:2012 protocol.[31]

Linearity

This method shows measurement linearity in the activities up to 20 mg/dL. Autoanaylzer's auto-dilution system can be used if the concentrations have higher values. See device manual for further information.

For the manual dilution procedure, dilute the sample 1:5 using 0.90% isotonic. After this process, multiply the result of the reworked sample by the dilution factor. Do not report the sample result after dilution if it is marked as lower than the linear lower limit. Rerun with a suitable dilution.

Linearity Studies data have been verified by using CLSI EP06-A:2003 protocol.[32]

Precision

Running system has been developed according to 20x2x2 "The Single Site" protocol. Repeatability and Within-Laboratory Precision/Within-Device values have been obtained according to the running results.

According to the protocol in use, 2 separate runs per day have been made for 20 days (no obligation for being consecutive days). This protocol has been applied to each low and high samples separately and 80 results have been obtained for each one. Statistically, the results have been obtained using 2-factor Nested-ANOVA model.[33]
Repeatability (Within Run) and Repeatability (Day to Day) SD (standard deviation) and CV% values of Calcium have been given in the table 1 and 2 respectively.

Table 1. Calcium Repeatability (Within Run) results obtained from samples in two different concentrations

Mean Concentration	SD	CV%	n
8.98 mg/dL	0.15	1.71	80
12.4 mg/dL	0.11	0.90	80

Note: This working system has been named "Within-Run Precision" in the previous CLSI - EP05-A2 manual.[34]

Table 2. Calcium Repeatability (Day to Day) results obtained from samples in two different concentrations

Mean Concentration	SD	CV%	n
8.98 mg/dL	0.36	4.05	80
12.4 mg/dL	0.46	3.73	80

Note: This working system has been named "Total Precision" in the previous CLSI - EP05-A2 manual.[34]

Method Comparison

As a result of the statistical evaluation of the method comparison data:

Passing-Bablock equation:[35]
y= 1.07x – 1.48 mg/dL
r=0.993

Interference

Endogenous interferant and analyte concentrations that have been used in the Calcium scanning tests has been determined according to "CLSI EP37-ED1:2018" and "CLSI EP07-ED3:2018" manuals.[36,37]

The total acceptable error rate, which is going to be used to detect whether the observed differential value obtained from Calcium interference scanning test is appropriate, is determined as ±10%.[38]

In Calcium test results, no significant interaction has been observed in the determined endogenous interferant and analyte concentrations or between interferants and analyte.

Interferant-Concentration	Calcium Target (mg/dL)	N*	Observed Recovery %
Hemoglobin 1260 mg/dL	8.48	3	101
Bilirubin 48.3 mg/dL	7.97	3	105
Lipemi 1651 mg/dL	8.72	3	108

** Total acceptable error rate determined as interference limit and repeatability (within run) pre-detected for the related method were used for the calculations of how many times the control and test samples prepared as a serum pool are going to be run repetitively. In the calculations, the accepted error rate for type 1 (α error) was 5% and for type 2 (β error) was 10% (90% power).*[37]

Note 1: Hemolysis, jaundice, lipemia, paraproteins and magnesium have been reported to interfere with photometric methods to produce a negative or positive false test result. Bichromatic readout, multiple wavelength corrections or blinding can be used to reduce interference. Lipemic samples can be ultracentrifuged or processed to remove the lipid fraction before analysis.[1]

Note 2: Although hemolysis can cause a negative error because red blood cells contain a lower concentration of calcium than plasma, more significant errors can result from spectral interference of hemoglobin. Depending on the method used, hemoglobin has been reported to produce either negative or positive interference. In photometric methods, blinding with serum treated with ethylene glycol-O,O′-bis(2-aminoethyl)-N,N,N,N′,N′-tetraacetic acid (EGTA) is recommended if hemolyzed samples must be analyzed.[1,39,40]

Note 3: Individual instruments and methods should be evaluated for their sensitivity to the interference from magnesium, hemoglobin, bilirubin, proteins, turbidity and other interferants.[1]

It should be noted that endogenous interferants, as well as various medicines and metabolites, anticoagulants (e.g. Heparin, EDTA, citrate, oxalate) and preservatives (e.g. sodium floride, iodoacetate, hydrochloride acide) such as additives, materials that may contact with samples during collection and processing (serum separator devices, sample collection containers and contents, catheters, catheter wash solutions, skin disinfectants, hand cleaners and lotions, glass washing detergents, powder gloves), dietary substances known to affect some specific tests (caffeine, beta-carotene, poppy seeds, etc.), or some substances present in a sample that cause foreign proteins (heterophilic antibodies, etc.), autoimmune response (autoantibodies, etc.), or due to malignancy (for example, interference by paraproteins with phosphate testing and indirect ion selective electrode methods) may show some negative effects that will cause various attempts and some misjudgements.[37]

These performance characteristics have been obtained using an autoanalyzer. Results may vary slightly when using different equipment or manual procedures.

WARNINGS AND PRECAUTIONS

IVD: For in Vitro Diagnostic use only.
Do not use expired reagents.
Reagents with two different lot numbers should not be interchanged.
For professional use.
Follow Good Laboratory Practice (GLP) guidelines.

CAUTION: Human source samples are processed with this product. All human source samples must be treated as potentially infectious materials and must be handled in accordance with OSHA (Occupational Safety and Health Administration) standards.

Danger

EUH032 : Releases a very toxic gas if contacts with acid.
H317 : May cause allergic skin reaction.

Precaution

P280 : Use protective gloves / clothes / glasses / mask.
P264 : Wash your hands properly after using.
P272 : Contaminated work clothes should not be allowed to be used outside of the workplace.

Intervention

P302+P352 : Wash with plenty of water and soap if it contacts with skin.
P333+P313 : Seek medical help if it irritates your skin or develops rash.
P362+P364 : Remove contaminated clothes and wash properly before using.

Disposal

P501 : Dispose the vials and contents according to the local regulations.

REFERENCES

1. Rifai, N., Chiu, R. W., & Young, I., et al., (2023) Tietz Textbook of Laboratory Medicine (7th ed.), Chapter 47: Bone and Mineral Metabolism, p.766-766.e85, Elsevier, St. Louis, Missouri 63043
2. Rizzoli R, Bonjour JP. Physiology of calcium and phosphate homeostasis. In: Seibel MJ, Robins SP, Bilezikian JP, editors. Dynamics of bone and cartilage metabolism. 2nd ed. San Diego: Academic Press; 2006. p. 345–60.
3. Rifai, N., Chiu, R. W., & Young, I., et al., (2023) Tietz Textbook of Laboratory Medicine (7th ed.), Chapter 46: Nutrition: Laboratory and Clinical Aspects, p.458-501.e7, Elsevier, St. Louis, Missouri 63043
4. Blaine J, Chonchol M, Levi M. Renal control of calcium, phosphate, and magnesium homeostasis. Clin J Am Soc Nephrol 2015;10:1257–72.

5. Fogh-Andersen N, Bjerrum PJ, Siggaard-Andersen O. Ionic binding, net charge, and Donnan effect of human serum albumin as a function of pH. Clin Chem 1993;39:48–52.
6. Kragh-Hansen U, Vorum H. Quantitative analyses of the interaction between calcium ions and human serum albumin. Clin Chem 1993;39:202–8.
7. Schmidt-Gayk Measurement of calcium, phosphate and magnesium. In: Seibel MJ, Robins SP, Bilezikian JP, editors. Dynamics of bone and cartilage metabolism. 2nd ed. San Diego: Academic Press; 2006 p. 487–505.
8. Pepe J, Colangelo L, Biamonte F, et al. Diagnosis and management of hypocalcemia. Endocrine 2020;69(3):485–95.
9. Samuell CT, Kasidas GP. Biochemical investigations in renal stone formers. Ann Clin Biochem 1995;32:112–22.
10. Bushinsky DA. Recurrent hypercalciuric nephrolithiasis—does diet help? N Engl J Med 2002;346:124–5.
11. Worcester EM, Coe FL. New insights into the pathogenesis of idiopathic hypercalciuria. Semin Nephrol 2008;28:120–32.
12. Park Y, Leitzmann MF, Subar AF, et al. Adolescent and mid-life diet: risk of colorectal cancer in the NIH-AARP Diet and Health Study. Arch Intern Med 2009;169:391–401.
13. Michaëlsson K, Melhus H, Lemming EW, et al. Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study. BMJ 2013;347:f228.
14. Jassam N, Hayden K, Dearman R, Allgar V, Barth JH. Prospective study comparing the outcome of a population-specific adjusted calcium equation to ionized calcium. Ann Clin Biochem 2020; 57:316–24.
15. James MT, Zhang J, Lyon AW, et al. Derivation and internal validation of an equation for albumin-adjusted calcium. BMC Clin Pathol 2008;8:12.
16. Jain A, Bhayana S, Vlasschaert M, et al. A formula to predict corrected calcium in haemodialysis patients. Nephrol Dial Transplant 2008;23:2884–8.
17. Sodi R, Bailey LB, Glaysher J, et al. Acidification and urine calcium: is it a preanalytical necessity? Ann Clin Biochm 2009;46:484–7.
18. Robinson JL, Seiden-Long I, de Koning L. Identification and implementation of hemolysis interference thresholds in serum ionized calcium measurement. Clin Biochem 2020;78:66–7.
19. Clinical and Laboratory Standards Institute (CLSI). Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline. CLSI Document EP25-A. Wayne, PA: CLSI; 2009.
20. Pesce, A. J., & Kaplan, L. D. (2009). Methods in Clinical Chemistry: Kaplan and Pesce's: Clinical Chemistry: Theory, Analysis, Correlation: Vol. I (5th ed.), Chapter: Calcium, p.296-303. Elseviers.
21. Renoe BW, McDonald JM, Ladenson JH. The effects of stasis with and without exercise on free calcium, various cations, and related parameters. Clin Chim Acta 1980;103:91–100.
22. Sherman SS, Hollis BW, Tobin JD. Vitamin D status and related parameters in a healthy population: the effects of age, sex, and season. J Clin Endocrinol Metab 1990;71:405–13
23. Endres DB, Morgan CH, Garry PJ, et al. Age-related changes in serum immunoreactive parathyroid hormone and its biological action in healthy men and women. J Clin Endocrinol Metab 1987;65:724–31.
24. Wandrup J. Critical analytical and clinical aspects of ionized calcium in neonates. Clin Chem 1989;35:2027–33.
25. Kovacs CS, Kronenberg HM. Maternal-fetal calcium and bone metabolism during pregnancy, puerperium, and lactation. Endocr Rev 1997;18:832–72.
26. Kovacs CS, Kronenberg HM. Pregnancy and lactation. In: Rosen CJ, Compston JE, Lian JB, editors. Primer on the metabolic bone diseases and disorders of mineral metabolism. 7th ed. Washington, DC: American Society for Bone and Mineral Research; 2008. p. 90–5.
27. Kovacs CS. Fetal calcium metabolism. In: Rosen CJ, Compston JE, Lian JB, editors. Primer on the metabolic bone diseases and disorders of mineral metabolism. 7th ed. Washington, DC: American Society for Bone and Mineral Research; 2008. p. 108–12.
28. Cardenas-Rivero N, Chernow B, Stoiko MA, et al. Hypocalcemia in critically ill children. J Pediatr 1989;114:946–51.
29. Clinical and Laboratory Standards Institute (CLSI). Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline – Third Edition. CLSI Document EP28-A3c. Wayne, PA: CLSI; 2010.
30. Clinical and Laboratory Standards Institute (CLSI). Establishing and Verifying an Extended Measuring Interval Through Specimen Dilution and Spiking – 1st Edition. CLSI Document EP34. Wayne, PA: CLSI; 2018.
31. Clinical and Laboratory Standards Institute (CLSI). Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition. CLSI Document EP17-A2. Wayne, PA: CLSI; 2012.
32. Clinical and Laboratory Standards Institute (CLSI). Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach - 1st Edition. CLSI Document EP06-A. Wayne, PA: CLSI; 2003.
33. Clinical and Laboratory Standards Institute (CLSI). Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition. CLSI Document EP05-A3. Wayne, PA: CLSI; 2014.
34. Clinical and Laboratory Standards Institute (CLSI). Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline - Second Edition. CLSI Document EP05-A2. Wayne, PA: CLSI; 2004.
35. Bablok W et al. A General Regression Procedure for Method Transformation. J Clin Chem Clin Biochem 1988;26:783-790.
36. Clinical and Laboratory Standards Institute (CLSI). Supplemental Tables for Interference Testing in Clinical Chemistry - First Edition. CLSI Document EP37. Wayne, PA: CLSI; 2018.

37. Clinical and Laboratory Standards Institute (CLSI). Interference Testing in Clinical Chemistry - Third Edition. CLSI Document EP07. Wayne, PA: CLSI; 2018.
38. CLIA proficiency testing criteria for acceptable analytical performance, as printed in the Federal Register July 11, 2022;87(131:41194-242.
39. Buckley BM, Russell LJ. The measurement of ionised calcium in blood plasma. Ann Clin Biochem 1988;25(Pt 5):447–65.
40. Dimeski G, Badrick T, John AS. Ion selective electrodes (ISEs) and interferences—a review. Clin Chim Acta 2010;411:309–17.
41. Rifai, N., Chiu, R. W., & Young, I., et al., (2023) Tietz Textbook of Laboratory Medicine (7th ed.), Chapter 49: Kidney Disease, p.603-675.e17, Elsevier, St. Louis, Missouri 63043
42. WHO Publication: Use of anticoagulants in diagnostic laboratory investigations, WHO/DIL/LAB/99.1 Rev.2:Jan 2002.
43. Burtis CA, Ashwood ER, editors. Tietz Fundamentals of Clinical Chemistry, 5th ed. Philadelphia, PA: WB Saunders; 2001:800.

Archem Sağlık Sanayi ve Tic. A.Ş.
Mahmutbey Mah. Halkalı Cad. No:124 Kat:4
Bağcılar/İstanbul/Türkiye
Tel: + 90 212 444 08 92
Fax: +90 212 629 98 89
info@archem.com.tr **www.archem.com.tr**

CE

SYMBOLS

IVD	In Vitro Diagnostic Medical Device
LOT	Lot Number
R1	Reagent 1
GTIN	Global Trade Item Number
REF	Reference Number
GLP	Good Laboratory Practices
FOR USE WITH	Identifies Products to Be Used Together
PRODUCT OF TURKEY	Product of Turkey
	Manufacturer
	Expiration Date
	Temperature Limits
	Consult Instructions for Use
	Caution
	Number of Tests