COPPER

Diagnostic reagent for determination of Copper concentration.
Liquid. Monoreagent. Store at +15/+25°C. For in Vitro Diagnostic Use (IVD). **Do not freeze.**

Ref No	Package	Ref No	Package	Ref No	Package	Ref No	Package
BB070	160 mL	DMC20	333 mL	MCU20	350 mL	TBCU20	400 mL
BYC200	350 mL	ER2040	60 mL	M3U20	200 mL	TBCU21	150 mL
BYC201	280 mL	HN335	300 mL	M3U21	80 mL	TCU20	600 mL
CU200N	500 mL	LB094	120 mL	M4U20	280 mL	TCU21	200 mL
CU201N	100 mL	LCU20	180 mL	PL2607	150 mL	TCU22	100 mL
KCU20	240 mL	LM270	240 mL	RCC200	44 mL	8AC200	350 mL
				RD200	100 mL	8AC201	280 mL

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

INTENDED USE

The test is applied for the quantitative determination of copper in human serum and plasma.

GENERAL INFORMATION

Copper (Cu) is a trace element with atomic number 29 and atomic weight 63.54, associated with a number of metalloproteins. It is present in biological systems in both Cu^{+} and Cu^{+2} forms, and the easy exchange between these ions gives the element important redox properties. Inside cells, an elaborate array of binding and transport proteins protect the genome from Cu-generated free radical attack.[33] This keeps the concentration of free Cu in the cytoplasm very low (≈10.15 mol/L). Numerous blue-colored Cu-containing proteins, most of which belong to the oxidase class, are found outside the cytoplasm on the surface of cell membranes or in vesicles. However, superoxide dismutase (SOD), a Cu metalloenzyme, protects against random free radical damage both in the cytoplasm and in blood plasma.[1] Cu is involved in various cellular processes as a cofactor of enzyme/protein systems involved in catecholamine metabolism, oxidative metabolism, neurotransmitter synthesis, iron absorption, free radical clearance and collagen cross-linking (lysyl oxidase).[34-36]

Only small amounts of Cu are present in biological fluids, and in fact none is present as a free ion.[1] Body concentrations of copper are generally low (100 to 150 mg), with the highest concentrations in the liver (10 to 20 mg) and brain.[2] The average safe daily intake of copper in adults is 1.5 to 3.0 mg (24 to 47 µmol).[3] It is abundant in foods such as beans, peas, whole grain products, liver, seafood (oysters, crabs, lobsters), meat, almonds and walnuts.

Approximately 30% to 50% of intestinal copper is absorbed through both passive and active (energy-dependent) mechanisms.[4,5] Some absorption also occurs via the gastric route or by inhalation and skin absorption.[6,7]

Cu absorption is decreased by other dietary components such as Zn (induces metallothionein, which binds Cu^{+2}), vitamin C (converts Cu^{+2} to insoluble and thus unabsorbed Cu^{+}), molybdate and Fe, while it is increased by amino acids and dietary sodium.[6-10] 90% of copper in plasma is bound to ceruloplasmin, with approximately 10% loosely bound or associated with albumin. A small proportion is complexed with low molecular weight compounds such as amino acids.[2]

Distinctive clinical copper deficiency is uncommon. However, it has been reported in malnourished children, infants fed a low protein diet, and cow's milk formula, after prolonged parenteral or enteral therapy,[37,38] after persistent and severe diarrhea or excessive Zn intake. Copper deficiency presents as a microcytic, hypochromic anemia with marked neutropenia and is resistant to iron therapy. In children and newborns, collagen and elastin synthesis may be impaired and bone disease (osteoporosis) may develop.[2] Subclinical copper deficiency may be more common than previously thought and has been suggested to be a risk factor for cardiovascular disease.[11]

Menkes disease, a rare X-linked recessive neurodegenerative disorder (prevalence 1 in 250,000 live births), is characterized by a failure of copper transport (efflux) across the intestinal mucosa due to a defect in the MNK gene, located on the long arm of chromosome 13 and encoding copper transporters.[12,13] As there are many forms of Menkes' disease, symptoms range from mild to severe. Affected babies are usually detected soon after birth, and most babies with untreated severe (classic) Menkes' form die within the first weeks of life. Low serum copper/seruloplasmin levels or prenatal measurement of the copper content of chorionic villus in the first trimester help to confirm the diagnosis.[2]

The toxicity of copper can be caused by a genetic defect or by acute or chronic copper ingestion. Acute toxicity has been reported in people who have consumed copper-containing solutions (intentionally or accidentally), in patients given excessive supplements, and in those on hemodialysis (leaching of the element from copper-containing dialysis membranes [cuprophane]). In case of acute toxicity, serum copper concentrations will be high,

while ceruloplasmin concentrations will be normal.[2] Chronic poisoning with copper leads to hepatic copper overload with severe liver disease (cirrhosis) in young children.[2] Toxicity can also result directly from Cu contamination of the diet and water supplies. Quality standards for Cu in drinking water have been published by WHO.[14] Guidelines for the maximum Cu content in drinking water have been suggested and they range from about 1 to 3 mg Cu/L.[1]

Wilson's disease is a genetic disorder of Cu metabolism that causes Cu to increase to toxic concentrations.[15] The prevalence of Wilson's disease is estimated to be 1/30,000 live births and the carrier frequency in the general population is 1/90. Although total plasma Cu decreases, the fraction not bound to ceruloplasmin increases, leading to Cu accumulation in the brain, eyes and kidneys. Cu accumulation in the eye can cause Kayser-Fleischer rings. Abnormalities in liver function tests can be recognized by an increase in urinary Cu output of more than 500 µg Cu/L (>8 µmol/L). The diagnosis may be difficult in Wilson's disease patients presenting with acute liver failure.[16,17] Rapid diagnosis is important as urgent liver transplantation may be required.[18] In these cases, elevated plasma Cu levels may be seen when ceruloplasmin is not high. The unbound plasma Cu fraction may increase to more than 80% of total plasma Cu (normal, 5% to 10%). Due to excessive release of Cu from necrotic liver, intravascular hemolysis and renal failure may develop.[1,19]

TEST PRINCIPLE

Colorimetric method

3,5-Di-Br-PAESA [4-(3,5-dibromo-2-pyridylazo)-N-ethyl-N-(3-sulfopropyl)aniline] interacts with copper to form a blue-violet complex and the absorbance value measured at a wavelength of 580 nm is directly proportional to the Cu concentration in the sample.

Annotation:

- A reference method for copper has not been published. In the absence of a reference method, flame atomic absorption spectrophotometry (FAAS) is the method of choice when the concentration is 1.5 µmol/L (96 µg/L) or higher. Flameless or electrothermal atomic absorption spectrophotometry (EAAS) is more sensitive than FAAS and has a detection limit of approximately 30 nmol/L (2 µg/L). However, EAAS is more sensitive to contamination. The test time is longer in EAAS, typically in minutes in EAAS compared to seconds per sample in flame methods.[2]

REAGENT COMPONENTS

Acetate buffer : ≤ 120 mmol/L
Surfactant
Preservatives

REAGENT PREPARATION

Reagent is ready for use.

REAGENT STABILITY AND STORAGE

Reagents are stable at +15/+25°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.[20]

SAMPLE REQUIREMENTS

Serum and plasma can be used and are collected according to the standard procedures. For plasma, sample collection tubes with Li heparin or Na heparin should be preferred. Multiple sample freezing and thawing should be avoided. The sample should be homogenized before testing.

Copper activity stability in serum and plasma[39,40]:

2 weeks at +20/+25ºC
2 weeks at +2/+8ºC
1 year at -20°C

Annotation:

- If possible, the first 5 mL of blood should be discarded or used for tests other than elemental analysis (e.g. general biochemistry). The use of sterile vacutainers suitable for trace elements is recommended. Although plasma can be used for analysis, heparin used as an anticoagulant may be contaminated with copper.[2]
- Trace metal-free tubes for pediatric samples are not currently available. To avoid the possibility of contamination, pediatric samples should be collected in anticoagulant-free tubes and centrifuged immediately after clotting to obtain a serum fraction. Capillary blood sampling is also more prone to contamination and should be avoided as much as possible.[2]
- Transferring serum or plasma to secondary tubes is another possible source of contamination. If transferring, trace metal-free tubes or polystyrene tubes can be suitable.[2]
- It is recommended not to use colored caps or caps with ring seals to avoid the possibility of contamination.[2] It is also advisable to check each new batch of primary/secondary collection tubes for contamination using water/ dilute acid/serum/plasma as the matrix.[21]

Contamination

As methods have become increasingly sensitive, allowing measurements in small volumes and down to trace (ppm/ppb)/ultratrace (ppb/ppt) quantities, the importance of contamination during the analytical process has increased. Contamination can originate from the

environment, reagents, apparatus (urine containers, blood tubes, etc.) and even the operator:

- Environmental pollution may be due to the presence of particulate/gaseous matter in the air, which may originate from laboratory vents and/or air conditioning units (especially when associated with inefficient filtration), but may also result from the slow degradation of solid objects, paints, cements or other building materials, plastics or chemical treatments on materials.[2] It is estimated that the air in the analytical laboratory may contain as much as 200 µg/m3 of particulate matter, including copper.[32]
- Although an expensive way to ensure a clean laboratory environment, the air entering the room can be cleaned with HEPA (high efficiency particulate air) filtration, which is capable of removing the vast majority of particulate material (>99.9% of particles 0.3 µm or larger). In addition, the room can be kept at positive pressure so that the airflow is only in one direction (i.e. out of the laboratory).[2]
- The risk of contamination can be minimized by good filtration of the air vents/air conditioning unit and regular cleaning of walls, equipment and floors with deionized water/detergent (and lint-free towels or dust-absorbing cleaning tools).[2]
- Deionized/double distilled water should be used for elemental analysis. However, it is important to remember that the cause of contamination is usually contaminants in the atmosphere and/or laboratory equipment rather than impurities in the water.[2]
- Careless manipulation of equipment or laboratory supplies (e.g. using bare hands) can cause contamination from dried or dead skin, sweat, and so on. The use of hand lotions or creams can also be a potential contaminant.[2]
- Touching a dirty or metallic surface with or without gloves can be another source of contamination. Wearing jewelry in the laboratory should also be avoided, as jewelry can contribute to contamination if it comes into contact with laboratory equipment or a sample.
  The analyst should also wear a lint-free lab coat and powder-free gloves when performing all analytical procedures.[2]

CALIBRATION AND QUALITY CONTROL

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

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

Copper Calibrator-Liquid
Ref.No: ZA77

Calibration stability is 7 days. Calibration stability depends on the application characteristics and cooling capacity of the autoanalyzer used.

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

Men	: 70 - 140 µg/dL
Women	: 80 - 155 µg/dL
Pregnant Women	: 118 - 302 µg/dL
Children	: 80 - 190 µg/dL
Newborn	: 20 - 70 µg/dL

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.[22]

Unit Conversion:
µmol/L= 0.157 µg/dL

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).[23]

The determined analytic measuring interval for Copper is 3 – 500 µg/dL.

Detection Capability

Limit of Detection (LoD): 2 µg/dL

Limit of Quantitation (LoQ): 3 µg/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.[24]

Linearity

This method shows measurement linearity in the activities up to 500 µg/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.[25]

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.[26]

Repeatability (Within Run) and Repeatability (Day to Day) SD (standard deviation) and CV% values of Copper have been given in the table 1 and 2 respectively.

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

Mean Concentration	SD	CV%	n
47 µg/dL	1.08	2.30	80
104 µg/dL	1.31	1.26	80

Note: This working system has been named "Within-Run Precision" in the previous CLSI - EP05-A2 manual.[27]

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

Mean Concentration	SD	CV%	n
47 µg/dL	1.31	2.78	80
104 µg/dL	3.21	3.30	80

Note: This working system has been named "Total Precision" in the previous CLSI - EP05-A2 manual.[27]

Method Comparison

As a result of the statistical evaluation of the method comparison data:
Passing-Bablock equation:[28]
y= 1.046x – 6.67 µg/dL
r=0.984

Interference

Endogenous interferant and analyte concentrations that have been used in the Copper scanning tests has been determined according to "CLSI EP37-ED1:2018" and "CLSI EP07-ED3:2018" manuals.[29,30]

The total acceptable error rate, which is going to be used to detect whether the observed differential value obtained from Copper interference scanning test is appropriate, is determined as ±25%.[31]

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

Interferant-Concentration	Copper Target (µg/dL)	N*	Observed Recovery %
Bilirubin 48 mg/dL	104	3	110
Lipemia 204 mg/dL	114	3	105

** 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).*[30]

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.[30]

Annotation:

- Non-hemolyzed and non-lipemic samples should be used.

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.
Contains sodium azide.

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.

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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

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