UREAL

Urea/BUN

Materials provided

REF		CONTENT	Analyzer(s) on which cobas c pack(s) can be used
08058806190*	08058806500	Urea/BUN (600 tests)	**cobas** c 303, **cobas** c 503, **cobas** c 703
08058806214*	08058806500	Urea/BUN (600 tests)	**cobas** c 303, **cobas** c 503, **cobas** c 703

* Some kits shown may not be available in all countries.

For reagents, refer to the "Reagents" section.

Materials required (but not provided)

REF	Description	Code
10759350190	Calibrator f.a.s. (12 × 3 mL)	20401
05117003190	PreciControl ClinChem Multi 1 (20 × 5 mL)	20391
05947626190	PreciControl ClinChem Multi 1 (4 × 5 mL)	20391
05117216190	PreciControl ClinChem Multi 2 (20 × 5 mL)	20392
05947774190	PreciControl ClinChem Multi 2 (4 × 5 mL)	20392
08063494190	Diluent NaCl 9 % (123 mL)	System-ID 2906 001
	General laboratory equipment	

System information

Short name	ACN (application code number)	Description
UREAL	21191	Serum/plasma
URELU	21190	Urine
U-BUN	21192	Serum/plasma
UBUNU	21193	Urine

Intended use

In vitro test for the quantitative determination of urea/urea nitrogen in human serum, plasma and urine on **cobas** c systems.

Summary

Measurements of urea/urea nitrogen in human serum, plasma and urine, performed with this assay, are used as screening tests and as an aid in diagnosis and monitoring of renal function.

Urea is the major end product of protein nitrogen metabolism. It is synthesized by the urea cycle in the liver from ammonia which is produced by amino acid deamination. Urea is excreted mostly by the kidneys but minimal amounts are also excreted in sweat and degraded in the intestines by bacterial action.[1]

Serum urea mass concentration is either specified for the complete urea molecule or for nitrogen equivalents [blood urea nitrogen (BUN)].[2] Determination of blood urea nitrogen is primarily used as a screening test for renal function. When used in conjunction with serum creatinine determinations it can aid in the differential diagnosis of the three types of azotemia: prerenal, renal, and postrenal. The urea to creatinine ratio has been proposed as a crude discriminator between prerenal and intrinsic azotemia.[1]

Elevations in blood urea nitrogen concentration are seen in inadequate renal perfusion, shock, diminished blood volume (prerenal causes), chronic nephritis, nephrosclerosis, tubular necrosis, glomerular-nephritis (renal causes), and urinary tract obstruction (postrenal causes). Transient elevations may also be seen during periods of high protein intake. Liver diseases may lead to unpredictable blood urea nitrogen concentrations, including abnormally low levels. Low blood urea nitrogen concentrations are not common, but can be found in cases such as malnutrition, lack of protein in the diet, or overhydration.[1,3]

Test principle

Kinetic test with urease and glutamate dehydrogenase.[4,5,6,7]

Urea is hydrolyzed by urease to form ammonium and carbonate.

$$\text{Urea} + 2\ H_2O \xrightarrow{\text{Urease}} 2\ NH_4^+ + CO_3^{2-}$$

In the second reaction 2-oxoglutarate reacts with ammonium in the presence of glutamate dehydrogenase (GLDH) and the coenzyme NADH to produce L-glutamate. In this reaction two moles of NADH are oxidized to NAD^+ for each mole of urea hydrolyzed.

$$NH_4^+ + \text{2-oxoglutarate} + \text{NADH} \xrightarrow{\text{GLDH}} \text{L-glutamate} + NAD^+ + H_2O$$

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The rate of decrease in the NADH concentration is directly proportional to the urea concentration in the specimen and is measured photometrically.

Reagents

R1	NaCl 9 %
R3	TRIS buffer: 220 mmol/L, pH 8.6; 2-oxoglutarate: 73 mmol/L; NADH: 2.5 mmol/L; ADP: 6.5 mmol/L; urease (jack bean): ≥ 300 µkat/L; GLDH (bovine liver): ≥ 80 µkat/L; preservative; nonreactive stabilizers

R1 is in position B and R3 is in position C.

Warnings and precautions

For in vitro diagnostic use for laboratory professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste

Warning: Handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards

Apply all relevant local disposal regulations to determine safe disposal.

The Safety Data Sheet is available for professional users on request.

Storage and stability

Shelf life at 2-8 °C	See expiration date on **cobas** c pack label.
On-board in use and refrigerated on the analyzer	8 weeks

Calibration

Application for serum/plasma (ACN 21191/21192)

Calibrators	S1: H_2O
	S2: C.f.a.s.
Calibration mode	Linear
Calibration frequency	Full calibration • after reagent lot change • every 4 weeks on-board • as required following quality control procedures

Application for urine (ACN 21190/21193)

Transfer of calibration from serum/plasma application (ACN 21191/21192)

The calibration interval may be extended based on acceptable calibration verification values determined by the laboratory.

Traceability: This method has been standardized against ID/MS.

Quality control

For quality control, use the control materials listed in the “Materials required (but not provided)” section or other suitable control material.

Serum/plasma:	PreciControl ClinChem Multi 1, PreciControl ClinChem Multi 2
Urine:	Quantitative urine controls are recommended for routine quality control.

Adjust the limits and control intervals based on the laboratory’s individual requirements. It is recommended to perform quality control after each lot calibration and, after that, at least every 8 weeks. If values fall outside the limits, each laboratory is advised to establish corrective measures.

Follow the applicable government regulations and local guidelines.

Specimen collection and preparation

For specimen collection and preparation, only use suitable tubes or collection containers.

Only the specimens listed below were tested and found acceptable.

Serum

Plasma: Li-heparin and K2 EDTA plasma. Do not use ammonium heparin.

Specimens derived from capillary blood were found acceptable.[8]

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing. Sample collection systems from various manufacturers may contain differing materials, which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

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Urea/BUN

Urine

Bacterial growth in the specimen and high atmospheric ammonia concentrations as well as contamination by ammonium ions may cause erroneously elevated results. If stabilizers are added to the sample, the sample index feature must not be used.

Stability in *serum/plasma*:[9]	7 days at 15-25 °C
	7 days at 2-8 °C
	1 year at (-15)-(-25) °C

Freeze only once.

Stability in *urine*:[9]	2 days at 15-25 °C
	7 days at 2-8 °C
	1 month at (-15)-(-25) °C

Freeze only once.

Centrifuge samples containing precipitates before performing the assay.

Refer to the "Limitations and interferences" section for details on possible sample interferences.

Test procedure

The product is ready for use.

For optimum performance of the assay, follow the instructions given in this document for the corresponding analyzer. For analyzer-specific assay instructions, refer to the corresponding User Guide.

The performance of applications not validated by Roche is not warranted and must be defined by the user.

Application for serum and plasma

Test definition			
Reporting time	10 min		
Wavelength (sub/main)	700/340 nm		
Reagent pipetting		Diluent (H_2O)	
R1	8 µL	66 µL	
R3	28 µL	81 µL	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	1.5 µL	–	–
Decreased	1.5 µL	25 µL	50 µL
Increased	1.5 µL	–	–

Application for urine

Test definition			
Reporting time	10 min		
Wavelength (sub/main)	700/340 nm		
Reagent pipetting		Diluent (H_2O)	
R1	8 µL	66 µL	
R3	28 µL	81 µL	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	1.5 µL	2.0 µL	98 µL
Decreased	1.5 µL	1.3 µL	116 µL
Increased	1.5 µL	–	–

For further information on the assay test definitions, refer to the application-parameters setting screen of the corresponding analyzer and of the corresponding assay.

Calculation

cobas c systems automatically calculate the analyte concentration of each sample in the unit mmol/L (mg/dL, g/L).

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Conversion factors:	mmol/L urea × 6.006 = mg/dL urea
	mmol/L urea × 0.06006 = g/L urea
	mmol/L urea nitrogen × 2.801 = mg/dL urea nitrogen
	mmol/L urea nitrogen × 0.02801 = g/L urea nitrogen
	mg/dL urea × 0.467 = mg/dL urea nitrogen

When 24-hour urine is used as the specimen, multiply the result by the 24-hour volume to obtain values in g or mmol/24 hours.

Limitations and interferences

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[10]

Serum/plasma

Criterion: recovery within ± 0.83 mmol/L of initial values for samples ≤ 8.3 mmol/L and within ± 10 % for samples > 8.3 mmol/L.

Icterus:[11] no significant interference up to an I index of 60 for conjugated and unconjugated bilirubin (approximate conjugated and unconjugated bilirubin concentration: 1026 µmol/L or 60 mg/dL).

Hemolysis:[11] no significant interference up to an H index of 1000 (approximate hemoglobin concentration: 621 µmol/L or 1000 mg/dL).

Lipemia (Intralipid):[11] no significant interference up to an L index of 1000. There is poor correlation between the L index (corresponds to turbidity) and the triglycerides concentration.

Ammonium ions may cause erroneously elevated results.

Drugs: No interference was found at therapeutic concentrations using common drug panels.[12,13]

Urine

Criterion: recovery within ± 15 mmol/L of initial values for samples ≤ 150 mmol/L and within ± 10 % for samples > 150 mmol/L.

Hemolysis: no significant interference up to an H index of 750 (approximate hemoglobin concentration: 466 µmol/L or 750 mg/dL).

Drugs: No interference was found at therapeutic concentrations using common drug panels.[13]

For diagnostic purposes, always assess the results in conjunction with the patient's medical history, clinical examination, and other findings.

Action required

Special wash programming: The use of special wash steps is mandatory when certain test combinations are run together on **cobas** c systems. All special wash programming necessary for avoiding carryover is available via **cobas** link. The latest version of the carryover evasion list can be found with the NaOHD - SMS - SCCS Method Sheet. For further instructions, refer to the User Guide.

Limits and ranges

Measuring range

Serum/plasma

0.5-40 mmol/L (3.0-240 mg/dL urea, 1.4-112 mg/dL urea nitrogen)

Determine samples that have higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:3 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 3.

Urine

1-2000 mmol/L (6-12000 mg/dL urea, 2.8-5600 mg/dL urea nitrogen)

Determine samples that have higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:1.8 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 1.8.

Determine samples having concentrations lower than the technical limit of 40 mmol/L (240 mg/dL urea and 112 mg/dL urea nitrogen) via the rerun function. Samples are measured undiluted.

Lower limits of measurement

Limit of Blank, Limit of Detection, and Limit of Quantitation

Serum/plasma

Limit of Blank = 0.5 mmol/L

Limit of Detection = 0.5 mmol/L

Limit of Quantitation = 0.5 mmol/L

Urine

Limit of Blank = 1.0 mmol/L

UREAL

Urea/BUN

Limit of Detection = 1.0 mmol/L

Limit of Quantitation = 1.0 mmol/L

The Limit of Blank, the Limit of Detection, and the Limit of Quantitation were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A2 requirements.

The Limit of Blank is the 95th-percentile value from n ≥ 60 measurements of analyte-free samples over several independent series. The Limit of Blank corresponds to the concentration below which analyte-free samples are found with a probability of 95 %.

The Limit of Detection is determined based on the Limit of Blank and the standard deviation of low-concentration samples.

The Limit of Detection corresponds to the lowest analyte concentration that can be detected (value above the Limit of Blank with a probability of 95 %).

The Limit of Quantitation is the lowest analyte concentration that can be reproducibly measured with a total error of 20 %. The Limit of Quantitation has been determined using low-concentration urea/urea nitrogen samples.

Expected values

mmol/L

Urea

Serum/plasma[14]

Adults	2.76-8.07 mmol/L

Urine

24-hour urine[15]	428-714 mmol/24 h, corresponding to 286-595 mmol/L[A)]

A) Based on average urine output of 1.2-1.5 L/24 h

Urea nitrogen (BUN):

Serum/plasma[15]

Adults (18-60 years)	2.14-7.14 mmol/L
Adults (60-90 years)	2.86-8.21 mmol/L
Infants (< 1 year)	1.43-6.78 mmol/L
Infants/children	1.79-6.43 mmol/L

Urine

24-hour urine[15]	428-714 mmol/24 h, corresponding to 286-595 mmol/L[A)]

A) Based on average urine output of 1.2-1.5 L/24 h

mg/dL

Urea

Serum/plasma[14]

Adults	16.6-48.5 mg/dL

Urine

24-hour urine[15]	25.7-42.9 g/24 h, 1.71-3.57 g/dL[A)]

A) Based on average urine output of 1.2-1.5 L/24 h

Urea nitrogen (BUN):

Serum/plasma[15]

Adults (18-60 years)	6-20 mg/dL
Adults (60-90 years)	8-23 mg/dL
Infants (< 1 year)	4-19 mg/dL
Infants/children	5-18 mg/dL

Urine

UREAL

Urea/BUN

24-hour urine[15]	12-20 g/24 h, corresponding to 801-1666 mg/dL[A)]

A) Based on average urine output of 1.2-1.5 L/24 h

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

Specific performance data

Representative performance data on the analyzers are given below. These data represent the performance of the analytical procedure itself.

Results obtained in individual laboratories may differ from the representative performance data due to heterogeneous sample materials, aging of analyzer components, and mixture of reagents running on the analyzer.

Precision

Precision was determined using human samples and controls in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP05-A3 requirements, with repeatability (n = 84) and intermediate precision (2 aliquots per run, 2 runs per day, 21 days). Results for repeatability and intermediate precision were obtained on the **cobas** c 503 analyzer.

Serum/plasma

Repeatability	Mean mmol/L	SD mmol/L	CV %
PCCC1[A)]	6.53	0.0408	0.6
PCCC2[B)]	18.3	0.0690	0.4
Human serum 1	1.31	0.0416	3.2
Human serum 2	5.12	0.0441	0.9
Human serum 3	7.67	0.0451	0.6
Human serum 4	18.7	0.101	0.5
Human serum 5	31.0	0.124	0.4

A) PreciControl ClinChem Multi 1

B) PreciControl ClinChem Multi 2

Intermediate precision	Mean mmol/L	SD mmol/L	CV %
PCCC1[A)]	6.50	0.0745	1.1
PCCC2[B)]	18.4	0.198	1.1
Human serum 1	1.31	0.0459	3.5
Human serum 2	5.12	0.0659	1.3
Human serum 3	7.67	0.0931	1.2
Human serum 4	18.7	0.226	1.2
Human serum 5	31.0	0.350	1.1

A) PreciControl ClinChem Multi 1

B) PreciControl ClinChem Multi 2

Urine

Repeatability	Mean mmol/L	SD mmol/L	CV %
Control 1[A)]	143	2.86	2.0
Control 2[A)]	239	3.68	1.5
Human urine 1	3.22	0.0435	1.4
Human urine 2	73.2	2.50	3.4
Human urine 3	407	3.28	0.8
Human urine 4	922	5.03	0.5
Human urine 5	1583	10.1	0.6

A) commercially available control material

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Urea/BUN

Intermediate precision	Mean mmol/L	SD mmol/L	CV %
Control 1[A)]	143	3.17	2.2
Control 2[A)]	239	4.32	1.8
Human urine 1	3.22	0.0547	1.7
Human urine 2	73.2	2.78	3.8
Human urine 3	411	4.93	1.2
Human urine 4	919	11.5	1.2
Human urine 5	1583	19.7	1.2

A) commercially available control material

The data obtained on the **cobas** c 503 analyzer are representative for the **cobas** c 303 analyzer and the **cobas** c 703 analyzer.

Method comparison

Urea values for human serum, plasma and urine samples obtained on a **cobas** c 503 analyzer (y) were compared with values determined on **cobas** c 501 analyzer (x), using the corresponding reagent.

Serum/plasma

Sample size (n) = 94

Passing/Bablok[16]	Linear regression
y = 1.009x + 0.0202 mmol/L	y = 1.006x + 0.0265 mmol/L
τ = 0.986	r = 1.000

The sample concentrations were between 0.600 and 38.1 mmol/L.

Urine

Sample size (n) = 91

Passing/Bablok[16]	Linear regression
y = 0.962x – 0.432 mmol/L	y = 0.960x + 0.586 mmol/L
τ = 0.982	r = 1.000

The sample concentrations were between 71.0 and 1964 mmol/L.

Urea values for human serum, plasma and urine samples obtained on a **cobas** c 303 analyzer (y) were compared with values determined on **cobas** c 501 analyzer (x), using the corresponding reagent.

Serum/plasma

Sample size (n) = 89

Passing/Bablok[16]	Linear regression
y = 1.017x + 0.0905 mmol/L	y = 1.015x + 0.148 mmol/L
τ = 0.986	r = 1.000

The sample concentrations were between 0.700 and 35.4 mmol/L.

Urine

Sample size (n) = 73

Passing/Bablok[16]	Linear regression
y = 0.981x + 0.901 mmol/L	y = 0.973x + 4.74 mmol/L
τ = 0.960	r = 0.999

The sample concentrations were between 41.0 and 1875 mmol/L.

Urea values for human serum, plasma and urine samples obtained on a **cobas** c 703 analyzer (y) were compared with values determined on **cobas** c 503 analyzer (x), using the corresponding reagent.

Serum/plasma

Sample size (n) = 74

Passing/Bablok[16]	Linear regression
y = 1.000x + 0.0800 mmol/L	y = 1.000x + 0.0683 mmol/L
τ = 0.983	r = 1.000

The sample concentrations were between 0.821 and 39.5 mmol/L.

Urine

Sample size (n) = 74

Passing/Bablok[16]	Linear regression
y = 0.948x – 1.68 mmol/L	y = 0.942x + 0.489 mmol/L
τ = 0.980	r = 1.000

The sample concentrations were between 46.4 and 1912 mmol/L.

Additional information

Additions, deletions, or changes are indicated by a change bar in the margin.

A point (period/stop) is always used in the English version of a Method Sheet as the decimal separator to mark the boundary between the integral and the fractional parts of a decimal numeral. The translated Method Sheets use decimal commas. Labels only use the decimal point as separator. Separators for thousands are not used.

Report any serious incident that has occurred in relation to the device to the manufacturer and the competent authority of the member state in which the user and/or patient is established.

Symbols

In addition to the ISO 15223-1 standard, Roche Diagnostics uses the following symbols and signs:

CONTENT	Contents of kit
→	Volume for reconstitution
GTIN	Global Trade Item Number
Rx only	For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

References

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CE 0123

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Change log

For this document version only:

Due to technical reasons, changes that have been made since the last version of this document are listed in the following table instead of indicated by change bars in the margin.

Section headers are indicated in bold letters.

In addition to the changes listed in the table below, this method sheet version contains several editorial and layout updates.

Section	Current version	Previous version
Materials provided	**Materials provided**	**Order information** **Materials provided**
Materials provided	**Materials provided** without System-ID	**Order information** with System-ID
Materials required (but not provided)	**Materials required (but not provided)**	**Order information** **Materials required (but not provided)**
Reagents	**Reagents**	**Reagents - working solutions**
Warnings and precautions	**Warnings and precautions**	**Precautions and warnings**
Specimen collection and preparation	Specimens derived from capillary blood were found acceptable. [Collier BB et al.]	
Test procedure	**Test procedure**	**Reagent handling** **Assay**
Limitations and interferences	**Limitations and interferences**	**Limitations - interference**
Additional information	**Additional information**	
Additional information	A point (period/stop) is always used in the English version of a Method Sheet as the decimal separator to mark the boundary between the integral and the fractional parts of a decimal numeral. The translated Method Sheets use decimal commas. Labels only use the decimal point as separator. Separators for thousands are not used.	A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.
References	Collier BB, Brandon WC, Chappell MR, et al. Maximizing Microsampling: Measurement of Comprehesnive Metabolic and Lipid Panels Using a Novel Capillary Blood Collection Device. JALM 2023 Nov;8(6):1115-1126.	