03289923500V15.0

CO2-L

cobas®

Bicarbonate Liquid

Order information

REF		CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
03289923190	03289923500	Bicarbonate Liquid (250 tests)	System-ID 07 6725 5	**cobas c** 311, **cobas c** 501/502 COBAS INTEGRA 400 plus

Materials required (but not provided):

		cobas c 311, **cobas c** 501/502	COBAS INTEGRA 400 plus
20751995190	Ammonia/Ethanol/CO2 Calibrator (2 x 4 mL)	Code 688	System-ID 07 5199 5
20752401190	Ammonia/Ethanol/CO2 Control Normal (5 x 4 mL)	Code 100	System-ID 07 5240 1
20753009190	Ammonia/Ethanol/CO2 Control Abnormal (5 x 4 mL)	Code 101	System-ID 07 5300 9
12149435122	Precinorm U plus (10 x 3 mL)	Code 300	System-ID 07 7999 7
12149443122	Precipath U plus (10 x 3 mL)	Code 301	System-ID 07 8000 6

English

Intended use

In vitro test for the quantitative determination of bicarbonate (HCO_3^-) in human serum and plasma on **cobas c** and COBAS INTEGRA systems.

Summary

Bicarbonate measurements, performed with this assay in human serum and plasma are used, in combination with pH determination, as an aid in the diagnosis and management of respiratory and metabolic acid-base disorders.

For the regulation of the blood acid/base balance, there are three major buffer systems: the bicarbonate, phosphate, and plasma protein buffer system. The bicarbonate buffer is of major relevance, because being coupled to the respiratory system. Bicarbonate is the second largest fraction of anions in plasma after chloride.[1] In addition to bicarbonate ion (HCO_3^-), the anionic fraction of the bicarbonate buffer system also includes the carbonate ion (CO_3^{2-}), and CO_2 carried as carbamino compounds with plasma proteins, such as hemoglobin. At the physiological pH of blood, the concentration of carbonate is only 1/1000 that of bicarbonate, and the carbamino compounds are present in only low quantities, so that both fractions are generally not mentioned specifically in clinical routine acid/base analysis. Because the dissolved CO_2 fraction (pCO_2; depending on the partial pressure), and carbonate fractions (H_2CO_3) are rather low, the terms bicarbonate and total carbon dioxide are often used interchangeably in clinical chemistry practice.[1] The equilibrium between HCO_3^- with H_2CO_3 thus acts as a buffer pair to minimize changes in blood hydrogen ion (H^+) concentration and thus the pH value. An increase in blood H^+ concentration (i.e., a decrease in blood pH) results in the reduction of plasma bicarbonate levels, whereas a decrease in blood H^+ concentration (increase in blood pH) causes an increase in plasma bicarbonate levels.[2] The interplay between the kidneys and respiratory system ensures the regulation of blood bicarbonate levels and helps maintain the body's acid-base balance.[1,2] The kidneys eliminate acids in the urine and regulate the concentration of bicarbonate in blood.[3] The respiratory system contributes to the regulation of blood bicarbonate levels through expiration and the control of CO_2 levels. When CO_2 levels rise, such as during increased metabolism or exercise, the respiratory system increases the rate and depth of breathing to eliminate excess CO_2.

Clinical conditions characterized by primary disturbances in bicarbonate ion concentrations are classified as metabolic disturbances of acid-base balance, while those characterized by primary disturbances in pCO_2 are classified as respiratory disturbances.[1] Acid-base disorders that are respiratory in nature arise as a result of abnormal CO_2 removal by the lungs, whereas metabolic disorders are caused by aberrant regulation of bicarbonate.[2,3] Disorders that cause an increase of bicarbonate ions (reduction of H^+) or decrease of bicarbonate ions (increase of H^+) are termed alkalosis and acidosis, respectively. Consequently, acid-base disturbances are traditionally classified by their cause as metabolic acidosis, metabolic alkalosis, respiratory acidosis, or respiratory alkalosis.[1]

Low bicarbonate levels have been associated with conditions such as renal diseases, diabetic ketoacidosis, severe diarrhea, and certain drug toxicities. High bicarbonate levels can occur in conditions like prolonged vomiting, certain kidney disorders, and certain diuretic use.[1,2] When CO_2 is abnormally retained by the lungs, e.g. in chronic obstructive pulmonary disease, the kidneys increase the production and reabsorption of bicarbonates to compensate for the respiratory acidosis caused by CO_2 retention. This helps in stabilizing the pH level in the blood.[1] Monitoring the bicarbonate levels in serum or plasma can thus provide valuable information about the body's acid-base status and helps in the diagnosis and management of these imbalances.[4,5]

Several different methods for the determination of bicarbonate in serum and plasma have been reported. Most of these procedures utilize acidification of the sample and conversion of all carbon dioxide forms to CO_2 gas.[1] The amount of gas formed is measured by manometric or volumetric devices, ion selective electrodes, or spectrophotometric techniques.[6,7] These methods are often cumbersome, time-consuming, technique-oriented, and/or require special equipment. Enzymatic procedures using phosphoenolpyruvate carboxylase (PEPC) have been described.[8,9]

Test principle

Bicarbonate reacts with phosphoenolpyruvate (PEP) in the presence of PEPC to produce oxaloacetate and phosphate:

$$PEP + HCO_3^- \xrightarrow{PEPC} \text{oxaloacetate} + H_2PO_4^-$$

The above reaction is coupled with one involving the transfer of a hydrogen ion from NADH analog to oxaloacetate using MDH.

$$\text{Oxaloacetate} + \text{NADH analog} + H^+ \xrightarrow{MDH} \text{malate} + NAD^+ \text{ analog}$$

The resultant consumption of NADH analog causes a decrease in absorbance, which is proportional to the concentration of bicarbonate in the sample being assayed.

Precautions and warnings

For in vitro diagnostic use for health care 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 the safe disposal.

Safety data sheet available for professional user on request.

Reagent handling

Ready for use

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 plasma

The preferred specimen is from venous blood collected anaerobically in the usual manner for bicarbonate analysis. Bicarbonate content in uncapped tubes decreases approximately 4 mmol/L after one hour.[10] It has been reported that alkalinized serum stored in open cups is stable for up to 4 hours.[10]

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all

available tubes of all manufacturers were tested. 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.

Centrifuge samples containing precipitates before performing the assay.

Separate from erythrocytes and store tightly stoppered.

See the limitations and interferences section for details about possible sample interferences.

Stability:	7 days at 4-8 °C[11]
	40 hours at 15-25 °C[12,13]
	Storage of serum at -20 °C or -80 °C for up to 6 months had no significant effect.[14]

Freeze only once.

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

See "Order information" section

General laboratory equipment

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

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

Calculation

The systems automatically calculate the analyte concentration of each sample.

Conversion factor: mmol/L x 1 = mEq/L[11]

Expected values[15]

22-29 mmol/L

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

cobas c systems

System information

For **cobas c** 311/501 analyzers:

CO2-L: ACN 156

SCO2L: ACN 763 (STAT, reaction time: 5) (for **cobas c** 501 analyzer)

SCO2L: ACN 763 (STAT, reaction time: 4) (for **cobas c** 311 analyzer)

For **cobas c** 502 analyzer:

CO2-L: ACN 8156

SCO2L: ACN 8763 (STAT, reaction time: 5)

Reagents - working solutions

R1 Phosphoenolpyruvate: ≥ 40 mmol/L; NADH analog: ≥ 2 mmol/L; MDH (porcine): ≥ 314.3 µkat/L; PEPC (microbial): ≥ 30.8 µkat/L

R1 is in position B.

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:	6 weeks

Application for serum and plasma

cobas c 311 **test definition**

Assay type	2-Point Rate		
Reaction time / Assay points	10 / 2-18 (STAT 4 / 2-18)		
Wavelength (sub/main)	505/415 nm		
Reaction direction	Decrease		
Unit	mmol/L		
Reagent pipetting		Diluent (H_2O)	
R1	50 µL	130 µL	
R2	–	–	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	Diluent (H_2O)
Normal	2 µL	–	–
Decreased	2 µL	–	–
Increased	2 µL	–	–

cobas c 501 **test definition**

Assay type	2-Point Rate		
Reaction time / Assay points	10 / 4-29 (STAT 5 / 4-29)		
Wavelength (sub/main)	505/415 nm		
Reaction direction	Decrease		
Unit	mmol/L		
Reagent pipetting		Diluent (H_2O)	
R1	50 µL	130 µL	
R2	–	–	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	Diluent (H_2O)
Normal	2 µL	–	–
Decreased	2 µL	–	–
Increased	2 µL	–	–

cobas c 502 **test definition**

Assay type	2-Point Rate		
Reaction time / Assay points	10 / 4-29 (STAT 5 / 4-29)		
Wavelength (sub/main)	505/415 nm		
Reaction direction	Decrease		
Unit	mmol/L		
Reagent pipetting		Diluent (H_2O)	
R1	50 µL	130 µL	
R2	–	–	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	Diluent (H_2O)
Normal	2 µL	–	–
Decreased	2 µL	–	–
Increased	4 µL	–	–

Calibration

Calibrators	S1: H_2O S2: Ammonia/Ethanol /CO_2 Calibrator
Calibration mode	Linear

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Calibration frequency	2-point calibration - after reagent lot change - as required following quality control procedures

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Traceability: This method has been standardized against a primary standard traceable to NIST.

Quality control

For quality control, use control materials as listed in the "Order information" section. In addition, other suitable control material can be used.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

Follow the applicable government regulations and local guidelines for quality control.

Limitations – interference

Criterion: Recovery within ± 2.2 mmol/L of initial values of samples ≤ 22 mmol/L and within ± 10 % for samples > 22 mmol/L.

Icterus:[16] 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:[16] No significant interference up to an H index of 600 (approximate hemoglobin concentration: 372.6 µmol/L or 600 mg/dL).

Lipemia (Intralipid):[16] No significant interference up to an L index of 1800. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Immunoglobulins: No significant interference from immunoglobulins up to a concentration of 35 g/L (233.5 µmol/L) (simulated by human immunoglobulin G).

Drugs: No interference was found at therapeutic concentrations using common drug panels.[17,18]

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[19]

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

An abnormally elevated concentration of ambient carbon dioxide (CO_2) may occur under certain environmental conditions in the laboratory. The fluctuating ambient CO_2 concentration may interfere with the CO_2-L assay leading to higher CO_2 results. Under these circumstances, the reduction of the re-calibration interval may become necessary if the laboratory is unable to keep the ambient CO_2 concentration at a normal level by appropriate countermeasures.

ACTION REQUIRED

Special Wash Programming: The use of special wash steps is mandatory when certain test combinations are run together on **cobas c** systems. The latest version of the carry-over evasion list can be found with the NaOHD-SMS-SmpCln1+2-SCCS Method Sheets. For further instructions refer to the operator's manual. **cobas c** 502 analyzer: All special wash programming necessary for avoiding carry-over is available via the **cobas** link, manual input is required in certain cases.

Where required, special wash/carry-over evasion programming must be implemented prior to reporting results with this test.

Limits and ranges

Measuring range

2-50 mmol/L

Lower limits of measurement

Lower detection limit of the test:

2 mmol/L

The lower detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying 3 standard deviations above that of the lowest standard (standard 1 + 3 SD, repeatability, n = 21).

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using human samples and controls in an internal protocol with repeatability (n = 21) and intermediate precision (3 aliquots per run, 1 run per day, 21 days). The following results were obtained on the **cobas c** 501 analyzer:

Repeatability	*Mean mmol/L*	*SD mmol/L*	*CV %*
Ammonia/Ethanol/CO2 Control Normal	16.1	0.2	1.0
Ammonia/Ethanol/CO2 Control Abnormal	26.5	0.2	0.7
Human serum 1	16.0	0.1	0.8
Human serum 2	27.0	0.2	0.8
Intermediate precision	*Mean mmol/L*	*SD mmol/L*	*CV %*
Ammonia/Ethanol/CO2 Control Normal	17.6	0.2	1.3
Ammonia/Ethanol/CO2 Control Abnormal	30.5	0.4	1.4
Human serum 3	9.90	0.23	2.3
Human serum 4	26.3	0.3	1.3

The data obtained on **cobas c** 501 analyzer(s) are representative for **cobas c** 311 analyzer(s).

Method comparison

Bicarbonate values for human serum and plasma samples obtained on a **cobas c** 501 analyzer (y) were compared with those determined using the corresponding reagent on a Roche/Hitachi 917 analyzer (x).

Sample size (n) = 73

Passing/Bablok[20]	Linear regression
y = 1.017x - 0.053 mmol/L	y = 1.007x + 0.087 mmol/L
τ = 0.976	r = 0.998

The sample concentrations were between 2.54 and 49.9 mmol/L.

The data obtained on **cobas c** 501 analyzer(s) are representative for **cobas c** 311 analyzer(s).

COBAS INTEGRA systems

System information

CO2-L: Test ID 0-625

Reagents - working solutions

R	Phosphoenolpyruvate: ≥ 40 mmol/L; NADH analog: ≥ 2 mmol/L; MDH (porcine): ≥ 314.3 µkat/L; PEPC (microbial): ≥ 30.8 µkat/L

R is in position B.

Storage and stability

Shelf life at 2-8 °C	See expiration date on **cobas c** pack label
On-board in use at 10-15 °C	6 weeks

Application for serum and plasma

Test definition

Measuring mode	Absorbance
Abs. calculation mode	Endpoint
Reaction mode	R-S
Reaction direction	Decrease
Wavelength A/B	409/512 nm
Calc. first/last	21/45
Unit	mmol/L

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Pipetting parameters

		Diluent (H_2O)
R	50 µL	120 µL
Sample	2 µL	10 µL
Total volume	182 µL	

Calibration

Calibrator	Roche Ammonia/Ethanol/CO_2 Calibrator
	Use deionized water as zero calibrator
Calibration mode	Linear regression
Calibration replicate	Duplicate recommended
Calibration interval	Each lot and as required following quality control procedures

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Traceability: This method has been standardized against a primary standard traceable to NIST.

Quality control

Reference range	Roche Ammonia/Ethanol/CO_2 Control Normal or Precinorm U plus
Pathological range	Roche Ammonia/Ethanol/CO_2 Control Abnormal or Precipath U plus
Control interval	24 hours recommended
Control sequence	User defined
Control after calibration	Recommended

For quality control, use control materials as listed in the "Order information" section. In addition, other suitable control material can be used.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

Follow the applicable government regulations and local guidelines for quality control.

Limitations - interference

Criterion: Recovery within ± 2.2 mmol/L of initial values of samples ≤ 22 mmol/L and within ± 10 % for samples > 22 mmol/L.

Icterus:[16] 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:[16] No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 621 µmol/L or 1000 mg/dL).

Lipemia (Intralipid):[16] No significant interference up to an L index of 2000. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Drugs: No interference was found at therapeutic concentrations using common drug panels.[17,18]

Immunoglobulins: No significant interference from immunoglobulins up to a concentration of 35 g/L (233.5 µmol/L) (simulated by human immunoglobulin G).

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[19]

An abnormally elevated concentration of ambient carbon dioxide (CO_2) may occur under certain environmental conditions in the laboratory. The fluctuating ambient CO_2 concentration may interfere with the CO2-L assay leading to higher CO_2 results. Under these circumstances, the reduction of the re-calibration interval may become necessary if the laboratory is unable to keep the ambient CO_2 concentration at a normal level by appropriate countermeasures.

For diagnostic purposes, the results should always be assessed 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 INTEGRA analyzers. Refer to the CLEAN Method Sheet for further instructions and for the latest version of the Extra wash cycle list.
Where required, special wash/carry-over evasion programming must be implemented prior to reporting results with this test.

Limits and ranges

Measuring range

2.0-50 mmol/L (2.0-50 mEq/L)

Lower limits of measurement

Lower detection limit of the test:
2.0 mmol/L (2.0 mEq/L)

The lower detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying 3 standard deviations above that of the lowest standard (lowest standard + 3 SD, repeatability, n = 21).

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using human samples and controls in an internal protocol with repeatability (n = 21) and intermediate precision (3 aliquots per run, 1 run per day, 21 days). The following results were obtained on the COBAS INTEGRA 800 analyzer:

	Level 1	Level 2
Mean	19.7 mmol/L (19.7 mEq/L)	35.4 mmol/L (35.4 mEq/L)
CV repeatability	0.6 %	0.5 %

	Level 1	Level 2
Mean	16.8 mmol/L (16.8 mEq/L)	28.8 mmol/L (28.8 mEq/L)
CV intermediate precision	3.5 %	3.8 %

The data obtained on COBAS INTEGRA 800 are representative for COBAS INTEGRA 400 analyzer(s).

Method comparison

Bicarbonate values for human serum and plasma samples obtained on a COBAS INTEGRA 800 analyzer using the COBAS INTEGRA Bicarbonate liquid reagent (y) were compared with those determined using the COBAS INTEGRA Carbon Dioxide reagent (CO2-S) on a COBAS INTEGRA 800 analyzer (x) and using the Bicarbonate liquid assay on a Roche/Hitachi 917 analyzer (x).

COBAS INTEGRA 800 analyzer	Sample size (n) = 57
Passing/Bablok[20]	Linear regression
y = 0.981x + 0.176 mmol/L	y = 0.973x + 0.355 mmol/L
τ = 0.984	r = 1.000
SD (md 95) = 0.400	Sy.x = 0.195

The sample concentrations were between 1.13 and 46.2 mmol/L (1.13 and 46.2 mEq/L)

Roche/Hitachi 917 analyzer	Sample size (n) = 57
Passing/Bablok[20]	Linear regression
y = 1.010x + 0.128 mmol/L	y = 1.004x + 0.467 mmol/L
τ = 0.969	r = 0.998
SD (md 95) = 1.06	Sy.x = 0.434

The sample concentrations were between 1.1 and 44.3 mmol/L (1.1 and 44.3 mEq/L).

The data obtained on COBAS INTEGRA 800 are representative for COBAS INTEGRA 400 analyzer(s).

CO2-L

Bicarbonate Liquid

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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.

Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard:

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.

CE 0123

Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim
www.roche.com
+800 5505 6606

Roche