Total Bilirubin (TBIL) - Serum, Plasma, Fluids
Beckman UniCel DxC Systems

Technical Procedure 3155

Prepared By	Date Adopted	Supersedes Procedure #
Michael Inn	October, 2000	Reformatted

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			09/26/2006	G. Kost
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06/28/2011	Removed sample type Fluids	M.Inn	07/06/2011	G. Kost
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For *In Vitro* Diagnostic Use Only

Principle

Intended Use

TBIL reagent, when used in conjunction with UniCel® DxC 800 System(s) and SYNCHRON® Systems Bilirubin Calibrator, is intended for quantitative determination of total bilirubin concentration in human serum, plasma or fluids.

Clinical Significance

Bilirubin measurements are used in the diagnosis and treatment of liver, hemolytic, hematological, and metabolic disorders, including hepatitis and gall bladder block.

The most common occurrence in newborns is physiological jaundice. All newborns have serum unconjugated bilirubin concentrations greater than the values of the normal adult population. About 50% of the newborn population is clinically jaundiced during the first five days of life. In a normal full term neonate, total bilirubin can increase to 4–5 mg/dL, and in a small percentage of cases, to as high as 10 mg/dL by 48 hours, with a return to normal values by 7–10 days. In 5% of neonates, unconjugated bilirubin values of greater than 15.0 mg/dL are seen.

Methodology

TBIL reagent is used to measure the total bilirubin concentration by a timed endpoint Diazo method.(1,2,3) In the reaction, the bilirubin reacts with diazo reagent in the presence of caffeine, benzoate, and acetate as accelerators to form azobilirubin.

The SYNCHRON® System(s) automatically proportions the appropriate sample and reagent volumes into a cuvette. The ratio used is one part sample to 35 parts reagent. The system monitors the change in absorbance at 520 nm (nanometers). This change in absorbance is directly proportional to the concentration of TBIL in the sample and is used by the System to calculate and express TBIL concentration.

Chemical Reaction Scheme

$$\text{Total Bilirubin} + \text{Diazo} + H^{+} \xrightarrow{\text{Caffeine, Benzoate, Acetate}} \text{Azobilirun (blue color)}$$

Specimen

Acceptable Sample Containers

13 x 75 PST, SST and Red Top BD tubes
PST, SST and Red Top BD microtainers
Original specimen container or 13 x 75 Clear Cap BD tube (min = 0.3 mL) for fluids

Type of Specimen

Biological fluid samples should be collected in the same manner routinely used for any laboratory test.(4) Freshly drawn serum or plasma are the preferred specimens. Acceptable anticoagulants are listed in *Procedural Notes* section of this chemistry information sheet. Whole blood or urine are not recommended for use as a sample.

Specimen Storage and Stability

1. Tubes of blood are to be kept closed at all times and in a vertical position. It is recommended that the serum or plasma be physically separated from contact with cells within two hours from the time of collection.(5)
2. Separated serum or plasma should not remain at room temperature longer than 8 hours. If assays are not completed within 8 hours, serum or plasma should be stored at +2°C to +8°C. If assays are not completed within 48 hours, or the separated sample is to be stored beyond 48 hours, samples should be frozen at -15°C to -20°C. Frozen samples should be thawed only once. Analyte deterioration may occur in samples that are repeatedly frozen and thawed.(5)

3. **Bilirubin is photosensitive. Protect samples from light**.

Sample Volume

The optimum volume, when using a 0.5 mL sample cup, is 0.3 mL of sample. For optimum primary sample tube volumes and minimum volumes, refer to the *Primary Tube Sample Template*.

Criteria for Unacceptable Specimens

Refer to the *Procedural Notes* section of this chemistry information sheet for information on unacceptable specimens.

Reagents

Contents

Each kit contains the following items: **Kit Reorder # 476861**

Two Total Bilirubin Reagent Cartridges (2 x 400 tests)

Volumes per Test

Sample Volume	8 µL
Total Reagent Volume	280 µL
Cartridge Volumes	
A	255 µL
B	25 µL
C	-----

Reactive Ingredients

Reagent Constituents

Sodium Benzoate	347 mmol/L
Caffeine	173.9 mmol/L
Sulfanilic acid	27 mmol/L
HCl	50 mmol/L
Sodium Nitrite	0.36 mmol/L
Sodium Acetate	609 mmol/L

Also non-reactive chemicals necessary for optimal system performance.

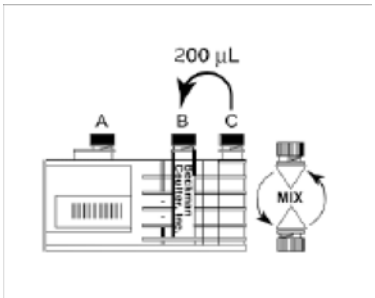
CAUTION: Avoid skin contact with reagent. Use water to wash reagent from skin.

Materials Needed But Not Supplied With Reagent Kit

SYNCHRON® Systems Bilirubin Calibrator
Deionized water (low level calibrator)
At least two levels of control material
Human Serum Albumin (azide free)

Reagent Preparation

1. Quantitatively transfer 200 µL (0.2 mL) of the contents from the smallest compartment (C) into the center compartment (B).
2. Replace the cartridge caps and gently invert the cartridge several times to ensure adequate mixing. Thorough mixing is necessary for successful calibration.
3. Date and initial cartridge and document in reagent log before loading each new cartridge.



Acceptable Reagent Performance

The acceptability of this reagent is determined by successful calibration and by ensuring that quality control results are within acceptance criteria, as defined in the Clinical Chemistry Quality Control Procedure #3000.T.

Reagent Storage and Stability

TBIL reagent when stored unopened at room temperature will obtain the shelf-life indicated on the cartridge label. Once prepared, the reagent cartridge is stable for 30 days at +2°C to +8°C unless the expiration date is exceeded. **DO NOT FREEZE**.

Equipment

This test is performed on the Beckman UniCel DxC 800 systems; Beckman-Coulter, Brea, California. For technical assistance, call the Beckman-Coulter hotline: 1-800-854-3633.

Refer to the UniCel DxC 800 systems *Reference Manual* for detailed instructions.

Calibration

Calibrator Required

SYNCHRON® Systems Bilirubin Calibrator (**Kit Reorder # 465915**)
Deionized water (low level calibrator)

Calibrator Preparation

No preparation is required.

Calibrator Storage and Stability

If unopened, the SYNCHRON® Systems Bilirubin Calibrator may be stored at -15°C to -20°C until the expiration date printed on the calibrator bottle.

CAUTION

Because this product is of human origin, it should be handled as though capable of transmitting infectious diseases. Each serum or plasma donor unit used in the preparation of this material was tested by United States Food and Drug Administration (FDA) approved methods and found to be negative for antibodies to HIV and HCV and nonreactive for HbsAg. Because no test method can offer complete assurance that HIV, hepatitis B virus, and hepatitis C virus or other infectious agents are absent, this material should be handled as though capable of transmitting infectious diseases. This product may also contain other human source material for which there is no approved test. The FDA recommends such samples to be handled as specified in Centers for Disease Control's Biosafety Level 2 guidelines.(6)

Calibration Information

NOTICE
Since Total Bilirubin is a calibrated chemistry and also requires "quantitative" reagent preparation it is important to follow proper reagent handling, preparation and storage procedures, especially when utilizing the within-lot calibration feature. Before reporting patient results on successive within-lot cartridges, always analyze and review calibration and quality control data.

1. The system must have a valid calibration in memory before controls or patient samples can be run.
2. Under typical operating conditions the TBIL reagent cartridge must be calibrated every 14 days and also with certain parts replacements or maintenance procedures, as defined in the UniCel DxC 800 Systems *Instructions for Use* (IFU) manual. This assay has within-lot calibration available. Refer to the UniCel DxC 800 System *Instructions For Use* (IFU) manual for information on this feature.
3. For detailed calibration instructions, refer to the UniCel DxC 800 System *Instructions For Use* (IFU) manual.
4. The system will automatically perform checks on the calibration and produce data at the end of calibration. In the event of a failed calibration, the data will be printed with error codes and the system will alert the operator of the failure. For information on error codes, refer to the UniCel DxC 800 System *Instructions For Use* (IFU) manual.

Traceability

Bilirubin measurand in this calibrator is traceable to NIST* SRM 916ca. The traceability process is based on prEN ISO 17511.

**NIST=National Institute of Standards and Technology*

The assigned values were established using representative samples from this lot of calibrator and are specific to the assay methodologies of the UniCel DxC reagents. Values assigned by other methodologies may be different. Such differences, if present, may be caused by inter-method bias.

Quality Control

At least two levels of control material should be analyzed each shift. In addition, these controls should be run with each new calibration, with each new reagent cartridge, and after specific maintenance or troubleshooting procedures as detailed in the UniCel DxC 800 System *Instructions For Use* manual. More frequent use of controls or the use of additional controls is left to the discretion of the user based on workload and workflow.

The following controls should be used in accordance with the package instructions for use inserts. Copies of these inserts can be found in the *Control IFUs* folder on the S drive (*S:\APS\ClinLab\PoliciesandProcedures\1000-8999CLINICALPATHOLOGY\3000-3999Chemistry\3000-3499AutomatedChemistry\ControlIFUs*). Quality control results should be evaluated and handled with respect to the Clinical Chemistry Quality Control Procedure #3000.T. Controls are compiled statistically in the LIS and reagent lot changes are documented on DxC Reagent Log sheets.

Quality Control Material

Control	Storage
MAS ChemTrak 1	+2°C to +8°C*
MAS ChemTrak 3	+2°C to +8°C*
MAS Bilirubin Control 3	+2°C to +8°C**

*MAS control is received frozen and stored at -15°C to -20°C. Each bottle of control in use is thawed and stored at +2°C to +8°C and is good for 14 days.
**Mas Bilirubin Control 3 is stored at 2°C to 8°C and opened vials are stable for 14 days. DO NOT FREEZE this control.

Testing Procedure

NOTICE
When using the within-lot calibration feature it is highly recommended that recovery be confirmed on subsequent cartridge(s) from the same lot number by analyzing quality control material prior to analyzing or reporting any patient results.

1. If necessary prepare reagent as defined in the Reagent Preparation section of this chemistry information sheet and load the reagent onto the system.
2. After reagent load is completed, calibration may be required.
3. Program samples and controls for analysis.
4. After loading samples and controls onto the system, follow the protocols for system operation.

For detailed testing procedures, refer to the UniCel DxC 800 System *Instructions For Use* (IFU) manual.

Calculations

UniCel DxC Systems perform all calculations internally to produce the final reported result. The system will calculate the final result for sample dilutions made by the operator when the dilution factor is entered into the system during sample programming.

If the dilution was programmed in Remisol, the final calculated result from a dilution will not be calculated by the DxC800 system but by Remisol.

Reporting Results

Equivalency between the SYNCHRON LX and UniCel DxC 800 Systems has been established. Chemistry results between these systems are in agreement and data from representative systems may be shown.

Reference Intervals

The following reference intervals were taken from literature and a study performed on SYNCHRON Systems.(7) UCDMC adult reference interval was determined from a normal study.

Reference Intervals

Intervals	Sample Type	Conventional Units			S.I Units
Literature	Serum or Plasma	0.3 - 1.2 mg/dL			5.1 - 20.5 µmol/L
UCDMC	Serum or Plasma	Premature	< 1 day	1 to 6 mg/dL	17.1 to 102.6 µmol/L
	Serum or Plasma		2 days	6 to 8 mg/dL	102.6 to 136.8 µmol/L
	Serum or Plasma		3 - 5 d	10 to15 mg/dL	171.0 to 256.5 µmol/L
	Serum or Plasma	mature	< 1 day	2 to 6 mg/dL	6.8 to 102.6 µmol/L
	Serum or Plasma		1 - 3 days	6 to 7 mg/dL	102.6 to 119.7 µmol/L
	Serum or Plasma		3 d to 1 m	4 to 12 mgdL	68.4 to 205.2 µmol/L
	Serum or Plasma		1 m to 12 yrs	0.2 to 0.9 mg/dL	3.42 to 15.39 µmol/L
	Serum or Plasma		> 12 yrs	0.0 to 1.2 mg/dL	0.0 to 20.5 µmol/L

Refer to References (8,9,10) for guidelines on establishing laboratory-specific reference intervals

Pediatric reference intervals are cited from literature. No in-house studies were performed. This information should serve as a general guideline.

A reference interval for fluids has not been determined by UCDHS. This result may be less accurate than for the usual sample type, and should be interpreted in the context of the patient's clinical condition.

Critical Values

Total bilirubin result **≥ 18.0 mg/dL** is considered a critical value for all newborns < 30 days old and should be called immediately to the attending physician or charge nurse.

Procedural Notes

Anticoagulant Test Results

1. If plasma is the sample of choice, the following anticoagulants were found to be compatible with this method based on a study of 20 healthy volunteers:

Acceptable Anticoagulants[a]

Anticoagulant	Level Tested for In Vitro Interference	Average Plasma-Serum Bias (mg/dL)
Sodium Heparin	29 Units/mL	NSI[b]
Lithium Heparin	29 Units/mL	NSI
Ammonium Heparin	29 Units/mL	NSI

[a] Data shown was collected using SYNCHRON CX Systems. Equivalency between SYNCHRON LX Systems has been established by Deming regression analysis to SYNCHRON CX Systems.

[b] NSI = No Significant Interference (within ±0.3 mg/dL or 6%).

2. The following anticoagulants were found to be incompatible with this method:

Incompatible Anticoagulants[a]

Anticoagulant	Level Tested for In Vitro Interference	Plasma-Serum Bias (mg/dL)[b]
Sodium Citrate	1.7 mg/mL	≤ -0.8
Potassium Oxalate/ Sodium Fluoride	4.0 / 5.0 mg/mL	≤ -0.4

[a] Data shown was collected using SYNCHRON CX Systems. Equivalency between SYNCHRON LX Systems has been established by Deming regression analysis to SYNCHRON CX Systems.

[b] Bias is based on worst case instead of average. Plus (+) or minus (-) signs in this column signify positive or negative bias.

Limitations

Viscous body fluid samples are unacceptable.

Interferences

1. The following substances were tested for interference with this methodology:

Interferences

Substance	Source	Maximum Level Tested	Observed Effect[a]
Hemoglobin	RBC Hemolysate[b]	100 mg/dL	≤ + 0.63 mg/dL
Lipemia	Intralipid[c]	200 mg/dL	≤ - 0.24 mg/dL
Azide[d]	NA[e]	5 mg/dL	≤ + 0.24 mg/dL
Citrate[d]	NA	900 mg/dL	≤ + 0.20 mg/dL
Oxalate[d]	NA	1000 mg/dL	≤ + 0.20 mg/dL
Gentisic Acid[d]	NA	5 mg/dL	≤ + 0.24 mg/dL
Acetoacetate[d]	NA	0.2 mg/mL 1.08 mg/mL	≤ + 0.7 mg/dL ≤ + 3.7 mg/dL

[a] Plus (+) or minus (-) signs in this column signify positive or negative interference.

[b] Hemolysis may cause falsely elevated results.

[c] Registered trademarks are the property of their respective owners.

[d] Data shown was collected using SYNCHRON LX/DxC Systems. Equivalency between SYBNCHRON LX Systems has been established by Deming regression analysis to SYNCHRON CX Systems.

[E] NA = Not applicable.

2. Lipemic samples more than slight should be ultra-centrifuged and the analysis performed on the infranate.
3. The Naproxen metabolite, O-desmethylnaproxen, has demonstrated a positive interference with the Jendrassik-Grof method for total Bilirubin measurement.(11)
4. Refer to References (12,13,14) for other interferences caused by drugs, disease and preanalytical variables.

Performance Characteristics

Analytical Measurement Range

The SYNCHRON® System(s) method for the determination of this analyte provides the following analytical ranges:

Analytical measurement Range (AMR)

Sample Type	Conventional Units	S.I. Units
Serum or Plasma	0.1 - 30.0 mg/dL	1.7 - 513 µmol/L

Clinical Reportable Range

Clinical Reportable Range (CRR)

Sample Type	Conventional Units	S.I. Units
Serum or Plasma	0.1 - diluted result mg/dL	1.7 - diluted result µmol/L

Samples with concentrations below the AMR and CRR (0.1 mg/dL) will be reported as "**< 0.1 mg/dL**".
Samples with concentrations greater than the AMR should be diluted with normal human serum albumin and reanalyzed.

If the dilution was programmed in Remisol, the final calculated result from a dilution will not be calculated by the DxC800 system but by Remisol.

Sensitivity

Sensitivity is defined as the lowest measurable concentration which can be distinguished from zero with 95% confidence. Sensitivity for TBIL determination is 0.1 mg/dL (1.7 µmol/L).

Equivalency

Equivalency was assessed by Deming regression analysis of patient samples to accepted clinical methods as determined by Beckman.

Serum or Plasma (in the range of 0.2 to 28.2 mg/dL):

Y (SYNCHRON LX Systems)	= 0.96X + 0.31
N	= 79
MEAN (SYNCHRON LX Systems)	= 6.75
MEAN (SYNCHRON CX7 DELTA)	= 6.69
CORRELATION COEFFICIENT (r)	= 0.9997

Refer to References (15) for guidelines on performing equivalency testing.

Equivalency assessed by Deming regression analysis of patient samples to accepted clinical methods as determined at UCDMC.

Serum or Plasma (in the range of 0.4 to 20.5 mg/dL):

Y (UniCel DxC800-4118)	= 0.986X - 0.24
N	= 26
MEAN (UniCel DxC800-4118)	= 4.73
MEAN (UniCel DxC800-1805)	= 5.05
CORRELATION COEFFICIENT (r)	= 0.9996

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Serum or Plasma (in the range of 0.4 to 17.5 mg/dL):

Y (UniCel DxC800-4427)	= 0.993X - 0.24
N	= 19
MEAN (UniCel DxC800-4427)	= 2.26
MEAN (UniCel DxC800-1805)	= 2.52
CORRELATION COEFFICIENT (r)	= 0.9990

Serum or Plasma (in the range of 0.4 to 17.5 mg/dL):

Y (UniCel DxC800-4449)	= 1.003X - 0.31
N	= 19
MEAN (UniCel DxC800-4449)	= 2.22
MEAN (UniCel DxC800-1805)	= 2.52
CORRELATION COEFFICIENT (r)	= 0.9990

Serum or Plasma (in the range of 0.1 to 18.0 mg/dL):

Y (UniCel DxC800-4427)	= 1.011X - 0.02
N	= 23
MEAN (UniCel DxC800-4427)	= 3.47
MEAN (UniCel DxC800-4118)	= 3.45
CORRELATION COEFFICIENT (r)	= 0.9996

Serum or Plasma (in the range of 0.1 to 18.0 mg/dL):

Y (UniCel DxC800-4449)	= 1.009X - 0.06
N	= 23
MEAN (UniCel DxC800-4449)	= 3.42
MEAN (UniCel DxC800-4118)	= 3.45
CORRELATION COEFFICIENT (r)	= 0.9996

Serum or Plasma (in the range of 0.3 to 18.4 mg/dL):

Y (UniCel DxC800-4449)	= 0.998X - 0.05
N	= 24
MEAN (UniCel DxC800-4449)	= 3.29
MEAN (UniCel DxC800-4427)	= 3.34
CORRELATION COEFFICIENT (r)	= 0.9995

Serum or Plasma (in the range of 3.0 to 17.2 mg/dL):

Y (Enzymatic NBIL)	= 1.041X - 0.28
N	= 40
MEAN (Enzymatic NBIL)	= 11.6
MEAN (Diazo TBIL)	= 11.4
CORRELATION COEFFICIENT (r)	= 0.9923

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Precision

A properly operating SYNCHRON® System(s) should exhibit precision values less than or equal to the following:

As determined by Beckman

Precision Values

Type of Precision	Sample Type	1 SD		Changeover Value[a]		%CV
			µmol/L	mg/dL	µmol/L	
Within-run	Serum/Plasma	0.15	2.6	5.0	86.7	3.0
Total	Serum/Plasma	0.22	3.8	5.0	86.7	4.5

[a] When the mean of the test precision data is less than or equal to the changeover value, compare the test SD to the SD guideline given above to determine the acceptability of the precision testing. When the mean of the test precision data is greater than the changeover value, compare the test % CV to the guideline given above to determine acceptability. Changeover value = (SD guideline/CV guideline) x 100.

Precision established at UCDMC

Type of Precision	Sample Type	n	Mean (mg/dL)	1 SD	%CV
DxC800-4118 Within-run	ULTIMATE 1	20	1.24	0.08	6.6
	ULTIMATE 3	20	8.43	0.11	1.3
	MAS ChemTrak 3 HiBil	20	21.8	0.30	1.4
DxC800-4427 Within-run	ULTIMATE 1	20	1.21	0.09	7.2
	ULTIMATE 3	20	8.51	0.13	1.5
	MAS ChemTrak 3 HiBil	20	21.5	0.36	1.7
DxC800-4449 Within-run	ULTIMATE 1	20	1.33	0.08	6.0
	ULTIMATE 3	20	8.65	0.13	1.5
	MAS ChemTrak 3 HiBil	20	21.5	0.25	1.1

Type of Imprecision	Sample Type	n	Mean (mg/dL)	SD	%CV
DxC800-4118 Day to Day	MAS ChemTrak 1	412	1.4	0.11	7.9
	MAS ChemTrak 3	389	7.9	0.18	2.3
	MAS ChemTrak 3 HiBil	20	21.9	0.30	1.4
DxC800-4427 Day to Day	MAS ChemTrak 1	401	1.3	0.11	8.5
	MAS ChemTrak 3	399	7.8	0.19	2.4
	MAS ChemTrak 3 HiBil	20	21.8	0.32	1.5
DxC800-4449 Day to Day	MAS ChemTrak 1	403	1.3	0.10	7.7
	MAS ChemTrak 3	399	7.7	0.19	2.5
	MAS ChemTrak 3 HiBil	20	21.8	0.33	1.5

Comparative performance data for a SYNCHRON LX® System evaluated using the NCCLS Proposed Guideline EP5-T2 appears in the table below.(16)

Comparative performance as determined by Beckman

NCCLS EP5-T2 Precision Estimate Method

Type of Imprecision	Sample Type	No. Systems	No. Data Points[a]	Test Mean Value (mg/dL)	EP5-T2 Calculated Point Estimates	
					SD	%CV
Within-run	Serum Control 1	1	80	1.7	0.1	6.1
	Serum Control 2	1	80	5.9	0.1	1.7
	Serum Control 3	1	80	8.9	0.1	1.2
	Serum Control 4	1	80	17.5	0.2	1.1
Total	Serum Control 4	1	80	1.7	0.1	6.1
	Serum Control 2	1	80	5.9	0.1	1.9
	Serum Control 3	1	80	8.9	0.1	1.3
	Serum Control 4	1	80	17.5	0.2	1.23

[a] The point estimate is based on the data from one system, run for twenty days, two runs per day, two observations per run on an instrument operated and maintained according to the manufacturer's instructions.

NOTICE

These degrees of precision and equivalency were obtained in typical testing procedures on a SYNCHRON LX® System and are not intended to represent the performance specifications for this reagent.

Additional Information

For more detailed information on UniCel DxC Systems, refer to the *Instructions for Use* and *Reference* manual.

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