BECKMAN COULTER

CE 2797

ACCESS
Immunoassay Systems

Instructions For Use

Access Total T3 Triiodothyronine

REF 33830

FOR PROFESSIONAL USE ONLY

For *in vitro* diagnostic use

Rx Only

For use on DxI Access Immunoassay Analyzers

PRINCIPLE

INTENDED USE

The Access Total T3 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of triiodothyronine levels in human serum and plasma using the Access Immunoassay Systems.

SUMMARY AND EXPLANATION

The clinical importance of total serum T3 determination is in the aid in diagnosis of thyroid disorders.[1,2,3,4]

The concentrations of thyroid hormones, and the degree of their biological effect, are controlled by the hypothalamo-hypophyseal-thyroid axis. Thyrotropin Releasing Hormone (TRH or TRF) is released by the hypothalamus in response to circulating concentrations of free thyroid hormones. TRH travels from the hypothalamus to the adenohypophysis (anterior pituitary) via a portal blood system where it initiates an intracellular cascade of events which result in the production and release of Thyroid Stimulating Hormone (hTSH or Thyrotropin). The target organ for hTSH is the thyroid gland where it binds its receptor and elicits its response via an adenylate cyclase second messenger system. The response of the thyroid gland to hTSH stimulation includes the synthesis, storage, secretion and metabolism of tetraiodo-thyronine (T4) and triiodothyronine (T3). More than 99% of the total concentration of T3 and T4 is bound by serum proteins, which is not available to elicit biological activity. It is only the free fraction (less than 1%) which is readily available to bind its receptor, and stimulate a response from the target organ or tissues.[5,6]

In euthyroid individuals, only a small proportion (20%) of the total concentration of T3 in the systemic circulation (serum) comes from direct secretion from the thyroid gland proper. The remaining fraction of total T3 is derived from enzymatic monodeiodination of T4 to T3 by the peripheral tissues.[7] The T3 molecule is the only thyroid hormone that appears to have any intrinsic biological activity, that is, the biological activity of T4 comes about only after monodeiodination to T3. The activity of these peripheral deiodinases is under strict control. This can be seen in developing hypothyroidism where conversion of T4 to T3 increases in a compensatory fashion to the developing hypo-thyroxinemia in an attempt to maintain normal concentrations of the biologically active T3.

Elevated concentrations of T3 can be found in Grave's disease, and most other classical causes of hyperthyroidism. During long periods of stimulation of the thyroid gland by thyroid-stimulating immunoglobulins (Grave's disease), the thyroid gland will secrete large quantities of T3, which significantly increase the T3/T4 ratio when compared to the euthyroid state.

METHODOLOGY

Assay type: two-step, competitive

The Access Total T3 assay is a competitive binding immunoenzymatic assay. Sample is added to a reaction vessel with a stripping agent to dissociate T3 from the binding proteins. T3 in the sample competes with the T3 analogue coupled to biotin for anti-T3 alkaline phosphatase conjugate. Of the resulting antigen: antibody complexes, the T3 analogue: antibody complexes are bound to the streptavidin coated solid phase.

After incubation, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is inversely proportional to the concentration of analyte in the sample. Analyte concentration is automatically determined from a stored calibration.

SPECIMEN

SPECIMEN COLLECTION AND PREPARATION

1. Serum and plasma (heparin) are the recommended samples.
2. Observe the following recommendations for handling, processing, and storing blood samples:[8]
   - Collect all blood samples observing routine precautions for venipuncture.
   - Allow serum samples to clot completely before centrifugation.
   - Keep tubes stoppered at all times.
   - Physically separate serum or plasma from contact with cells as soon as possible.
   - Store samples tightly stoppered at room temperature (15 to 30°C) for no longer than eight hours.
   - If the assay will not be completed within eight hours, refrigerate the samples at 2 to 8°C.
   - If the assay will not be completed within 48 hours, or for shipment of samples, freeze at -20°C or colder.
   - Thaw samples only once.
3. Use the following guidelines when preparing specimens:
   - Ensure residual fibrin and cellular matter has been removed prior to analysis.
   - Follow blood collection tube manufacturer's recommendations for centrifugation.
4. Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variations in these products may exist between manufacturers and, at times, from lot-to-lot.

REAGENTS

CONTENTS

Access Total T3 Reagent Pack

Ref. No. 33830: 100 determinations, 2 packs, 50 tests/pack

The same reagent formulation is used on all Access Immunoassay Systems.

Well	Contents	Ingredients
R1a:	3.22 mL	Mouse monoclonal anti-T3 alkaline phosphatase (bovine) conjugate and Dynabeads* paramagnetic particles coated with streptavidin in a TRIS buffer with protein (aves and murine), surfactant, < 0.1% sodium azide, and 0.1% ProClin** 300.
R1b:	7 mL	T3 analogue coupled to biotin in a TRIS buffer with protein (aves), surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.

Well	Contents	Ingredients
R1c:	3.1 mL	0.4N Sodium hydroxide (NaOH) solution with 8-Anilino-1-Napthalenesulfonic Acid (ANS).
R1d:	3.1 mL	0.4N Hydrochloric acid (HCl) solution.

*Dynabeads is a registered trademark of Dynal A.S., Oslo, Norway.

**ProClin is a trademark of LANXESS Corp.

WARNING AND PRECAUTIONS

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- For hazards presented by the product refer to the following sections: REACTIVE INGREDIENTS and GHS HAZARD CLASSIFICATION.

REACTIVE INGREDIENTS

⚠ CAUTION

Sodium azide preservative may form explosive compounds in metal drain lines. See NIOSH Bulletin: Explosive Azide Hazard (8/16/76).
To avoid the possible build-up of azide compounds, flush wastepipes with water after the disposal of undiluted reagent. Sodium azide disposal must be in accordance with appropriate local regulations.

GHS HAZARD CLASSIFICATION

T3-ALP Conjugate/ Dynabeads PMP (Compartment R1a)

WARNING

H317	May cause an allergic skin reaction.
H412	Harmful to aquatic life with long lasting effects.
P273	Avoid release to the environment.
P280	Wear protective gloves, protective clothing and eye/face protection.
P333+P313	If skin irritation or rash occurs: Get medical advice/attention.
P362+P364	Take off contaminated clothing and wash it before use.
	reaction mass of: 5-chloro-2-methyl-4-isothiazolin -3-one [EC# 247-500-7] and 2-methyl-4-isothiazolin-3-one [EC# 220-239-6](3:1) < 0.05%

T3-Biotin Conjugate (Compartment R1b)	WARNING	
		
	H317	May cause an allergic skin reaction.
	H412	Harmful to aquatic life with long lasting effects.
	P273	Avoid release to the environment.
	P280	Wear protective gloves, protective clothing and eye/face protection.
	P333+P313	If skin irritation or rash occurs: Get medical advice/attention.
	P362+P364	Take off contaminated clothing and wash it before use.
		reaction mass of: 5-chloro-2-methyl-4-isothiazolin -3-one [EC# 247-500-7] and 2-methyl-4-isothiazolin-3-one [EC# 220-239-6](3:1) < 0.05%
0.4 N NaOH solution with ANS (Compartment R1c)	DANGER	
		
	H314	Causes severe skin burns and eye damage.
	P280	Wear protective gloves, protective clothing and eye/face protection.
	P301+P330+P331	IF SWALLOWED: rinse mouth. Do NOT induce vomiting.
	P303+P361+P353	IF ON SKIN (or hair): Rinse skin with water.
	P305+P351+P338	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
	P310	Immediately call a POISON CENTER or doctor/physician.
		Sodium Hydroxide < 2%
0.4 N HCl solution (Compartment R1d)	DANGER	
		
	H314	Causes severe skin burns and eye damage.
	P280	Wear protective gloves, protective clothing and eye/face protection.
	P301+P330+P331	IF SWALLOWED: rinse mouth. Do NOT induce vomiting.
	P303+P361+P353	IF ON SKIN (or hair): Rinse skin with water.
	P305+P351+P338	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.

P310	Immediately call a POISON CENTER or doctor/physician.
	Hydrochloric Acid < 4%

SDS	Safety Data Sheet is available at beckmancoulter.com/techdocs

MATERIALS NEEDED BUT NOT SUPPLIED WITH REAGENT KIT

1. Access Total T3 Calibrators
   Provided at zero and approximately 0.5, 1.0, 2.0, 4.0 and 8.0 ng/mL (0.8, 1.5, 3.1, 6.1 and 12.3 nmol/L).
   Ref. No. 33835
2. Quality Control (QC) materials: commercial control material.
3. Lumi-Phos PRO
   Ref. No. B96000
4. UniCel DxI Wash Buffer II
   Ref. No. A16793

REAGENT PREPARATION

Provided ready to use.

REAGENT STORAGE AND STABILITY

Stability	
Unopened at 2 to 10°C	Up to stated expiration date
After opening at 2 to 10°C	28 days

- Store upright.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Signs of possible deterioration are a broken elastomeric layer on the pack or quality control values out of range.
- If the reagent pack is damaged (e.g., broken elastomer), discard the pack.

CALIBRATION

CALIBRATION INFORMATION

An active calibration is required for all tests. Calibration is required every 14 days. See calibrator Instructions For Use (IFU) for additional calibration information. Refer to the appropriate system manuals and/or Help system for information on calibration method, configuring calibrators, calibrator test request entry, and reviewing calibration data.

QUALITY CONTROL

Quality control materials are essential for monitoring the system performance. Quality controls with varying concentration ranges should be run individually at least once every 24 hours when the assay is being performed.[9] Quality control ranges should be determined by each laboratory's individual requirements. Follow applicable regulations and guidelines for quality control.

TESTING PROCEDURE(S)

PROCEDURE

1. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.
2. Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.
3. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
4. Use 55 µL of sample for each determination in addition to the sample container and system dead volumes. Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.
5. The system default unit of measure for sample results is ng/mL. To change sample reporting units to the International System of Units (SI units), nmol/L, refer to the appropriate system manuals and/or Help system. To manually convert concentrations, multiply ng/mL by multiplication factor 1.536 (T3 M.W. equals 651 daltons) to obtain nmol/L.

LIMITATIONS

1. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce human anti-animal antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other antibodies such as human anti-goat antibodies may be present in patient samples.[10,11] Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.
2. Other potential interferences in the patient sample could be present and may cause erroneous results in immunoassays. Some examples that have been documented in literature include rheumatoid factor, endogenous alkaline phosphatase, fibrin, and proteins capable of binding to alkaline phosphatase.[12] Carefully evaluate results if the sample is suspected of having these types of interferences.
3. The results should be interpreted in light of the total clinical presentation of the patient, including: symptoms, clinical history, data from additional tests, and other appropriate information.
4. This assay is susceptible to interference from high levels of biotin. The recommended daily intake for biotin is 30 µg. High doses of biotin (up to 30 mg per day) may be taken as a dietary supplement aimed at improving hair loss, nail growth, or skin condition.[13]

   Some pharmacokinetic studies have shown that serum concentrations of biotin can reach up to 300 ng/mL when subjects taking supplements containing 20 mg biotin[14] or 1,160 ng/mL for subjects taking doses of biotin up to 300 mg.[13] These studies were performed in apparently healthy subjects and some patients may be taking supplements with biotin at levels > 20 mg per day.

   Clearance rates of biotin may differ between patients tested with this device (e.g., patients with renal impairment), which may lead to higher than expected, or prolonged, concentrations in serum. If medically practicable, patients receiving biotin supplements should discontinue use prior to sample draws to minimize the risk of interference. Specimens with biotin concentrations ≤ 1 ng/mL demonstrated non-significant bias (≤ 10%) in results. Biotin concentrations > 1 ng/mL can lead to significant (> 10%) positive bias in Total T3 results.

   If unexpected results are obtained, and biotin interference is suspected, the Beckman Coulter TSH assay may provide a better assessment of thyroid function as it is not susceptible to biotin interference.

RESULTS INTERPRETATION

Test results are determined automatically by the system software. Test results can be reviewed using the appropriate screen. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing sample results.

REPORTING RESULTS

MEASURING INTERVAL

Approximately 0.42 – 8.0 ng/mL (0.65 – 12.3 nmol/L)

Samples can be accurately measured within the measuring interval defined as the lower Limit of Detection (LoD) and the highest calibrator value.

1. If a sample contains less than the lower limit for the assay, report the result as less than that value.
2. If a sample contains more than the stated value of the highest calibrator, report the result as greater than that value. Alternatively, the sample may be diluted to obtain a result.
    - For manual dilutions, dilute one volume of sample with 1 volume of Access Total T3 Calibrator S0.

Refer to the appropriate system manuals and/or Help system for instructions on entering a sample dilution in a test request. The system reports the results adjusted for the dilution.

EXPECTED VALUES

1. Each laboratory should validate or establish its own reference intervals to assure proper representation of specific populations.
2. Using the Access Total T3 assay, concentrations of serum T3 were measured in 239 ambulatory subjects without any known thyroid disorders. The median value was 1.18 ng/mL (1.81 nmol/L) with a 95% non parametric range of 0.87-1.78 ng/mL (1.34-2.73 nmol/L).
3. Values below the lower limit of the Expected Values range can be caused by a number of conditions including non-thyroidal illness, acute and chronic stress and hypothyroidism.[15]
4. This assay is not validated for testing newborn and neonatal specimens for total T3 levels.

PERFORMANCE CHARACTERISTICS

ASSAY CRITERIA AND REPRESENTATIVE DATA

Representative data is provided for illustration only. Performance obtained in individual laboratories may vary.

METHODS COMPARISON

A study based on CLSI EP09c, 3rd Edition[16] using Passing-Bablok regression and Pearson's correlation compared the Access 2 Immunoassay System and the DxI 9000 Access Immunoassay Analyzer.

N	Concentration Range* (ng/mL)	Slope	Slope 95% CI	Intercept	Intercept 95% CI	Correlation Coefficient R
134	0.45 – 7.3	1.05	1.03 – 1.08	-0.011	-0.045 - 0.019	1.00

*Range is Access 2 values

LINEARITY

A study based on CLSI EP06-Ed2[17] performed on the DxI 9000 Access Immunoassay Analyzer determined the assay demonstrated linearity across the measuring interval.

IMPRECISION

The assay was designed to have within-laboratory imprecision as listed below:

- ≤ 0.20 ng/mL (0.31 nmol/L) SD at concentrations ≤ 2.0 ng/mL (3.1 nmol/L)
- ≤ 10.0% CV at concentrations > 2.0 ng/mL (3.1 nmol/L)
- A study based on CLSI EP05-A3[18] performed on the DxI 9000 Access Immunoassay Analyzer tested multiple samples in duplicate in 2 runs per day for a minimum of 20 days.

ng/mL			Repeatability (Within-Run)		Between-Run		Between-Day		Within-Laboratory	
Sample	N	Mean	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Sample 1	88	0.83	0.03	3.8	0.02	2.7	0.03	3.9	0.05	6.1
Sample 2	88	1.7	0.08	4.6	0.06	3.4	0.06	3.4	0.12	6.6
Sample 3	88	3.4	0.08	2.4	0.06	1.7	0.08	2.3	0.13	3.7
Sample 4	86	7.3	0.13	1.8	0.05	0.7	0.16	2.2	0.22	3.0

ANALYTICAL SPECIFICITY / INTERFERENCES

Samples containing up to 10 mg/dL (171 µmol/L) bilirubin, lipemic samples containing the equivalent of 1,800 mg/dL (20.52 mmol/L) triolein or up to 400 mg/dL (10.4 mmol/L) cholesterol, and hemolyzed samples containing up to 1,000 mg/dL (10 g/L) hemoglobin do not affect the concentration of total T3 assayed. In addition, total protein concentrations ranging from 5.0 to 9.0 g/dL (50 to 90 g/L) do not affect the concentration of total T3 assayed.

The following potential cross-reactants were spiked into normal serum samples and found to give the following % cross-reactivity expressed by weight.

Cross-Reactant	Concentration (ng/mL)	Cross-reactivity (%)
L-T3	1	≥ 100
D-T3	1	≥ 100
R-T3	2	< 0.1
Tetraiodothyroacetic acid	25	0.20
D-T4	100	0.44
L-T4	100	< 0.1
3,5-L-T2	1,000	0.44
Phenytoin	1,000	< 0.1
Phenylbutazone	1,000	< 0.1
Monoiodotyrosine	1,000	< 0.1
Sodium Salicylate	1,000	< 0.1

Cross-Reactant	Concentration (ng/mL)	Cross-reactivity (%)
Aspirin	1,000	< 0.1
6-*N*-Propyl-2-Thiouracil	1,000	< 0.1
Diiodo-L-Tyrosine	1,000	< 0.1

Biotin

The following concentrations of biotin were spiked into normal serum samples at high and low Total T3 concentrations and found to give the following percent change in result response.

		Biotin (ng/mL)				
Analyte Range	**Analyte Concentration**	**1**	**3**	**5**	**7.5**	**10**
Low	0.51 - 0.57 ng/mL	0%	15%	16%	26%	41%
Low	0.87 - 1.04 ng/mL	-1%	6%	9%	12%	26%
Low	0.95 - 1.05 ng/mL	7%	4%	11%	14%	23%
High	1.2 - 1.4 ng/mL	0%	3%	7%	13%	20%
High	1.3 - 1.5 ng/mL	1%	3%	10%	12%	18%
High	1.5 - 1.6 ng/mL	1%	3%	6%	9%	14%

		Biotin (ng/mL)			
Analyte Range	**Analyte Concentration**	**100**	**300**	**600**	**1,200**
Low	0.65 - 0.71 ng/mL	86%	431%	817%	*
High	2.6 - 2.8 ng/mL	96%	*	*	*

* = Result above assay measuring range

DETECTION CAPABILITY

Limit of Blank (LoB), Limit of Detection (LoD), and Limit of Quantitation (LoQ) studies were conducted on the DxI 9000 Access Immunoassay Analyzer following CLSI guideline EP17-A2.[19] The LoB study included multiple reagent lots and 3 instruments over a minimum of 3 days. The LoD and LoQ studies included multiple reagent lots and 3 instruments over a minimum of 5 days.

	Maximum Observed Result		Design Criteria	
	ng/mL	**nmol/L**	**ng/mL**	**nmol/L**
Limit of Blank (LoB)	0.24	0.38	≤ 0.27	≤ 0.41
Limit of Detection (LoD)	0.33	0.51	≤ 0.42	≤ 0.65
Limit of Quantitation (LoQ) ≤ 20% within-lab CV	0.33	0.51	≤ 0.54	≤ 0.83

ADDITIONAL INFORMATION

For a patient/user/third party in the European Union and in countries with identical regulatory regime (Regulation 2017/746/EU on In vitro Diagnostic Medical Devices); if, during the use of this device or as a result of its use, a serious incident has occurred, please report it to the manufacturer and/or its authorized representative and to your national authority.

REVISION HISTORY

Revision A

New release of DxI Access Immunoassay Analyzer reagent IFU.

Revision B

Added Translations.

Revision C

Added Translations.

Revision D

Updated ProClin trademark statement.

Revision E

Added Translations.

SYMBOLS KEY

Glossary of Symbols is available at beckmancoulter.com/techdocs (document number C02724).

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