BECKMAN COULTER

ACCESS
Immunoassay Systems

# Instructions For Use



# Access Total T3 Triiodothyronine

REF 33830

**FOR PROFESSIONAL USE ONLY**

**Rx Only**

**ANNUAL REVIEW**

| Reviewed by | Date | Reviewed by | Date |
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# 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 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.[1,2]

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.[3] 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. 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.

The clinical importance of total serum T3 determination is in the diagnosis of thyroid disorders. Elevated concentrations of T3 can be found in Grave's disease, and most other classical causes of hyperthyroidism. Decreased concentrations occur in primary hypothyroid diseases such as Hashimoto's thyroiditis and neonatal hypothyroidism or secondary hypothyroidism due to defects at the hypothalamo-hypophyseal level.[1]

### METHODOLOGY

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. Separation in a magnetic field and washing removes the sample T3: antibody complexes and other materials not bound to the solid phase.

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 total T3 in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

## 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:[4]
   - 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

### PRODUCT INFORMATION

**Access Total T3 Reagent Pack**

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

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.

- Stable at 2 to 10°C for 28 days after initial use.
- If the reagent pack is damaged (i.e., broken elastomer), discard the pack.
- Signs of possible deterioration are a broken elastomeric layer on the pack or control values out of range.

| | |
|---|---|
| **R1a:** | 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:** | T3 analogue coupled to biotin in a TRIS buffer with protein (aves), surfactant, < 0.1% sodium azide, and 0.1% ProClin 300. |
| **R1c:** | 0.4N Sodium hydroxide (NaOH) solution with 8-Anilino-1-Napthalenesulfonic Acid (ANS). |
| **R1d:** | 0.4N Hydrochloric acid (HCl) solution. |

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

**ProClin™ is a trademark of The Dow Chemical Company (“Dow”) or an affiliated company of Dow.

## 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. |
| 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. |
| | 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. |
| | P304+P340 | IF INHALED: Remove person to fresh air and keep at rest in a position comfortable for breathing. |
| | 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. |
| P304+P340 | IF INHALED: Remove person to fresh air and keep at rest in a position comfortable for breathing. |
| 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% |

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

### 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).
   Cat. No. 33835
2. Quality Control (QC) materials: commercial control material.
3. Access Substrate
   Cat. No. 81906
4. Access Wash Buffer II, Cat. No. A16792
   UniCel DxI Wash Buffer II, Cat. No. A16793

### EQUIPMENT AND MATERIALS

| | |
|---|---|
| R1 | Access Total T3 Reagent Packs |

## CALIBRATION

### CALIBRATION INFORMATION

An active calibration curve is required for all tests. For the Access Total T3 assay, calibration is required every 14 days. Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

## QUALITY CONTROL

Quality control materials simulate the characteristics of patient samples and are essential for monitoring the system performance of immunochemical assays. Because samples can be processed at any time in a “random access” format rather than a “batch” format, quality control materials should be included in each 24-hour time period.[5] Include commercially available quality control materials that cover at least two levels of analyte. More frequent use of controls or the use of additional controls is left to the discretion of the user based on good laboratory practices or laboratory accreditation requirements and applicable laws. Follow manufacturer's instructions for reconstitution and storage. Each laboratory should establish mean values and acceptable ranges to assure proper performance. Quality control results that do not fall within acceptable ranges may indicate invalid test results. Examine all test results generated since

obtaining the last acceptable quality control test point for this analyte. Refer to the appropriate system manuals and/or Help system for information about reviewing quality control results.

# TESTING PROCEDURE(S)

### PROCEDURAL COMMENTS

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. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
3. Use fifty five (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.
4. 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.

### PROCEDURE

Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.

# RESULTS INTERPRETATION

Patient test results are determined automatically by the system software using a smoothing spline math model with no inflection points. The amount of analyte in the sample is determined from the measured light production by means of the stored calibration data. Patient 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

### EXPECTED RESULTS

1. Each laboratory should establish its own reference ranges 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.[6]
4. This assay is not validated for testing newborn and neonatal specimens for total T3 levels.

# PROCEDURAL NOTES

### LIMITATIONS

1. Samples can be accurately measured within the analytic range of the lower limit of detection and the highest calibrator value [approximately 0.1 to 8.0 ng/mL (0.2-12.3 nmol/L)].
    - If a sample contains less than the lower limit of detection for the assay, report the results as less than that value [i.e., < 0.1 ng/mL (< 0.2 nmol/L)].

- If a sample contains more than the stated value of the highest Access Total T3 Calibrator (S5), dilute one volume of sample with one volume of Access Total T3 Calibrator S0 (zero). 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.

2. 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 antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples.[7,8]

   Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.

3. The Access Total T3 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.[9]

   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[10] or 1,160 ng/mL for subjects taking doses of biotin up to 300 mg.[9] 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.

# PERFORMANCE CHARACTERISTICS

### PERFORMANCE CHARACTERISTICS

### METHODS COMPARISON

A comparison of 153 serum values using the Access Total T3 assay on the Access Immunoassay system and a commercially available enzyme immunoassay kit gave the following statistical data using Deming calculations:[11]

| n | Range of Observations (ng/mL) | Intercept (ng/mL) | Slope | Correlation Coefficient (r) |
|---|---|---|---|---|
| 153 | 0.36-6.08 | 0.077 | 1.020 | 0.978 |

A comparison of 150 paired serum and plasma (heparin) samples using the Access Total T3 assay on the Access Immunoassay System gave the following statistical data:

| n | Range of Observations (ng/mL) | Intercept (ng/mL) | Slope | Correlation Coefficient (r) |
|---|---|---|---|---|
| 150 | 0.52-4.78 | 0.026 | 0.985 | 0.975 |

## DILUTION RECOVERY (LINEARITY)

Multiple gravimetrically prepared dilutions of two samples containing various triiodothyronine levels with Access Total T3 Calibrator S0 (zero) resulted in the following data:

| Sample 1 | Expected Concentration (ng/mL) | Determined Concentration (ng/mL) | Recovery (%) |
|---|---|---|---|
| Neat | N/A | 7.41 | N/A |
| 79.9 | 5.92 | 6.01 | 101.5 |
| 60.1 | 4.45 | 4.43 | 99.6 |
| 40.1 | 2.97 | 3.20 | 107.7 |
| 19.9 | 1.47 | 1.37 | 93.2 |
| 9.7 | 0.72 | 0.67 | 93.1 |
| 4.9 | 0.36 | 0.35 | 97.2 |
| | | **Mean % Recovery** | **98.7** |

| Sample 2 | Expected Concentration (ng/mL) | Determined Concentration (ng/mL) | Recovery (%) |
|---|---|---|---|
| Neat | N/A | 6.54 | N/A |
| 90.2 | 5.90 | 6.24 | 105.8 |
| 80.7 | 5.28 | 5.26 | 99.6 |
| 51.1 | 3.34 | 2.87 | 85.9 |
| 40.3 | 2.64 | 2.34 | 88.6 |
| 15.5 | 1.01 | 0.95 | 94.1 |
| 5.2 | 0.34 | 0.32 | 94.1 |
| | | **Mean % Recovery** | **94.7** |

## SPIKING RECOVERY

Two serum samples with low triiodothyronine levels were used for this study. Six known amounts of triiodothyronine were added to each serum sample. The concentration of triiodothyronine was determined before and after the additions of exogenous triiodothyronine. The results listed below provide data on accuracy.

| Sample 1 T3 Added (ng/mL) | Expected Concentration (ng/mL) | Determined Concentration (ng/mL) | Recovery (%) |
|---|---|---|---|
| N/A | Neat | 0.81 | N/A |
| 0.60 | 1.41 | 1.50 | 106.4 |
| 0.84 | 1.65 | 1.68 | 101.8 |
| 1.43 | 2.24 | 2.25 | 100.4 |

| Sample 1 T3 Added (ng/mL) | Expected Concentration (ng/mL) | Determined Concentration (ng/mL) | Recovery (%) |
|---|---|---|---|
| 2.90 | 3.71 | 3.51 | 94.6 |
| 4.21 | 5.02 | 5.22 | 104.0 |
| 6.62 | 7.43 | 7.15 | 96.2 |
| | | **Mean % Recovery** | **100.6** |

| Sample 2 T3 Added (ng/mL) | Expected Concentration (ng/mL) | Determined Concentration (ng/mL) | Recovery (%) |
|---|---|---|---|
| N/A | Neat | 0.68 | N/A |
| 0.56 | 1.24 | 1.39 | 112.1 |
| 0.79 | 1.47 | 1.51 | 102.7 |
| 1.22 | 1.90 | 2.02 | 106.3 |
| 2.83 | 3.51 | 3.08 | 87.7 |
| 4.05 | 4.73 | 4.67 | 98.7 |
| 6.23 | 6.91 | 6.74 | 97.5 |
| | | **Mean % Recovery** | **100.8** |

## IMPRECISION

This assay exhibits total imprecision of less than 10% across the assay range. One study, using commercially available human serum based control material generating a total of 20 assays, 2 replicates per assay, over 14 days provides the following data, analyzed via analysis of variance (ANOVA).[12,13]

| | Grand Mean (n=40) (ng/mL) | SD (ng/mL) | Within Run (%CV) |
|---|---|---|---|
| Level 1 | 0.69 | 0.036 | 5.22 |
| Level 2 | 1.42 | 0.058 | 4.11 |
| Level 3 | 2.95 | 0.095 | 3.22 |

| | Grand Mean (n=40) (ng/mL) | SD (ng/mL) | Total Imprecision (%CV) |
|---|---|---|---|
| Level 1 | 0.69 | 0.063 | 9.12 |
| Level 2 | 1.42 | 0.100 | 6.98 |
| Level 3 | 2.95 | 0.140 | 4.74 |

## 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 |
| 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

### ANALYTICAL SENSITIVITY

The lowest detectable level of triiodothyronine distinguishable from zero (Access Total T3 Calibrator S0) with 95% confidence is 0.1 ng/mL (0.2 nmol/L). This value is determined by processing a complete six point calibration curve, controls, and 10 replicates of the zero calibrator in multiple assays. The analytical sensitivity value is interpolated from the curve at the point that is two standard deviations from the fitted zero calibrator signal.

## ADDITIONAL INFORMATION



### SYMBOLS KEY

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

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