

**TurboTSH [<sup>125</sup>I] IRMA KIT**

(REF: RK-1CT5)

The <sup>125</sup>I-hTSH IRMA system provides direct quantitative *in vitro* determination of human Thyroid Stimulating Hormone (hTSH) in human serum. hTSH can be assayed in the range of 0-100 µIU/ml using 100/200 µl serum samples.

**Introduction**

The Thyroid Stimulating Hormone (thyrotropin or TSH) is a glycoprotein with a molecular weight of 28000, secreted by the adenohypophysis. Like other glycoprotein hormones (FSH, LH and HCG), TSH contains two different subunits, an α- and a β-chain, linked by noncovalent bonds. The primary structure of α subunits of TSH and of the gonadotrophins is the same, whilst their β subunits are different. The β subunits are responsible for the immunological and biological specificity of these hormones.

The synthesis and the release of TSH are controlled by the circulatory level of thyroid hormones; triiodothyronine (T3) and thyroxin (T4) and by the hypothalamic Thyrotropin-Releasing Hormone (TRH). Thyroid hormones regulate the secretion of TSH by a negative feedback mechanism. An elevation of T3 or T4 will suppress, and their fall will, in turn, increase the level of TSH in serum. The increased concentration of TSH in the serum is the earliest and best indicator of primary hypothyroidism.

The determination of TSH by immunoassay methods plays a crucial role in the diagnosis of thyroid disorders and in the evaluation of the functional integrity of the hypothalamic-pituitary axis.

The outstanding sensitivity of the present hTSH IRMA system makes it particularly suitable for the measurement of subnormal hTSH levels, a key to both the diagnosis and treatment follow up of hyperthyroid patients.

**Principle of method**

The technology uses two high affinity monoclonal antibodies in an immunoradiometric assay (IRMA) system.

The <sup>125</sup>I labeled signal-antibody binds to an epitope of the TSH molecule spatially different from that recognized by the biotin-capture-antibody. The two antibodies react simultaneously with the antigen present in standards or samples, which leads to the formation of a capture antibody - antigen - signal antibody complex, also referred to as a "sandwich".

During a 1-hour incubation period immuno-complex is immobilized to the reactive surface of streptavidin-coated test tubes. Reaction mixture is then discarded, test tubes washed exhaustively, and the radioactivity is measured in a gamma counter.

The concentration of antigen is directly proportional to the radioactivity measured in test tubes. By constructing a calibration curve plotting binding values against a series of calibrators containing known amount of hTSH, the unknown concentration of hTSH in patient samples can be determined.

**Contents of the kit**

1. 1 bottle TRACER, Ready to use. 105 ml per vial, containing < 4.5 MBq <sup>125</sup>I-signal and capture antibody in buffer with red dye and 0.1 % NaN<sub>3</sub>.
2. 8x2 vials STANDARD (8x2 x 1.5 ml), containing 0 (S<sub>0</sub>), 0.06 (S<sub>0.06</sub>), 0.15 (S<sub>0.15</sub>), 0.6 (S<sub>0.6</sub>), 2.5 (S<sub>2.5</sub>), 15 (S<sub>15</sub>), 50 (S<sub>50</sub>) and 100 (S<sub>100</sub>) µIU/ml hTSH (WHO 2nd IRP 80/558) in serum with 0.1% NaN<sub>3</sub>.
3. 2x2 vials CONTROL SERUM. Low (CI), and high (CII). 1.5 ml, containing 0.1% NaN<sub>3</sub>. The concentration of the control serum is specified in the quality certificate enclosed.
4. 10 boxes COATED TUBE, Ready to use. 10x50 reactive test tubes, 12x75 mm, packed in plastic boxes.
5. 1 bottle WASH BUFFER CONCENTRATE (100 ml), containing 0.1% NaN<sub>3</sub>. See *Preparation of reagents*.  
Quality certificate  
Pack leaflet

**Materials, tools and equipment required**

Test tube rack, precision pipettes with disposable tips (100, 200 and 2000 µl), distilled water, vortex mixer, shaker, plastic foil, adsorbent tissue, gamma counter

**Recommended tools and equipment**

repeating pipettes (e.g. Eppendorf or else), dispenser with 1-L reservoir (instead of the 2-ml pipette)

**Specimen collection and storage**

Serum samples can be prepared according to common procedures used routinely in clinical laboratory practice. Samples can be stored at 2-8 °C if the assay is carried out within 24 hours, otherwise aliquots should be prepared and stored deep-frozen (-20°C). Frozen samples should be thawed and thoroughly mixed before assaying. Repeated freezing and thawing should be avoided. Do not use lipemic, hemolyzed or turbid specimens.

**Preparation of reagents, storage**

Add the wash buffer concentrate (100 ml) to 5 L distilled water to obtain 5.1 L wash solution. Upon dilution store at 2-8°C until expiration. Store the rest of reagents between 28°C after opening. At this temperature each reagent is stable until expiry date. The actual expiry date is given on the package label and in the quality certificate.

**CAUTION!**

Equilibrate all reagents and serum samples to room temperature. Mix all reagents and samples thoroughly before use. Avoid excessive foaming.

**The Way of Use**

The assay can be used in different procedures. There are three options for running the assay. The procedures are labeled as "A", "B" and "C". Working in accordance to "A" and "B" you need a good laboratory shaker. In case of OPTION C you need a water bath thermostat. The test tubes must be in contact with the water so air conditioned thermostat is not applicable. Patient sample values and expected values are the same for all procedures.

**OPTION "A": The Basic Procedure**

It is very economical on sample consumption. Only 100 µl sample volume is needed. The

sensitivity attainable is 0.011 µIU/ml. When the KIT has less than 3 weeks to its expiration standard 0.06 µIU/ml can be omitted. However if sample consumption is not critical we recommend you to work according to OPTION B. Shaking is needed.

Standard solution 50 µIU/ml can also be omitted if the curve-fitting algorithm of the gamma counter gives similar results with or without this point.

**OPTION "B": The 3rd Generation Method**

It works in the same way as OPTION "A" except the sample volume, which is 200 µl. The sensitivity attainable is 0.005 µIU/ml. Shaking is needed.

**OPTION "C": The Water Bath Procedure**

No shaking is applied during incubation. A good laboratory thermostat is important. The sensitivity attainable is 0.020 µIU/ml. When the KIT has less than 3 weeks to its expiration standard 0.06 µIU/ml can be omitted. Use this method if you have problems with your shakers but you need the results quickly. Use 200 µl sample volume only!

**OPTION – A.****The assay procedure (Option-A)**

(For a quick guide, refer to Table 1.)

1. Equilibrate reagents & samples to room temperature before use.
2. Label coated tubes in duplicate for each standard, control serum & samples.
3. Homogenize all reagents & samples by gentle mixing to avoid foaming.
4. Pipette 100 µl of standards, control & samples into the properly labeled tubes. Use rack to hold the tubes. Do not touch or scratch the inner bottom of the tubes with pipette tip.
5. Pipette 200 µl of tracer into each tube. (Set aside 2 tubes for total counts.)
6. Fix the test tube rack firmly onto the shaker plate. Turn on the shaker and adjust an adequate speed so that liquid is constantly rotating or shaking in each tube.
7. Incubate tubes for 1 hour, shaking at room temperature.
8. Add 2.0 ml of diluted wash buffer to each tube. Decant the supernatant from all tubes by the inversion of the rack. In the upside down position place the rack on an absorbent paper for 2 minutes.
9. Return the tube-rack to an upright position, and repeat step-8 two more times.
10. Count each tube for at least 60 seconds in a gamma counter.
11. Calculate the hTSH concentrations.

**Table 1. Assay Protocol, Pipetting Guide for Option-A.** (all volumes in microlitres)

Tubes	Total	Standard	Control	Sample
Standard		100		
Control			100	
Sample				100
Tracer	(200)	200	200	200
Shake for 1 hour at room temperature				
Wash b.		2000	2000	2000
Decant the fluid & blot on filter paper				
Wash b.		2000	2000	2000
Decant the fluid & blot on filter paper				
Wash b.		2000	2000	2000
Decant the fluid & blot on filter paper				
Count radioactivity (60 sec/tube)				
Calculate the results				

**Table 2. Typical assay data for Option-A.**

Tubes	Count cpm	Mean cpm	B/T%
Total	406194 404399	405297	-
S0 (NSB)	58 67	63	0.015
S0.06	265 297	281	0.069
S0.15	615 587	601	0.148
S0.6	2158 2218	2188	0.54
S2.5	8377 8490	8434	2.08
S15	48394 50214	49304	12.16
S50	146568 147342	146955	36.26
S100 (Bmax)	243184 240624	241904	59.68
CI	1144 1201	1173	0.31
CII	62189 63957	63073	19.4

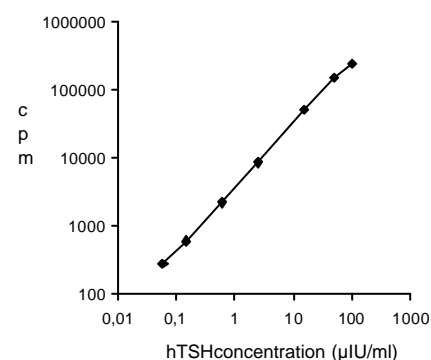


Figure 1: A typical standard curve (Do not use to calculate unknown samples)

**Characterization of assay (Option-A)**

Sensitivity

The analytical sensitivity or minimum detectable limit is calculated by the interpolation of the mean counts of zero standard plus 2 standard deviation from the standard curve. Determination was carried out using 20 replicates of zero standard response.

The value of **analytical sensitivity** is **0.011 µIU/ml** measured using fresh tracer.

The functional sensitivity is a measure of the hTSH concentration that is significantly different from zero as determined by the inter-assay precision profile (22 % CV).

The value of **functional sensitivity** is: **0.07 µIU/ml**.

Hook effect

There is no high dose hook effect up to an hTSH concentration 500 µIU/ml.

Precision

The within-assay (intra-assay) precision was determined with 15 replicates within a single run using pooled human serum samples. CV values are summarized below:

**Table 3/1.**

intra-assay	
mean (µIU/ml)	CV %
0.179	3.8
0.738	3.5
6.25	4.2

The between-assay (inter-assay) precision was determined using pooled human serum samples in independent assay runs. The number of measurements on a sample was a function of sample volume available. Three different operators took part in the investigation process and four different tracer batches were used at different ages of the reagents. Four different lots of coated tubes were used to determine the inter-assay precision profile. Results are presented below.

**Table 3/2.**

number of assay runs	inter-assay	
	mean (µIU/ml)	CV %
13	0.093	19.5
19	2.98	4.4
19	20.37	7.4

Linearity – dilution test

Individual human serum samples were diluted with the zero standard of the KIT. The diluted samples were measured according to KIT protocol.

**Table 4.**

sample No.	dilution factor	expected µIU/ml	observed µIU/ml	recovery %
1	1		27.46	
1	2.00	13.74	13.85	100.9
1	4.02	6.82	7.38	108.2
1	8.05	3.41	3.67	107.4
2	1		13.07	
2	2.02	6.48	6.68	103.0
2	4.06	3.22	3.33	103.2
2	8.14	1.60	1.55	96.5
3	1		56.18	
3	2.00	28.02	27.82	99.3
3	4.02	13.97	13.78	98.6
3	8.02	7.01	7.57	108.1
4	1		1.12	
4	2.02	0.556	0.581	104.4
4	4.07	0.276	0.302	109.5
4	8.18	0.137	0.155	113.0

Recovery – addition test

Individual human serum samples were spiked with known amount of an elevated stock sample. Recovery % is to be interpreted as = (observed-base)/added\*100. The results are summarised below.

**Table 5.**

sample	base µIU/ml	added µIU/ml	expected µIU/ml	observed µIU/ml	Recovery
1	8.28	17.18	25.46	25.00	97.3
2	7.50	18.60	26.09	26.65	103.0
3	8.65	18.44	27.08	26.21	95.3
4	9.11	16.29	25.40	24.57	94.9

5	5.79	17.87	23.66	23.92	101.5
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**OPTION – B.**

**The assay procedure (Option-B)**

(For a quick guide , refer to Table 6.)

1. Equilibrate reagents & samples to room temperature before use.
2. Label coated tubes in duplicate for each standard, control serum & samples.
3. Homogenize all reagents & samples by gentle mixing to avoid foaming.
4. Pipette 200 µl of standards, control & samples into the properly labeled tubes. Use rack to hold the tubes. Do not touch or scratch the inner bottom of the tubes with pipette tip.
5. Pipette 200 µl of tracer into each tube. (Set aside 2 tubes for total counts.)
6. Fix the test tube rack firmly onto the shaker plate. Turn on the shaker and adjust an adequate speed so that liquid is constantly rotating or shaking in each tube.
7. Incubate tubes for 1 hour, shaking at room temperature.
8. Add 2.0 ml of diluted wash buffer to each tube. Decant the supernatant from all tubes by the inversion of the rack. In the upside down position place the rack on an absorbent paper for 2 minutes.
9. Return the tube-rack to an upright position, and repeat step-8 two more times.
10. Count each tube for at least 60 seconds in a gamma counter.
11. Calculate the hTSH concentrations.

**Table 6. Assay Protocol, Pipetting Guide for Option-B.** (all volumes in microlitres)

Tubes	Total	Standard	Control	Sample
Standard		200		
Control			200	
Sample				200
Tracer	(200)	200	200	200
Shake for 1 hour at room temperature				
Wash b.		2000	2000	2000
Decant the fluid & blot on filter paper				
Wash b.		2000	2000	2000
Decant the fluid & blot on filter paper				
Wash b.		2000	2000	2000
Decant the fluid & blot on filter paper				
Count radioactivity (60 sec/tube)				
Calculate the results				

**Table 7. Typical assay data for Option-B.**

Tubes	Count cpm	Mean cpm	B/T%
Total	405254 402194	403724	-
S0 (NSB)	57 49	53	0.013
S0.06	468 435	452	0.069
S0.15	1095 1035	1065	0.264

S0.6	3936 4151	4044	1.00
S2.5	16214 15233	15724	3.89
S15	86741 88695	87718	21.73
S50	232356 229654	231005	57.22
S100 (Bmax)	311395 312518	311957	77.27
CI	2256 2099	2177	0.33
CII	115658 118590	117124	19.9

assay precision profile. Results are presented below.

**Table 8/2.**

inter-assay		
number of assay runs	mean (µIU/ml)	CV %
21	0.062	8.7
22	1.20	2.9
22	18.83	2.6

**Linearity – dilution test**

Individual human serum samples were diluted with the zero standard of the KIT. The diluted samples were measured according to KIT protocol.

**Table 9.**

sample No.	dilution factor	expected µIU/ml	observed µIU/ml	recovery %
1	1		27.73	
1	2.00	13.87	13.71	98.8
1	4.02	6.89	7.35	106.6
1	8.05	3.45	3.39	98.4
2	1		13.07	
2	2.02	6.48	6.69	103.3
2	4.06	3.22	3.31	102.8
2	8.14	1.60	1.54	96.1
3	1		57.14	
3	2.00	28.49	26.71	93.7
3	4.02	14.21	13.81	97.2
3	8.02	7.13	7.24	101.6
4	1		1.16	
4	2.02	0.573	0.536	93.6
4	4.07	0.284	0.259	91.2
4	8.18	0.141	0.126	89.2

**Recovery – addition test**

Individual human serum samples were spiked with known amount of an elevated stock sample. Recovery % is to be interpreted as = (observed-base)/added\*100. The results are summarised below.

**Table 10.**

sample	base µIU/ml	added µIU/ml	expected µIU/ml	observed µIU/ml	Recovery %
1	10.08	15.71	25.78	26.24	102.9
2	14.63	13.33	27.96	27.38	95.6
3	9.88	13.49	23.37	22.76	95.5
4	0.769	14.27	15.03	15.04	100.0
5	1.50	14.63	16.13	16.01	99.2

**OPTION – C.**

**The assay procedure (Option-C)**

(For a quick guide, refer to Table 11.)

1. Equilibrate reagents & samples to room temperature before use.
2. Label coated tubes in duplicate for each standard, control serum & samples.
3. Homogenize all reagents & samples by gentle mixing to avoid foaming.
4. Pipette 200 µl of standards, control & samples into the properly labeled tubes. Use rack to hold the tubes. Do not touch or scratch the inner bottom of the tubes with pipette tip.
5. Pipette 200 µl of tracer into each tube. (Set aside 2 tubes for total counts.)
6. Vortexmix all tubes gently.
7. Incubate tubes for 1 hour in warm water bath thermostat (36-38 °C).

8. Add 2.0 ml of diluted wash buffer to each tube. Decant the supernatant from all tubes by the inversion of the rack. In the upside down position place the rack on an absorbent paper for 2 minutes.
9. Return the tube-rack to an upright position, and repeat step-8 two more times.
10. Count each tube for at least 60 seconds in a gamma counter.
11. Calculate the hTSH concentrations.

**Table 11. Assay Protocol, Pipetting Guide for Option-C.** (all volumes in microlitres)

Tubes	Total	Standard	Control	Sample
Standard		<b>200</b>		
Control			<b>200</b>	
Sample				<b>200</b>
Tracer	<b>(200)</b>	<b>200</b>	<b>200</b>	<b>200</b>
Votex mix				
Incubate for 1 hour in water bath (36-38 °C)				
Wash b.		<b>2000</b>	<b>2000</b>	<b>2000</b>
Decant the fluid & blot on filter paper				
Wash b.		<b>2000</b>	<b>2000</b>	<b>2000</b>
Decant the fluid & blot on filter paper				
Wash b.		<b>2000</b>	<b>2000</b>	<b>2000</b>
Decant the fluid & blot on filter paper				
Count radioactivity (60 sec/tube)				
Calculate the results				

**Table 12. Typical assay data for Option-C**

Tubes	Count cpm	Mean cpm	B/T%
Total	402020 398564	400292	-
S0 (NSB)	71 60	66	0.017
S0.06	197 168	183	0.046
S0.15	347 388	368	0.092
S0.6	1361 1305	1333	0.333
S2.5	5339 5120	5230	1.307
S15	27317 26655	26986	6.74
S50	70967 68173	69570	17.38
S100 (Bmax)	87101 85910	86506	21.61
CI	754 698	726	0.32
CII	34536 35398	34967	19.5

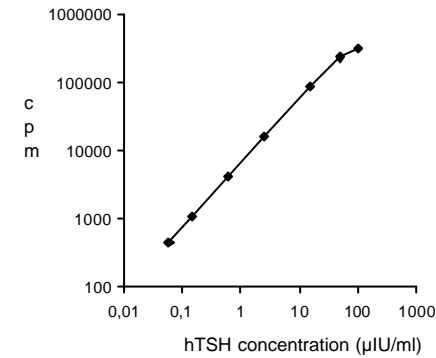


Figure 2: A typical standard curve (Do not use to calculate unknown samples)

**Characterization of assay (Option-B.)**

**Sensitivity**

The analytical sensitivity or minimum detectable limit is calculated by the interpolation of the mean counts of zero standard plus 2 standard deviation from the standard curve. Determination was carried out using 20 replicates of zero standard response.

The value of **analytical sensitivity** is **0.005 µIU/ml** measured using fresh tracer.

The functional sensitivity is a measure of the hTSH concentration that is significantly different from zero as determined by the inter-assay precision profile (22 % CV).

The value of **functional sensitivity** is: **0.03 µIU/ml**.

**Hook effect**

There is no high dose hook effect up to an hTSH concentration 500 µIU/ml.

**Precision**

The within-assay (intra-assay) precision was determined with 15 replicates within a single run using pooled human serum samples. CV values are summarized below:

**Table 8/1.**

intra-assay	
mean (µIU/ml)	CV %
0.091	8.3
0.527	3.2
18.55	2.1

The between-assay (inter-assay) precision was determined using pooled human serum samples in independent assay runs. The number of measurements on a sample was a function of sample volume available. Three different operators took part in the investigation process and four different tracer batches were used at different ages of the reagents. Four different lots of coated tubes were used to determine the inter-

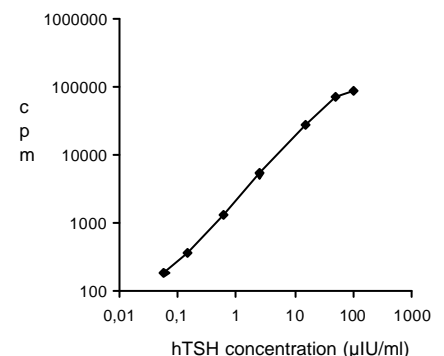


Figure 3: A typical standard curve (Do not use to calculate unknown samples)

## Characterization of assay (Option-C)

### Sensitivity

The analytical sensitivity or minimum detectable limit is calculated by the interpolation of the mean counts of zero standard plus 2 standard deviation from the standard curve. Determination was carried out using 20 replicates of zero standard response.

The value of **analytical sensitivity** is **0.020**  $\mu\text{IU/ml}$  measured using fresh tracer.

The functional sensitivity is a measure of the hTSH concentration that is significantly different from zero as determined by the inter-assay precision profile (22 % CV).

The value of **functional sensitivity** is: **0.11**  $\mu\text{IU/ml}$ .

### Hook effect

There is no high dose hook effect up to an hTSH concentration 500  $\mu\text{IU/ml}$ .

### Precision

The within-assay (intra-assay) precision was determined with 15 replicates within a single run using pooled human serum samples. CV values are summarized below:

**Table 13/1.**

intra-assay	
mean ( $\mu\text{IU/ml}$ )	CV %
0.170	7.3
1.81	4.4
6.27	3.2

The between-assay (inter-assay) precision was determined using pooled human serum samples in independent assay runs. The number of measurements on a sample was a function of sample volume available. Three different operators took part in the investigation process and four different tracer batches were used at different ages of the reagents. Four different lots of coated tubes were used to determine the inter-assay precision profile. Results are presented below.

**Table 13/2.**

number of assay runs	inter-assay	
	mean ( $\mu\text{IU/ml}$ )	CV %
19	0.177	12.6
20	1.72	3.8
19	19.60	5.9

### Linearity – dilution test

Individual human serum samples were diluted with the zero standard of the KIT. The diluted samples were measured according to KIT protocol.

**Table 14.**

sample No.	dilution factor	expected $\mu\text{IU/ml}$	observed $\mu\text{IU/ml}$	recovery %
1	1		11.31	
1	2.02	5.59	5.96	106.6
1	4.09	2.77	3.04	109.8
1	8.31	1.36	1.38	101.6
2	1		24.57	
2	2.02	12.14	11.61	95.7
2	4.10	5.99	5.88	98.2
2	8.33	2.95	3.08	104.2
3	1		33.46	
3	2.02	16.60	17.60	106.0
3	4.08	8.20	9.44	115.2
3	8.21	4.07	4.90	120.1

## Option independent data

### Specificity

No cross reactivity with hFSH and hLH can be detected in normal physiological concentrations. 2 000 mIU/ml hCG gives an apparent 3.5  $\mu\text{IU/ml}$  increase in hTSH concentration.

### Expected Values

Expected euthyroid range is 0.27  $\mu\text{IU/ml}$  - 3.75  $\mu\text{IU/ml}$ .

It is recommended that each laboratory determine a reference range for euthyroids for its own patient population, since this may vary in different laboratories or regions.

### Calculation of results

The calculation is illustrated using representative data. The assay data collected should be similar to those shown in Table 2.

Calculate the average count per minute (cpm) for each pair of assay tubes. Calculate the normalized percent binding for each standard, control & sample respectively by using the following equation:

$$B/T (\%) = \frac{\text{Std, Cntrl, Sample (cpm)}}{T (\text{cpm})} \times 100$$

Using logarithmic graph paper plot B/T (%) for each standard versus the corresponding concentration of hTSH.

Determine the hTSH concentration of the controls & unknown samples by interpolation from the standard curve.

Automated data processing systems are also applicable.

### Additional information

Components from various lots or from kits of different manufacturers should not be mixed or interchanged.

**Note for the washing step:** Decantation is the most critical step of the assay procedure. Pay a special attention not to contaminate the outer surface of tubes, when turning the test tube-rack upside down. Even a small contamination may introduce a high, unidentified background resulting in a substantial over-estimation of concentration. The error associated may become particularly high in the low range of concentration, which is of vital importance for the reliable determination of subnormal TSH-values. On the same reason, regular checking of the instrument background is inevitable. This is particularly important, when multi-channel counters are used. Make ensure that background values and variation between individual channels are within the range of acceptance as specified in counter's service book.

**Note for the shaking step:** The rack must hold the tubes tight during shaking in order to shake all the tubes with the same speed and strength.

### Precaution

#### Radioactivity

This product contains radioactive material. It is the responsibility of the user to ensure that local regulations or code of practice related to the handling of radioactive materials are satisfied.

## Biohazard










Human blood products used in the kit have been obtained from healthy human donors. They were tested individually by using approved methods (EIA, enzyme immunoassay), and were found to be negative, for the presence of both Human Immunodeficiency Virus antibody (Anti-HIV-1) and Hepatitis B surface Antigen (HBsAg).

Care should always be taken when handling human specimens to be tested with diagnostic kits. Even if the subject has been tested, no method can offer complete assurance that Hepatitis B Virus, Human Immunodeficiency Virus (HIV-1), or other infectious agents are absent. Human blood samples should therefore be handled as *potentially infectious materials*.

## Chemical hazard

Components contain sodium azide as an antimicrobial agent. Dispose of waste by flushing with copious amount of water to avoid build-up of explosive metallic azides in copper and lead plumbing. The total azide present in each pack is 235 mg.

### LEGEND

	Use by	<b>CONTROL</b>	Control
	Batch code	<b>CAL</b>	Standard
	Caution, consult accompanying documents	<b>CT</b>	Coated tube
	Biological risk	<b>TRAC</b>	Tracer
	Consult operating instructions	<b>WASHB</b>	Wash buffer
	In vitro diagnostic medical device		Temperature limitation Store between 2-8°C
	Manufacturer		
<b>REF</b>	Catalogue number		
	Radioactive Material		
<b>CE</b>			

WEB oldal: <http://www.izotop.hu>

Technical e-mail: [immuno@izotop.hu](mailto:immuno@izotop.hu)

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