Expert opinion in respect with biological passport of haematological data

Code report	:	10aKREUZ13.u
Client	:	Mr. Roman Kreuziger
Date	:	25th of August 2013

Commission :

Mr. Roman Kreuziger requested to Dr Douwe de Boer to assist him in a case of so-called irregularities, which were found in the haematological passport of Mr. Kreuziger. The International Cycling Union (UCI) requires explanations and in absence of a satisfactory explanation from the rider, it is considered highly likely that a prohibited substance or a prohibited method has been used. Mr. Kreuziger supplied Dr de Boer relevant information including the haematological data of a total number of 54 tests as made available in documentation of the biological passport of haematological data, also indicated in this report as the Athlete Haematological Passport (AHP). Additionally, endocrinological data of a total number of 8 medical tests as performed in the context of a pathological condition were made available. Other relevant information were the letter of the UCI announcing a potential violation of the anti-doping rules (28th of June 2013), the report of investigation of ABP no. BPY2524M36 (24th of June 2013), the Athlete Biological Passport Documentation Package including the Laboratory Documentation Packages (LDPs) of the separate samples (23rd of June 2013), the Addendum/Errata of the Athlete Biological Passport Documentation Package (24th of June 2013), the competition schedule of the rider, the list and results of the urine tests for EPO and the evaluation of expert panel of the UCI (14th of June 2013).

This report relates to the expert opinion of Dr de Boer in respect with the AHP, discusses some specific observations and points out some explanations were it is required.

It must be stated that several kinds of pre-analytical, physiological and pathological causes can affect the haematological data of the AHP and all those causes in principal must be considered before it can be concluded that the likelihood of the use (a) prohibited substance(s) and/or (a) prohibited method(s) is legally highly likely.

The information in respect with possible pre-analytical, physiological and pathological causes, which was also supplied by Mr. Kreuziger to Dr de Boer, was also covering some pathological background information.

Relevant pathological information was that since 2004 the rider was receiving Euthyrox, because of hypothyroidism. Moreover, in 2005 the rider suffered from an infection with the citomegalovirus, which seemingly reappeared in 2010.

Hypothyroidism

Because family members were suffering from hypothyroidism, the rider underwent an endocrinological check-up. The result of that check-up was that a subclinical hypothyroidism was also diagnosed in his situation. Subsequently, he was receiving since 2004 Euthyrox® (*levo*-thyroxine) in order to correct his subclinical hypothyroidism. In the LDPs the rider frequently indicated that he was taking "Euthyrox®" or "Euritox®" in a specified dosage. In these LDPs it was also reported that the dosage of *levo*-thyroxine was increased in 2011 and further increased in 2012. This information was consistent with information that the rider supplied with the endocrinological examinations as performed by the endocrinologist Dr. G. Brogi (Italy, Pisa). The rider indicated separately to have applied iron supplementation.

Citomegalovirus

In 2005 the rider was suffering from an infection with cytomegalovirus (CMV), which seemingly reappeared in 2010. The rider did not take specific medication to treat the CMV infection and tried to deal with the infection by taking appropriate periods of rest.

1.1 Introduction

The current concept of the biological passport has been initiated by the UCI. In general *An athlete biological passport is an individual, electronic record for professional athletes, in which profiles of haematological makers of doping and results of doping tests are collated over a period of time. Doping violations can be*

detected by noting variances from an athlete's established levels outside permissible limits.

The Swiss anti-doping laboratory in Lausanne (LAD) has developed in cooperation with other anti-doping authorities a sophisticated result management system for the AHP. In the Anti-Doping Administration Management System (ADAMS) of the World Anti-Doping Agency (WADA), the following parameters resulting from a full blood count are today reported for the AHP in ADAMS:

- HCT: haematocrit;
- HGB: haemoglobin;
- RBC: red blood cells count;
- RET%: the percentage of reticulocyte;
- RET#: reticulocytes count;
- MCV: mean corpuscular volume;
- MCH: mean corpuscular haemoglobin;
- MCHC: mean corpuscular haemoglobin concentration.

In addition, the multi-parametric markers OFF-score (index of stimulation) and ABPS (Abnormal Blood Profile Score) are calculated amongst others from this set of parameters.

There are heterogeneous and confounding factors for the AHP, which have been and/or are being applied:

- gender (fixed factor);
- ethnic origin (fixed factor);
- age (fixed factor);
- altitude (time-varying factor);
- type of sport (fixed factor);
- instrument related technology (time-varying factor).

The result management of the AHP requires specific software, which is as far as known not available for other parties outside the anti-doping field. In this software the data of the AHP are corrected for confounding factors. Obviously, in the expert opinion of Dr de Boer that specific software did not analyse the AHP of the respective rider and consequently those data were also not corrected for the respective confounding factors (see Appendices 1 to 5). Nevertheless, an impression can be obtained, which within its limitations can point out some issues.

1.2 Thyroid hormones and haematological indices and hormones

A recent study reviewed in its introduction the current knowledge in respect with the relation between thyroid hormones and haematological indices[1]. They wrote:

Thyroid hormones are essential for erythropoiesis, as shown by studies of the thyroid hormone receptor α (TRα) knockout mouse, which exhibits a reduced number of erythrocyte progenitor cells and impaired erythroid maturation in the foetus, with reduced haematocrit and impaired stress erythropoiesis response in the adult.[2] There appear to be multiple mechanisms by which thyroid hormones stimulate erythropoiesis, including increased erythropoietin production and responsiveness,[3,4,5] and effects on iron transport and utilization.[3,6,7] The relationship between thyroid hormones and iron status is complex and bidirectional, in that thyroid hormones increase iron absorption and incorporation into erythrocytes, whereas iron deficiency impairs thyroid hormone secretion and metabolism and compounds the adverse effects of iodine deficiency on thyroid function[8] Furthermore, when iron deficiency and subclinical hypothyroidism coexist, combined treatment with thyroxine and iron is more effective than iron alone in correcting the anaemia.[7]

Anaemia has long been recognized as a complication of overt hypothyroidism, occurring in up to 25% of patients.[3,9] Red cell mass is frequently reduced in hypothyroid patients, but may go undetected by routine measures such as haemoglobin concentrations because of a concomitant reduction in plasma volume.[10] Only two studies have examined whether subclinical hypothyroidism (defined as raised serum TSH concentration with normal free T4) is associated with altered erythrocyte parameters. In a case–control study, mean serum iron and ferritin concentrations were lower in a group of 57 women

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[1] Bremner *et al.* Significant association between thyroid hormones and erythrocytes indices in euthyroid subjects. Clinical Endocrinology 2012: 76: 304.

[2] Kendrick *et al.* Erythroid defects in $TR\alpha^{-/-}$ mice. Blood 2008: 111; 3205

[3] Fein *et al.* Anemia in thyroid diseases. Medical Clinics of North America 1975: 59; 1133.

[4] Touam *et al.* (2004) Hypothyroidism and resistance to human recombinant erythropoietin. Nephrology, Dialysis, Transplantation 2004:19; 1020.

[5] Christ-Crain *et al.* Effect of restoration of euthyroidism on peripheral blood cells and erythropoietin in women with subclinical hypothyroidism. Hormones 2003: 2; 237.

[6] Donati *et al.* Erythropoiesis in hypothyroidism. Proceedings of the Society for Experimental Biology and Medicine 1973: 144, 78.

[7] Cinemre *et al.* Hematologic effects of levothyroxine in iron-deficient subclinical hypothyroid patients: a randomized, double-blind, controlled study. Journal of Clinical Endocrinology and Metabolism 2009: 94, 151.

[8] Zimmermann *et al.* The impact of iron and selenium deficiencies on iodine and thyroid metabolism: biochemistry and relevance to public health. Thyroid 2002: 12, 867.

[9] Horton *et al.* The haematology of hypothyroidism. Quarterly Journal of Medicine 1976: 45; 101.

[10] Das *et al.* Erythropoiesis and erythropoietin in hypo- and hyperthyroidism. Journal of Clinical Endocrinology and Metabolism 1975: 40; 211.

with subclinical hypothyroidism than in euthyroid controls, but the prevalence of iron deficiency anaemia did not differ significantly between the groups.[11] *In a randomized, controlled trial in 63 women with subclinical hypothyroidism, thyroxine treatment significantly increased serum erythropoietin concentrations, but did not affect haemoglobin or haematocrit.*[5]

In hyperthyroidism, red cell mass is typically increased; but, because of an accompanying increase in plasma volume, circulating haemoglobin concentrations are usually normal.[12] *A subgroup of hyperthyroid patients do, however, develop anaemia, which is reversible with treatment of the thyrotoxicosis.*[13] *The mechanisms of this are uncertain, but may include impaired iron utilization, ineffective erythropoiesis and, in long-standing severe hyperthyroidism, malnutrition.*[12,14,15]

The influence of exercise on thyroid hormones is that they act synergistically with other hormones to elicit energy production as those hormones are important regulators of energy metabolism[16,17]. In hypothyroid and hyperthyroid rats, thyroid hormones together with for example corticosterone and leptin may impair exercise capacity through its known effects on glycogen metabolism[18]. Therefore, adequate treatment of hypo- and hyperthyroidism in athletes seems to be rational and thus essential. *Levo*-thyroxine treatment of hypothyroidism is a very common option. The results of such a treatment of subclinical hypothyroidism or overt hypothyroidism and its associated anaemia with or without iron supplementation may lead to significant improvement of certain haematological indices and/or levels of hormones like erythropoietin (EPO)[5,7,19].

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[11] Duntas *et al.* Incidence of sideropenia and effects of iron repletion treatment in women with subclinical hypothyroidism. Experimental and Clinical Endocrinology and Diabetes 1999: 107; 356.

[12] Ford and Carter. The haematology of hyperthyroidism: abnormalities of erythrocytes, leucocytes, thrombocytes and haemostasis. Postgraduate Medical Journal 1988: 64; 735.

[13] De Groot. Graves' disease and the manifestations of thyrotoxicosis. In: L.J. De Groot ed. Thyroid Disease Manager 2010. Available at: http://www.thyroidmanager.org (accessed 20 April 2011 by Bremner *et al.* and 14 August 2013 by Douwe de Boer).

[14] Rivlin and Wagner. Anemia in hyperthyroidism. Annals of Internal Medicine 1969: 70; 507.

[15] Nightingale *et al.* The haematology of hyperthyroidism. Quarterly Journal of Medicine 1978: 47; 35.

[16] Kanaka-Gantenbein *et al.* The impact of exercise on thyroid hormones metabolism in children and adolescents. Hormone and Metabolic Research 2005: 37; 563.

[17] Neto *et al.* Decreased serum T3 after an exercise session is independent of glucocorticoid peak. Hormone and Metabolic Research 2013: http://dx.doi.org/10.1055/s-0033-1351279

[18] Casimoro *et al.* Maximum acute exercise tolerance in hyperthyroid and hypothyroid rats subjected to forced swimming. Hormone and Metabolic Research 2008: 40; 276.

[19] Kazemi Jahromi *et al.* The association between hypothyroidism and anemia: a clinical study 2010: 4; 6.

1.3 Observations requiring explanation

Several data points were specified by the UCI, which are required to clarify. The remarkable data points that were identified, were starting from **Sample 34 (ADAMS no. 33)** following until **Sample 62 (ADAMS no. 54)** (for exact numbering and collection dates see Appendix 6A).

However, based on for example the data of the MCV values, it can be stated especially in one sample that the MCV and the haematocrit values were significant higher than the overall respective mean values (see Appendix 6B). Especially, those of **Sample 17 (ADAMS no. 17)** were elevated. Therefore, also that sample was identified as being remarkable just because of its MCV and haematocrit value.

Additionally, the samples supplied by the rider himself (**Sample 33, 42, 47 to 50, 52 and 58 (no ADAMS numbering)**; see Appendix 6A and C) require some remarks and explanation.

1.4 Possible explanations for remarkable observations

Samples 17 (ADAMS no. 17): In respect with this sample it was observed that the MCV value was relatively elevated compared to the overall mean MCV level.

The Laboratory Document Package of the respective sample indicated that the sample was analysed 24,5 hours after sample collection, which is adequate if storage temperature before and during transport was adequate. Data were documented in respect with the storage temperature of that sample before transport (LDP sample 770573 page 8), showing that the storage temperature during the first 6 hours was significantly elevated. Therefore, the storage can be criticized and some of the results seriously be questioned. Consequently, the results of the sample are in principal not adequate and for this evaluation were eliminated.

Sample 34 (ADAMS no. 33): In respect with this sample it was observed that the concentration of Thyroid-Stimulating Hormone (also known as TSH or thyrotropin) value was slightly elevated (Appendix 1 and 6). Consequently, a subclinical hypothyroidism was diagnosed and it was concluded that the treatment using the initial dosage of 50 µg of *levo*-thyroxine was not adequate anymore. Based on that the therapeutic dosage was increased to 75 µg of *levo*-thyroxine. In respect with the preceding samples **Sample 31 to 33 (ADAMS no. 30 to 32)** two results out of three for the concentration of haemoglobin were relatively low, i.e. < 146 g/L (Appendix 2), while the overall mean concentration of haemoglobin was 152,9 ± 5,4 g/L (n = 55). This relative decrease in the concentration of haemoglobin is consistent with the subclinical hypothyroidism.

Sample 43, 48 to 51, 53 and 59 (no ADAMS numbering): These samples were taken during as a follow-up of the change of the dosage of the treatment. After increasing the initial dosage from 50 µg to 75 µg of *levo*-thyroxine, the TSH value was decreased in **Sample 43 (no ADAMS numbering)** to a normal reference level including with normal reference levels for free thyroxine (FT4) and free triiodothyronine (FT3). However, some months later **Sample 48 to 51 (no ADAMS numbering)** it became obvious that a further increase of the dosage of *levo*-thyroxine was required. Based on that the therapeutic dosage was increased to 100 µg of *levo*-thyroxine. Follow-up checks (**Sample 53 and 59 (no ADAMS numbering**) proved that the final increase was adequate to treat the subclinical hypothyroidism (Appendices 3 and 4).

In **Sample 48 (no ADAMS numbering)** antibody levels against Thyroid peroxidase (also known as TPO or thyroperoxidase) and Thyreoglobuline (TG) were also checked and proved to be significantly elevated for anti-TPO and not elevated for anti-TG (not presented in Appendix; level for antiTPO was 897 U/mL and for anti-TG 10 U/mL [reference range < 20 U/mL]). This observation is consistent with an autoimmune-based thyroid disorder and explains the observed subclinical thypothyroidism [TSH > 5 mIU/L].

Sample 34 to 61 (ADAMS no. 33 to 54): In respect with this series of samples the expert panel indicated that the average level for the percentage of reticulocytes was above 1.5%, which is supposed to be far beyond the athletes previous levels.

The percentage of reticulocytes in that period was undeniably elevated, but especially with the diagnosed subclinical hypothyroidism and the increasing therapeutic dosage of *levo*-thyroxine that elevation has a rational explanation.

First of all, the expert panel used in Figure 1 of their report of investigation of ABP no. BPY2524M36 (24th of June 2013) not exact the data that were made available for the rider; namely not available were at least those of 2007 and it is not clear which data of the period of 2008 until 2012 were used and which not; moreover, those of 2013 were available, but apparently were not considered. However, that discrepancy and/or incompleteness does probably not influence the overall observation, namely that the percentage of reticulocytes in time was increasing.

Secondly, the expert panel classified the data in Figure 1 based on the years at which the samples were collected. This classification appears to be rational, but in the context of the diagnosed subclinical hypothyroidism and the increasing therapeutic dosage of *levo*-thyroxine should be adapted. Therefore, Dr de Boer applied the following changes: the classification was based primarily on the therapeutic dosages of *levo*-thyroxine as declared on all the sample collection forms (see respective LDP's) and secondly in the period of 2008 and 2010 based on semesters. The last change was performed because of the large number of data points, which made a sub-classification for that period conceivable[20]. These (sub)-classifications were applied for the concentration of haemoglobin as well as the percentage of reticulocytes (Appendix 5).

In Appendix 5 it is demonstrated that in the so-called semesters[21] 2008/2009-1, 2009-2, 2010-1 and 2010-2/2011, when 50 µg of *levo*-thyroxine was administered, that the concentration of haemoglobin as well as that of the percentage of the reticulocytes fluctuates; relatively high in the first semester and relatively low in the second semester. The relatively high percentage of the reticulocytes is the cause of the relatively high concentration of haemoglobin and *vice versa*. In the period when 75 µg of *levo*-thyroxine was administered, the percentage of the reticulocytes

[20] The minimum number of 6 observations was defined as a requirement for sub-classification.

[21] Strictly, speaking it is not always a semester.

increases compared to the preceding semesters, obviously amongst others because of the increased dosage of *levo*-thyroxine. Another reason why the percentage of the reticulocytes may have increased, is the combination with the incidental decrease of the concentration of haemoglobin, which occurred at the end of the semester 2010-2/2011 and which might have been due the non-corrected subclinical hypothyroidism. Despite this increase of the percentage of the reticulocytes, the concentration of haemoglobin did not respond adequately, very likely because the diagnosed subclinical hypothyroidism was not corrected adequately by the therapy of 75 µg of *levo*-thyroxine. The variation in the concentration of haemoglobin in the period when 75 µg of *levo*-thyroxine was administered was substantial.

Because of the inadequate correction, the therapeutic dosage of *levo*-thyroxine was further increased to 100 µg. This way the diagnosed subclinical hypothyroidism was corrected adequately. The variation in the concentration of haemoglobin did not diminish further compared to the period when 75 µg of *levo*-thyroxine was administered. This is very probably because of the fact that even in euthyroid subjects, small differences in thyroid function are associated with significant differences in erythrocyte indices[22].

The pattern with a higher concentration of haemoglobin at the end of the stage race than at the start in the Giro 2012, which is considered to be in contrast to other stage races of the rider, can also be attributed to the fact that even if euthyroid subjects, small differences in thyroid function are associated with significant differences in erythrocyte indices. Moreover, the statuses of a *levo*-thyroxine-supplemented and non-supplemented euthyroid subject are not identical, because the thyroid gland produces thyroxine (T4) and triiodothyronine (T3), while supplementation is achieved with T4 only. Although in principal T4 is transformed peripherally by iodothyronine deiodinases to T3 also, the exact contribution of different tissue deiodinases to the establishment of a euthyroid state is difficult to establish. After all, in blood the peripheral concentrations are not determined and also the efficiency of the deiodinases is not identical for every subject. Moreover, exercise itself has influence

[22] Bremner *et al.* Significant association between thyroid hormones and erythrocytes indices in euthyroid subjects. Clinical Endocrinology 2012: 76: 304.

on T3 kinetics in man[23]. In combination with incidently supplemented iron[24], overall differences in erythrocyte indices may have been enhanced in the rider after changing the dosage of a *levo*-thyroxine. Therefore, the situation in 2012 was for the rider not identical compared to that of previous years and any comparison should be done in the context of changes in the thyroid status.

In 2005 the rider was suffering from an infection with cytomegalovirus (CMV), which seemingly reappeared in 2010. These infections occured before the period that required explanation by the UCI and therefore, this was not taken into account.

1.5 Conclusions:

The extensive haematological profile BPY2524M36 can be assigned as difficult to assess due to various reasons. Remarkable and/or other observations can be explained by a diagnosed subclinical hypothyroidism and the attempts to correct this thyroid disorder by therapeutic dosages of of *levo*-thyroxine.

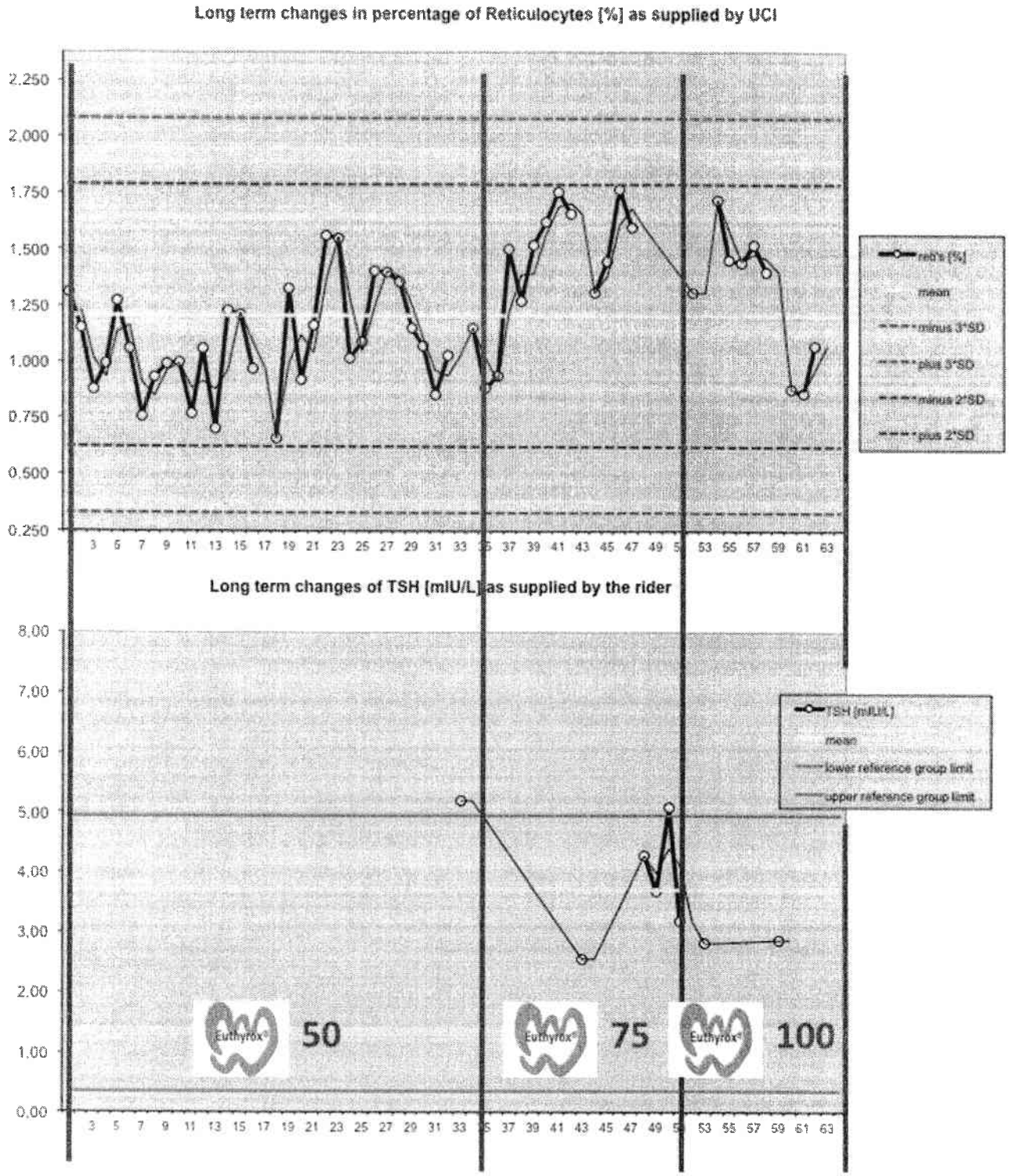
The fact that even in euthyroid subjects, small differences in thyroid function are associated with significant differences in erythrocyte indices, amongst others explains the variations during the period of for example 2012 compared to previous years.

[23] Rone *et al.* The effect of endurance training on serum triiodothyronine kinetics in man: physical conditioning marked by enhanced thyroid hormone metabolism. Clinical endocrinology 1992: 37; 325.

[24] Cinemre *et al.* Hematologic effects of levothyroxine in iron-deficient subclinical hypothyroid patients: a randomized, double-blind, controlled study. Journal of Clinical Endocrinology and Metabolism 2009: 94, 151.

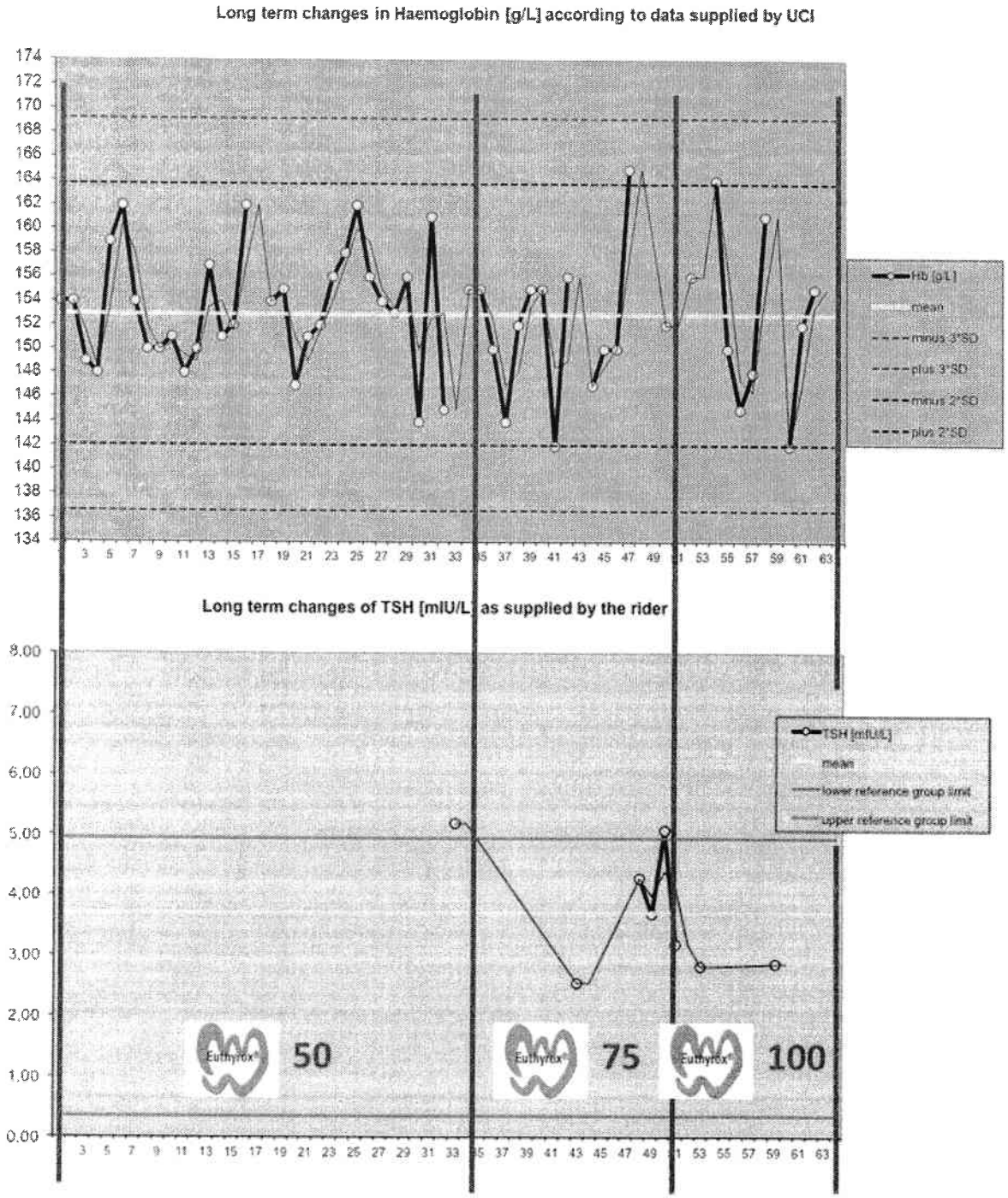
Appendix 1

(for corresponding dates of data points see Appendix 6; first graphic includes all relevant data points as supplied by the UCI and second graphic contains only data of TSH as supplied by the rider)



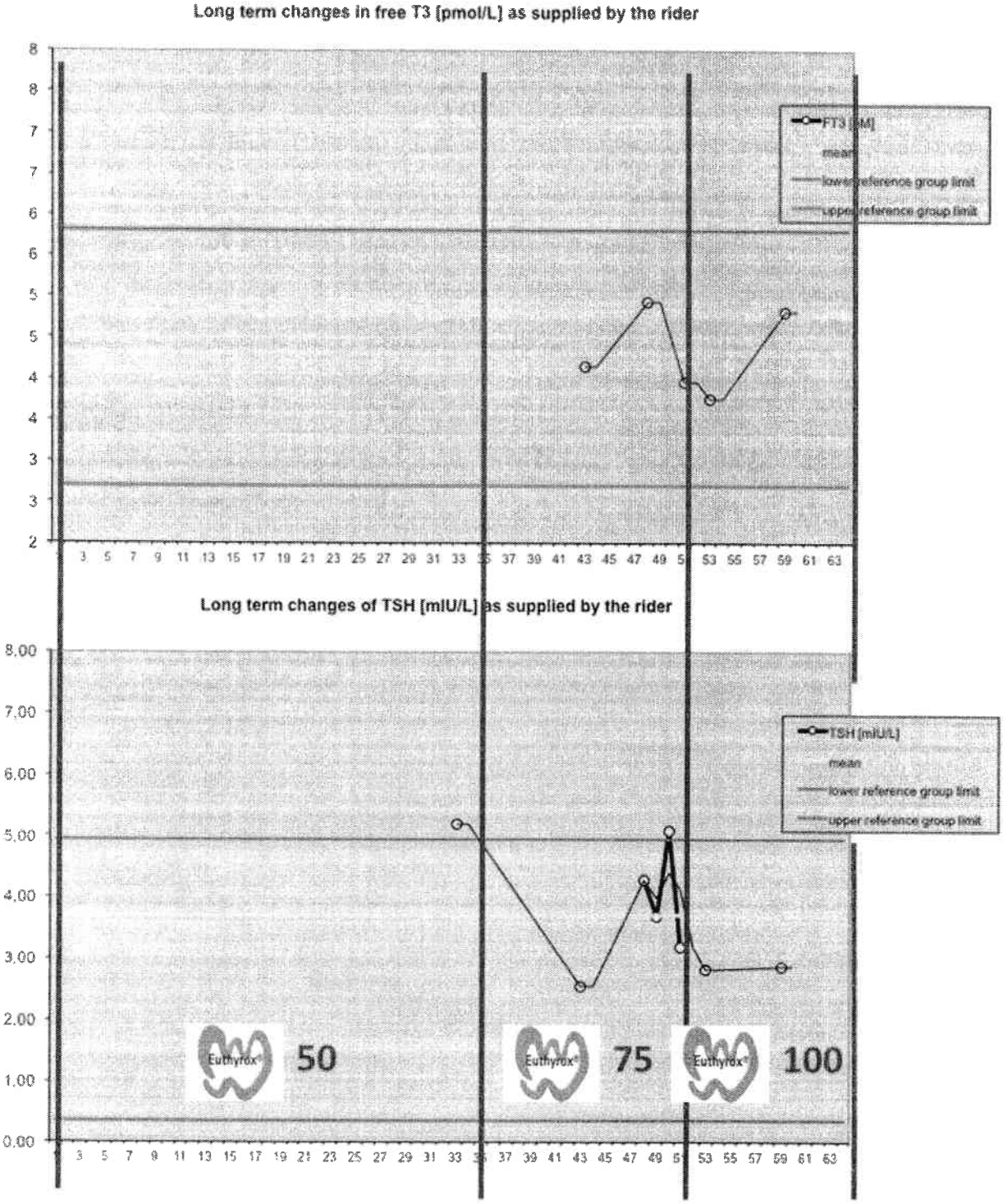
Appendix 2

(for corresponding dates of data points see Appendix 6; first graphic includes all relevant data points as supplied by the UCI and second graphic contains only data of TSH as supplied by the rider)



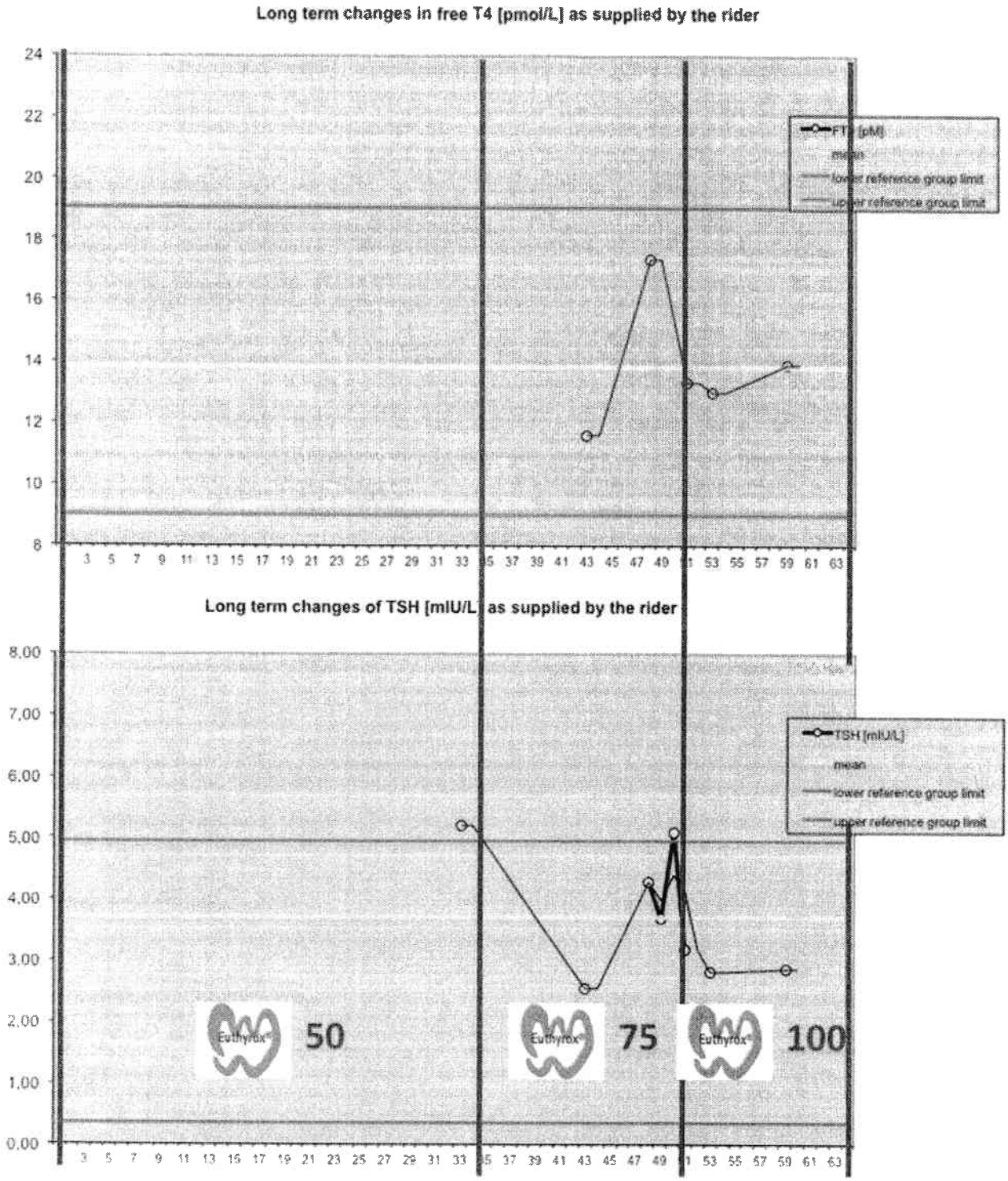
Appendix 3

(for corresponding dates of data points see Appendix 6; first as well as second graphic includes all relevant data points as supplied by the rider)



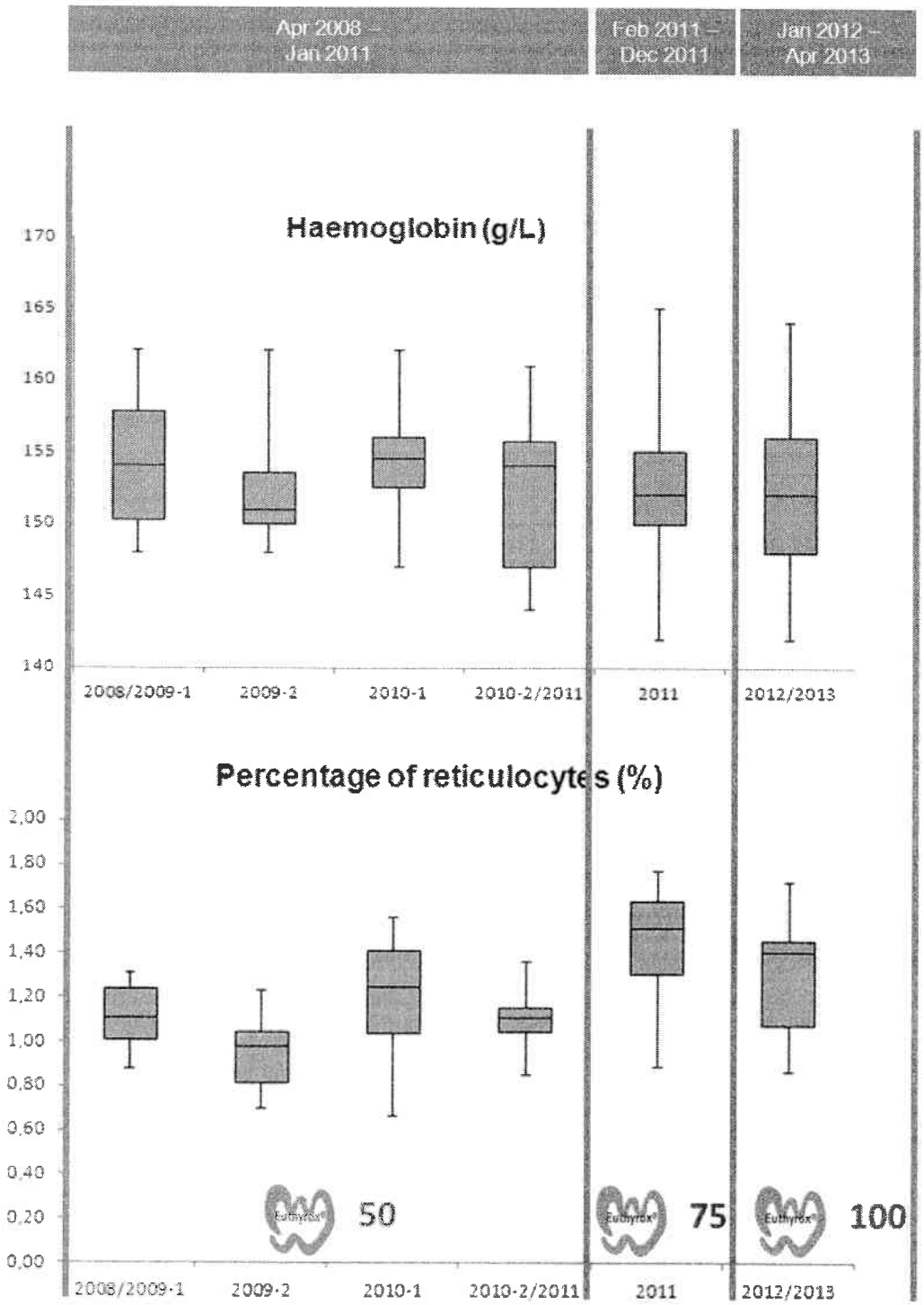
Appendix 4

(for corresponding dates of data points see Appendix 6; first as well as second graphic includes all relevant data points as supplied by the rider)



Appendix 5

(for corresponding dates of data points see Appendix 6; both graphics include all relevant data points including those as supplied by the rider; 2008/2009-1 corresponds to **Sample 1 to 6 (ADAMS no. 1 to 6)**); 2009-2 to **Sample 7 to 16 (ADAMS no. 7 to 16)**; 2010-1 to **Sample 18 to 28 (ADAMS no. 18 to 28)**; 2010-2/2011 to **Sample 29 to 34 (ADAMS no. 29 to 33)**; 2011 to **Sample 35 to 50 (ADAMS no. 34 to 45)**; 2012 to **Sample 51 to 62 (ADAMS no. 46 to 54)**.



Appendix 6A

datapoint	date of sampling	date of analysis	difference sampling and analysis (hrs)	ADAMS #	origin of data
1	23-04-08 7:45	23-04-13 9:01	1,3	1	Ghent WADA
2	30-04-08 7:45	30-04-08 11:42	4,0	2	Lausanne WADA
3	3-07-08 9:58	4-07-08 8:52	22,9	3	Lausanne WADA
4	15-07-08 19:29	16-07-08 11:14	15,8	4	Lausanne WADA
5	28-04-09 8:46	28-04-09 11:05	2,3	5	Lausanne WADA
6	7-06-09 8:05	8-06-09 10:21	26,3	6	Cologne WADA
7	2-07-09 9:26	2-07-09 18:43	9,3	7	Lausanne WADA
8	10-07-09 8:05	11-07-09 8:59	24,9	8	Lausanne WADA
9	11-07-09 9:45	12-07-09 9:28	23,7	9	Lausanne WADA
10	13-07-09 9:54	14-07-09 14:30	28,6	10	Lausanne WADA
11	20-07-09 10:45	20-07-09 16:45	6,0	11	Lausanne WADA
12	15-08-09 18:05	16-08-09 18:22	24,3	12	Cologne WADA
13	27-08-09 8:50	27-08-09 19:31	10,7	13	Lausanne WADA
14	11-09-09 9:07	12-09-09 9:54	24,8	14	Lausanne WADA
15	28-09-09 16:35	29-09-09 11:03	16,5	15	Cologne WADA
16	28-11-09 18:35	29-11-09 17:20	22,8	16	Cologne WADA
17	15-02-10 9:37	16-02-10 10:04	24,5	17	Cologne WADA
18	23-02-10 6:23	24-02-10 15:37	33,2	18	Lausanne WADA
19	1-03-10 7:13	2-03-10 13:37	30,4	19	Dresden WADA
20	15-03-10 9:23	16-03-10 11:37	26,2	20	Cologne WADA
21	19-03-10 19:07	20-03-10 8:19	13,2	21	Lausanne WADA
22	6-04-10 19:50	7-04-10 15:55	20,1	22	Madrid WADA
23	11-04-10 21:53	12-04-10 16:08	18,3	23	Madrid WADA
24	23-04-10 7:12	23-04-10 14:35	7,4	24	Ghent WADA
25	27-04-10 8:20	27-04-10 18:31	10,2	25	Lausanne WADA
26	17-05-10 7:36	18-05-10 12:28	14,9	26	Dresden WADA
27	4-06-10 20:18	5-06-10 15:30	19,2	27	Cologne WADA
28	8-06-10 20:18	10-06-10 15:11	42,5	28	Dresden WADA
29	1-07-10 8:36	1-07-10 18:28	9,9	29	Lausanne WADA
30	21-07-10 8:34	22-07-10 15:18	6,7	30	Lausanne WADA
31	26-08-10 9:35	26-08-10 20:04	10,5	31	Lausanne WADA
32	6-09-10 11:00	7-09-10 15:55	28,9	32	Lausanne WADA
33	2-12-10 0:00				Medical data supplied by rider
34	24-01-11 8:31	25-01-11 10:17		33	Cologne WADA
35	6-03-11 7:48	7-03-10 9:27	25,7	34	Chatenay Malabry WADA
36	9-03-11 20:38	11-03-11 8:34	35,9	35	Chatenay Malabry WADA
37	14-03-11 7:03	15-03-11 15:13	32,2	36	Dresden WADA
38	25-04-11 8:24	26-04-11 14:25	30,0	37	Lausanne WADA
39	5-05-11 10:07	5-05-11 18:49	8,7	38	Lausanne WADA
40	20-05-11 8:57	20-05-11 18:04	9,9	39	Lausanne WADA
41	29-05-11 10:01	29-05-11 15:39	5,6	40	Lausanne WADA
42	8-06-11 8:06	9-06-11 9:38	25,8	41	Dresden WADA
43	16-06-11 0:00				Medical data supplied by rider
44	30-06-11 8:14	30-06-11 22:45	13,5	42	Lausanne WADA
45	15-07-11 9:35	16-07-11 12:00	26,4	43	Lausanne WADA
46	20-07-11 8:05	20-07-11 16:18	8,2	44	Lausanne WADA
47	1-08-11 6:30	2-08-11 10:28	28,0	45	Dresden WADA
48	2-11-11 0:00				Medical data supplied by rider
49	2-12-11 0:00				Medical data supplied by rider
50	19-01-12 0:00				Medical data supplied by rider
51	7-03-12 0:00				Medical data supplied by rider
52	11-04-12 14:02	12-04-12 13:54	23,9	46	Dresden WADA
53	17-04-12 0:00				Medical data supplied by rider
54	24-04-12 8:57	24-04-12 11:57	3,0	47	Lausanne WADA
55	3-05-12 7:40	3-05-12 22:58	14,5	48	Lausanne WADA
56	14-05-12 9:20	15-05-12 8:35	23,3	49	Lausanne WADA
57	20-05-12 9:30	20-05-12 16:05	6,6	50	Lausanne WADA
58	24-05-12 10:07	25-05-12 7:48	21,7	51	Lausanne WADA
59	11-06-12 0:00				Medical data supplied by rider
60	20-06-12 9:10	21-06-12 10:22	25,2	52	Cologne WADA
61	6-03-13 8:15	7-03-13 8:54	24,7	53	Lausanne WADA
62	9-04-13 9:47	10-04-13 11:50	26,0	54	Cologne WADA

Appendix 6B

datapoint	Hb [g/L]	reti´s [x10^9/L]	reti's [%]	SI	MCV [fL]	MCH [fmol]	MCHC [fM]	RBC [x10^{12}/L]	Ht [%]	trombo´s [x10^9/L]	MPV [fL]	TSH [mIU/L]	free T3 [pmol/L]	free T4 [pmol/L]
1	154,0	67,7	1,31	85,3	88,2	1,850	21,0	5,17	45,6	254	11,6			
2	154,0	59,6	1,15	89,6	87,5	1,844	21,1	5,18	45,3	249	11,1			
3	149,0	44,4	0,88	92,7	89,3	1,831	20,5	5,05	45,1	210	11,2			
4	148,0	49,5	0,99	88,3	90,4	1,837	20,3	5,00	45,2	280	11,0			
5	159,0	68,2	1,27	91,4	89,4	1,837	20,5	5,37	48,0	247	10,9			
6	162,0	57,7	1,06	100,2	89,9	1,850	20,5	5,44	48,9	288	11,4			
7	154,0	38,8	0,76	101,7	90,8	1,868	20,6	5,11	46,4	275	11,2			
8	150,0	46,9	0,93	92,1	91,3	1,850	20,9	5,04	46,0	234	11,7			
9	150,0	50,6	0,99	90,3	91,4	1,825	19,9	5,11	46,7	223	12,1			
10	151,0	50,7	1,00	91,0	92,3	1,850	20,0	5,07	46,8	244	11,9			
11	148,0	38,4	0,77	95,4	91,2	1,844	20,2	4,99	45,5	271	11,2			
12	150,0	53,6	1,06	88,2	89,3	1,837	20,6	5,06	45,2	245	11,6			
13	157,0	37,0	0,70	106,8	90,2	1,844	20,4	5,29	47,7	260	11,3			
14	151,0	63,1	1,23	84,5	90,8	1,825	20,4	5,13	46,6	236	11,4			
15	152,0	62,4	1,21	86,0	89,3	1,831	20,5	5,16	46,1	264	11,5			
16	162,0	53,4	0,97	102,9	86,2	1,825	21,2	5,51	47,5	292	11,8			
17	164,0	66,7	1,20	98,3	94,4	1,831	19,4	5,56	52,5	224	12,3	sample not adequate		
18	154,0	34,1	0,66	105,3	89,9	1,850	20,5	5,17	46,5	253	12,0			
19	155,0	68,8	1,32	86,0	91,2	1,850	20,2	5,20	47,5	247				
20	147,0	45,3	0,92	89,4	92,1	1,856	20,2	4,92	45,3	284	11,6			
21	151,0	59,2	1,16	86,4	89,2	1,850	20,6	5,10	45,5	267	11,1			
22	152,0	78,3	1,56	77,1	90,8	1,881	20,7	5,02	45,6	299	12,1			
23	156,0	80,6	1,55	81,3	93,8	1,862	19,9	5,20	48,8	287	12,7			
24	158,0	52,3	1,02	97,4	92,2	1,912	20,7	5,13	47,3	193	13,2			
25	162,0	59,2	1,09	99,4	90,6	1,850	20,4	5,43	49,2	224	11,6			
26	156,0	73,2	1,41	84,8	90,2	1,868	20,7	5,20	46,8	141				
27	154,0	72,7	1,40	83,0	88,1	1,844	20,9	5,19	45,7	290	11,7			
28	153,0	69,2	1,36	83,1	90,3	1,881	20,9	5,10	45,6	279				
29	156,0	59,9	1,15	91,7	91,4	1,856	20,4	5,21	47,6	267	11,6			
30	144,0	51,8	1,07	81,9	90,9	1,850	20,3	4,84	44,0	287	11,8			
31	161,0	46,0	0,85	105,7	90,2	1,850	20,5	5,41	48,8	246	11,8			

Appendix 6C

datapoint	Hb [g/L]	reti´s [x10^9/L]	reti's [%]	SI	MCV [fL]	MCH [fmol]	MCHC [fM]	RBC [x10^{12}/L]	Ht [%]	trombo´s [x10^9/L]	MPV [fL]	TSH [mIU/L]	free T3 [pmol/L]	free T4 [pmol/L]
32	145,0	50,7	1,03	84,1	94,3	1,831	19,4	4,92	46,4	242	12,3			
33												5,19		
34	155,0	60,6	1,15	90,7	89,2	1,825	20,5	5,27	47,0	258	11,8			
35	155,0	47,2	0,88	98,6	88,7	1,837	20,7	5,35	46,5	248	11,4			
36	150,0	47,7	0,94	91,8	87,8	1,837	20,9	5,07	44,5	251	11,8			
37	144,0	73,7	1,50	70,4	90,9	1,844	20,3	4,90	44,1	269				
38	152,0	63,5	1,27	84,4	90,6	1,837	20,9	5,00	45,3	253	12,3			
39	155,0	78,4	1,52	81,0	90,9	1,862	20,5	5,16	46,9	245	11,4			
40	155,0	84,1	1,62	78,5	90,1	1,862	20,7	5,18	46,5	222	11,2			
41	142,0	84,1	1,76	62,4	90,0	1,844	20,5	4,78	43,0	254	10,9			
42	156,0	85,5	1,66	78,7	94,0	1,881	20,0	5,15	48,4	286	11,8			
43												2,55	4,1	11,6
44	147,0	63,9	1,31	78,3	90,2	1,868	20,7	4,88	44,0	229	11,5			
45	150,0	71,2	1,45	77,7	89,8	1,893	21,2	4,91	44,0	275	11,5			
46	150,0	88,1	1,77	70,2	89,0	1,868	21,0	4,98	44,3	283	11,1			
47	165,0	84,8	1,60	89,1	89,8	1,930	21,5	5,30	47,6	248	11,7			
48												4,29	4,9	17,3
49												3,69		
50												5,08		
51												3,18	4,0	13,3
52	156,0	66,5	1,31	87,4	91,1	1,906	20,9	5,08	46,3	227	12,1			
53												2,81	3,8	13,0
54	164,0	95,1	1,72	85,3	91,0	1,844	20,4	5,53	50,3	244	11,4			
55	150,0	72,4	1,45	77,7	90,9	1,875	20,7	4,98	45,1	273	11,2			
56	145,0	69,0	1,44	73,0	90,2	1,881	20,9	4,79	43,2	255	11,3			
57	148,0	74,9	1,52	74,0	90,9	1,862	20,5	4,93	44,8	274	11,4			
58	161,0	74,9	1,40	90,0	89,9	1,868	20,8	5,35	48,1	298	11,4			
59												2,86	4,8	13,9
60	142,0	41,7	0,88	85,7	92,6	1,862	20,0	4,74	43,9	236	11,6			
61	152,0	43,6	0,86	96,4	89,9	1,862	20,7	5,07	45,6	270	11,6			
62	155,0	56,5	1,07	92,9	89,6	1,825	20,4	5,28	47,3	272	11,9			

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