



## **Smokeless Tobacco Sub-Group**

# **Technical Report**

## **CORESTA Reference Products 2011 Analysis**

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APPENDIX A: Statistical Report: CORESTA Smokeless Tobacco Inter-laboratory Study: Analysis of CORESTA Reference Products for pH, nicotine, moisture, NAB, NAT, NNK, NNN and total TSNAs, 2010 & 2011.

## 1. Summary

In 2011 the CORESTA Smokeless Tobacco Sub-Group (STS) conducted the first Working Group 4 (WG4) study designed to establish baseline values in an ongoing effort to assess the stability of the four CORESTA Reference Products (CRPs). Twelve laboratories participated in this initial study. The participating laboratories reported the levels of nicotine, pH, moisture (oven volatiles) and tobacco specific nitrosamines (TSNAs) using CORESTA Recommended Methods (CRMs) or draft CRMs. These data will serve as a baseline for future WG4 studies that will be conducted on an annual basis in order to monitor stability of the CRPs. Tabulated data are presented along with repeatability (r) and reproducibility (R). Additionally, tabulated data and r&R are presented for an earlier study conducted in 2010 as a point of comparison. Unlike the 2011 study, methods were not specified in the 2010 study. For this reason, the 2010 results are not compared to the 2011 results as a measure of product stability.

## 2. Introduction

In November 2008, the Smokeless Tobacco Sub-Group (STS) was established by recommendation of the CORESTA Scientific Commission. In 2009, STS Working Group Three (WG3) cooperated to design and manufacture four CORESTA Reference Products (CRPs) referred to as CRP-1, CRP-2, CRP-3, and CRP-4. Except for CRP-1, these products were intended as replacements for the Smokeless Tobacco Research Products: 2S3 (Moist Snuff), 1S2 (Dry Snuff) and 2S1 (Loose-leaf Chewing Tobacco), which were greater than ten years old.

At the Amelia Island, Florida STS meeting (October 2009), Working Group Four (WG4) was organized to proceed with the chemical characterization of the four CRPs. The protocol for the first WG4 study<sup>1</sup> was distributed in December 2009 and the study was conducted in 2010. This study included 43 analytes and did not specify methods of analysis. Many of the results from this study showed a wide range in analyte results, which is not unexpected since the methods were not harmonized. The recommendations from the 2010 study were to monitor the stability of the CRPs on an annual basis, by determining the levels of nicotine, pH, moisture (oven volatiles) and TSNAs using CORESTA Recommended Methods (CRMs) or draft CRMs. This annual analysis would allow the STS to determine when the CRPs should be remanufactured.

At the STS Meeting in Hamburg, Germany (May 2011), it was decided to adopt the recommendations from the 2010 WG4 study and initiate the *first* annual analysis of the four CRPs using CRMs. The first WG4 study using CRMs was conducted in 2011 and is the focus of this Technical Report. Therefore, the data generated in 2011 will serve as the baseline for future WG4 stability analyses.

CRP-1 through CRP-4 continue to be stored at -20°C and distributed by the North Carolina State University (NCSU) Tobacco Analytical Services Lab under the direction of Dr. David Danehower<sup>2</sup>, Associate Professor in the Department of Crop Science. In 2012, this responsibility was assigned to Dr. Ramsey Lewis<sup>3</sup>, with CRP sample requests being directed to Karen Andres<sup>4</sup>.

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1 Smokeless Tobacco Sub-Group Technical Report: CORESTA Reference Products 2010 Analysis, February, 2014

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## 2.1 Objective

The participating laboratories in the 2011 WG4 analysis of the four CRPs were to provide analytical results for pH, moisture (oven volatiles), nicotine, and the four TSNAs (N-Nitrosornicotine (NNN), N-Nitrosoanatabine (NAT), N-Nitrosoanabasine (NAB) and 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK)). This work was conducted using the applicable CRMs or draft CRMs.

The 2011 study was the first study to support a general assessment of stability for the CRPs. Additional study objectives were: to provide more robust data using the new or updated CRMs; to support laboratory operations; and to provide data for an interlaboratory comparison of results. It is intended that the 2011 study will serve as the baseline for the determination of stability. This study will be repeated on an annual basis, as is currently done for the CORESTA Monitor Test Piece.

As mentioned in the introduction, a 2010 WG4 study was conducted for the determination of a wide range of analytes in the CRPs. However, the 2010 study did not specify methods of analysis. The 2010 pH, moisture (oven volatiles), nicotine, and TSNA data are included in this report only as a point of reference and will not be compared to the 2011 data as a measure of stability. A decision regarding the inclusion or exclusion of the 2010 data in the stability analysis will be evaluated as additional stability data are collected in subsequent years by WG4.

## 3. Organisation

### 3.1 Participants

A list of the participating laboratories is provided in Table 1. The laboratories are listed in alphabetical order. Letter codes were assigned to each laboratory and do not correspond to the order in the table below. Since the statistical analysis would include repeatability and reproducibility for data from 2010 and 2011, the laboratory letter codes were maintained between the tables for both years. Data are not reported in either time period for laboratory K. Furthermore, not all laboratories participated in both time points or submitted data for all analyses.

**Table 1: List of Participating Laboratories in 2011 WG4 Study**

Participating Laboratories
Arista Laboratories
British American Tobacco Southampton
Borgwaldt Hamburg
Eurofins Food & Agro Sweden AB
Global Laboratory Services
Imperial Tobacco Group Reemstma
Japan Tobacco, Inc.
Japan Tobacco International-Ökolab
Labstat International
Pöschl Tabak GmbH & Co. KG
RJ Reynolds Tobacco
Swedish Match Northern Europe

## 3.2 Protocol

Specific details from the protocol are described below:

### Sample Shipment

Samples of the four CRPs were shipped by NCSU to each of the participating laboratories of WG4 during the week of August 1, 2011. It was requested that the analyses be completed by September 9, 2011.

**Table 2: Sample Identification**

Product Type
CRP1 - Swedish style snus pouch
CRP2 - American-style loose moist snuff
CRP3 - American-style loose dry snuff powder
CRP4 - American-style loose-leaf chewing tobacco

### Within Laboratory Sample Preparation

The laboratories were directed to thaw the samples at room temperature for at least 2 hours before use. After this initial thawing, the samples were to be stored at approximately 4°C in between use. Additionally:

- The snus pouch (CRP-1) was to be cut into 2 halves and placed directly into the extraction vessel. Both the snus and pouch material were analysed.
- The moist snuff reference product (CRP-2) and the dry snuff reference product (CRP-3) did not require sample grinding and were analysed as received.
- The loose leaf reference product (CRP-4) was to be ground according the participating laboratory's standard procedure.

### Sample Analysis and Data Reporting

The WG4 participating laboratories were instructed to conduct triplicate analyses for the following analytes: pH, moisture (oven volatiles), nicotine, and TSNAs. The laboratories were requested to use the following CRMs or draft CRMs:

- pH: CRM N° 69, Determination of pH in Smokeless Tobacco Products
- Moisture (oven volatiles): Draft CRM N° 76, Determination of Moisture Content (Oven Volatiles) of Smokeless Tobacco Products
- Nicotine: CRM N° 62, Determination of Nicotine in Tobacco and Tobacco Products by Gas Chromatographic Analysis
- TSNAs: Draft CRM N° 72, Determination of Tobacco Specific Nitrosamines in Smokeless Tobacco Products by Liquid Chromatography - Tandem Mass Spectrometry

Participating laboratories were requested to document any deviations from the (draft) CRMs and submit the deviations with their results. All test results were to be reported *as-is* with no correction for moisture content. The limits of detection (LODs) and limits of quantification (LOQs) were provided by the participating laboratories. The results were not to be rounded and, ideally, reported to at least one more digit than typically required.

The spread sheet with the results of the analysis and the comments were to be sent by e-mail to John E. Bunch, Study Coordinator, by September 9, 2011.

## 4. Data – Raw

Data from the 2010 and 2011 studies are listed in the tables 3 and 4, respectively. If a laboratory did not participate in the study, or did not submit data for a given analysis, the cells were left blank.

**Table 3: 2010 WG4 Data from CORESTA Technical Report: CORESTA Reference Products 2010 Analysis, March 2012\***

Laboratory code	Product	Replicate	Nicotine (%)	pH	Moisture (%)	NAB (ppm)	NAT (ppm)	NNK (ppm)	NNN (ppm)	TSNA Total (ppm)
A	CRP1	1	0,9700	7,98	51,33	0,040	0,669	0,233	0,642	1,583
A	CRP1	2	0,9600	7,97	51,24	0,046	0,563	0,240	0,734	1,582
A	CRP1	3	0,9710	7,98	51,44	0,041	0,616	0,206	0,655	1,516
A	CRP2	1	1,2670	7,73	54,87	0,162	1,962	0,499	1,798	4,421
A	CRP2	2	1,2720	7,72	54,86	0,156	2,032	0,575	2,060	4,823
A	CRP2	3	1,2650	7,72	54,80	0,151	1,896	0,486	1,799	4,332
A	CRP3	1	2,2600	6,78	8,12	0,391	6,708	5,050	9,718	21,867
A	CRP3	2	2,2520	6,79	8,27	0,389	6,970	4,600	9,325	21,284
A	CRP3	3	2,2590	6,79	8,19	0,413	6,308	4,628	9,312	20,661
A	CRP4	1	1,0890	5,93	21,68	0,066	1,256	0,505	2,214	4,041
A	CRP4	2	1,1030	5,94	21,74	0,063	1,310	0,468	2,054	3,894
A	CRP4	3	1,0880	5,93	21,77	0,057	1,362	0,456	2,115	3,990
B	CRP1	1	1,0100	8,01		0,031	0,483	0,234	0,668	1,416
B	CRP1	2	0,9880	8,02		0,031	0,485	0,234	0,674	1,424
B	CRP1	3	1,0400	8,01		0,032	0,513	0,235	0,667	1,447
B	CRP2	1	1,3300	7,75		0,169	1,820	0,514	1,960	4,463
B	CRP2	2	1,3200	7,74		0,165	1,780	0,481	1,920	4,346
B	CRP2	3	1,2800	7,77		0,173	1,820	0,537	1,930	4,460
B	CRP3	1	2,3200	6,75		0,428	5,250	4,240	8,080	17,998
B	CRP3	2	2,3500	6,77		0,418	5,330	4,340	8,020	18,108
B	CRP3	3	2,3200	6,83		0,421	5,300	3,980	8,070	17,771
B	CRP4	1	1,2200	5,98		0,050	0,970	0,395	1,730	3,145
B	CRP4	2	1,2000	5,93		0,051	0,979	0,390	1,640	3,060
B	CRP4	3	1,2000	5,92		0,050	0,960	0,362	1,680	3,052
C	CRP1	1	1,1121							
C	CRP1	2	1,1257							
C	CRP1	3	1,1175							
C	CRP2	1	1,4486							
C	CRP2	2	1,3908							
C	CRP2	3	1,3575							
C	CRP3	1	1,8642							
C	CRP3	2	1,7850							
C	CRP3	3	1,7194							
C	CRP4	1	1,2710							
C	CRP4	2	1,2848							

Laboratory code	Product	Replicate	Nicotine (%)	pH	Moisture (%)	NAB (ppm)	NAT (ppm)	NNK (ppm)	NNN (ppm)	TSNA Total (ppm)
C	CRP4	3	1,3535							
D	CRP1	1	0,8800		52,00					
D	CRP1	2	1,0320		51,60					
D	CRP1	3	0,8810		51,60					
D	CRP2	1	1,2120		54,40					
D	CRP2	2	1,2710		54,40					
D	CRP2	3	1,3180		54,20					
D	CRP3	1	2,0170		8,46					
D	CRP3	2	2,1200		8,45					
D	CRP3	3	1,9430		8,36					
D	CRP4	1	1,0390		21,90					
D	CRP4	2	1,0780		21,80					
D	CRP4	3	1,0820		21,70					
E	CRP1	1	1,0300		56,10	0,030	0,590	0,230	0,680	1,530
E	CRP1	2	1,0400		56,10	0,030	0,580	0,230	0,690	1,530
E	CRP1	3	1,0700		56,10	0,030	0,570	0,230	0,690	1,520
E	CRP2	1	1,4000		53,10	0,170	1,960	0,490	1,970	4,590
E	CRP2	2	1,3700		53,10	0,160	1,970	0,500	1,910	4,540
E	CRP2	3	1,3800		53,10	0,150	1,890	0,470	1,850	4,360
E	CRP3	1	2,3100		7,30	0,480	5,670	4,790	8,660	19,600
E	CRP3	2	2,3400		7,30	0,410	5,000	4,250	8,890	18,550
E	CRP3	3	2,3200		7,30	0,440	5,150	4,370	8,960	18,920
E	CRP4	1	1,2300		21,90	0,060	1,280	0,420	1,930	3,690
E	CRP4	2	1,2500		21,90	0,070	1,220	0,470	1,910	3,670
E	CRP4	3	1,2600		21,90	0,060	1,220	0,420	1,880	3,580
L	CRP1	1	0,9010	7,93	51,51	0,060	0,700	0,230	0,910	1,900
L	CRP1	2	0,8990	7,94	51,85	0,060	0,680	0,230	0,900	1,870
L	CRP1	3	0,9050	7,97	51,12	0,060	0,730	0,240	0,890	1,920
L	CRP2	1	1,1730	7,70	54,82	0,210	2,180	0,450	2,080	4,920
L	CRP2	2	1,1880	7,71	54,67	0,210	2,230	0,440	2,120	5,000
L	CRP2	3	1,1920	7,71	54,58	0,210	2,040	0,400	2,000	4,650
L	CRP3	1	2,1060	6,80	9,03	0,460	5,850	2,690	6,800	15,800
L	CRP3	2	2,1180	6,82	8,81	0,450	5,810	2,790	6,930	15,980
L	CRP3	3	2,1120	6,81	8,85	0,470	6,460	2,810	6,970	16,710
L	CRP4	1	0,9960	5,88	22,80	0,080	1,590	0,430	2,420	4,520
L	CRP4	2	0,9880	5,90	22,90	0,090	1,670	0,460	2,430	4,650
L	CRP4	3	0,9030	6,10	22,50	0,080	1,510	0,380	2,200	4,170
M	CRP1	1	0,9180	8,09	51,90	0,000	0,458	0,190	0,579	1,227
M	CRP1	2	0,9010	8,06	51,70	0,000	0,445	0,189	0,575	1,209
M	CRP1	3	0,9080	8,03	51,30	0,000	0,442	0,187	0,588	1,217
M	CRP2	1	1,2030	7,85	54,64	0,121	1,485	0,389	1,591	3,586
M	CRP2	2	1,2090	7,80	54,81	0,118	1,471	0,370	1,548	3,507
M	CRP2	3	1,2130	7,80	54,60	0,119	1,502	0,392	1,570	3,583

Laboratory code	Product	Replicate	Nicotine (%)	pH	Moisture (%)	NAB (ppm)	NAT (ppm)	NNK (ppm)	NNN (ppm)	TSNA Total (ppm)
M	CRP3	1	2,0640	6,86	8,09	0,334	4,986	3,577	7,378	16,275
M	CRP3	2	2,0560	6,78	7,94	0,335	4,906	3,565	7,400	16,206
M	CRP3	3	2,0510	6,80	7,93	0,323	4,881	3,594	7,342	16,140
M	CRP4	1	0,9950	6,00	22,66	0,051	1,011	0,355	1,720	3,137
M	CRP4	2	0,9940	5,92	22,40	0,051	1,008	0,370	1,741	3,170
M	CRP4	3	0,9960	6,01	22,84	0,053	1,024	0,368	1,721	3,166
N	CRP1	1	0,9400	7,76	51,85	0,024	0,427	0,182	0,478	1,111
N	CRP1	2	0,9300	7,75	51,53	0,018	0,489	0,209	0,527	1,243
N	CRP1	3	0,9500	7,78	50,73	0,029	0,459	0,202	0,542	1,232
N	CRP2	1	1,2000	7,50	54,93	0,123	1,786	0,394	1,439	3,742
N	CRP2	2	1,2000	7,47	54,74	0,128	1,597	0,411	1,581	3,717
N	CRP2	3	1,2000	7,56	54,80	0,133	1,739	0,402	1,474	3,748
N	CRP3	1	2,0900	6,70	8,45	0,313	5,073	3,052	6,906	15,344
N	CRP3	2	2,1000	6,71	8,41	0,393	5,499	3,997	6,916	16,805
N	CRP3	3	2,1000	6,71	8,44	0,293	5,411	3,458	6,358	15,520
N	CRP4	1	1,0400	5,94	20,96	0,050	1,070	0,350	1,670	3,140
N	CRP4	2	1,0500	5,92	20,49	0,050	1,070	0,420	1,630	3,170
N	CRP4	3	1,0800	5,91	20,62	0,050	1,070	0,340	1,530	2,990

\*Only pH, moisture (oven volatiles), nicotine, and TSNA data from the 2010 study are shown.

**Table 4: 2011 WG4 Data**

Laboratory code	Product	Replicate	Nicotine (%)	pH	Moisture (%)	NAB (ppm)	NAT (ppm)	NNK (ppm)	NNN (ppm)	TSNA Total (ppm)
A	CRP1	1	0,9547	7,92	52,51	0,037	0,500	0,203	0,694	1,434
A	CRP1	2	0,8915	7,94	52,96	0,034	0,564	0,207	0,705	1,510
A	CRP1	3	0,9625	7,98	51,78	0,037	0,584	0,222	0,722	1,564
A	CRP2	1	1,2407	7,66	53,82	0,161	1,858	0,412	1,995	4,426
A	CRP2	2	1,2431	7,67	54,62	0,160	1,962	0,424	2,034	4,579
A	CRP2	3	1,2330	7,66	55,07	0,154	1,874	0,462	2,012	4,502
A	CRP3	1	2,1870	6,72	9,24	0,405	6,038	4,220	8,725	19,389
A	CRP3	2	2,1880	6,71	9,09	0,420	6,489	4,148	9,532	20,590
A	CRP3	3	2,2065	6,71	9,13	0,416	6,362	4,020	8,587	19,385
A	CRP4	1	1,1008	5,84	21,61	0,072	1,293	0,400	2,184	3,948
A	CRP4	2	1,1018	5,85	22,36	0,065	1,321	0,397	2,117	3,900
A	CRP4	3	1,0906	5,84	22,01	0,062	1,345	0,439	2,302	4,147
B	CRP1	1	0,9900	7,85		0,030	0,520	0,230	0,710	1,490
B	CRP1	2	1,0100	7,88		0,030	0,560	0,220	0,730	1,540
B	CRP1	3	1,0100	7,87		0,030	0,540	0,220	0,720	1,510
B	CRP2	1	1,2900	7,70		0,170	1,900	0,490	1,810	4,370
B	CRP2	2	1,2300	7,70		0,170	1,800	0,480	1,830	4,280
B	CRP2	3	1,2600	7,71		0,170	1,850	0,480	1,820	4,320
B	CRP3	1	2,2200	6,82		0,380	5,420	3,810	8,280	17,890



Laboratory code	Product	Replicate	Nicotine (%)	pH	Moisture (%)	NAB (ppm)	NAT (ppm)	NNK (ppm)	NNN (ppm)	TSNA Total (ppm)
B	CRP3	2	2,2000	6,80		0,400	5,420	3,880	8,180	17,880
B	CRP3	3	2,2200	6,78		0,410	5,370	3,850	8,240	17,870
B	CRP4	1	1,1600	5,91		0,060	1,180	0,510	2,020	3,770
B	CRP4	2	1,1800	5,83		0,060	1,210	0,500	2,010	3,780
B	CRP4	3	1,2400	5,86		0,060	1,210	0,510	2,020	3,800
C	CRP1	1	0,9080	7,91	51,52	0,030	0,537	0,214	0,720	1,501
C	CRP1	2	0,9070	7,95	50,82	0,030	0,556	0,223	0,730	1,539
C	CRP1	3	0,9330	7,96	50,21	0,031	0,560	0,224	0,730	1,545
C	CRP2	1	1,0920	7,68	54,31	0,153	2,049	0,482	2,085	4,769
C	CRP2	2	1,1420	7,69	54,05	0,153	2,107	0,482	2,053	4,795
C	CRP2	3	1,1470	7,69	54,56	0,151	2,079	0,496	2,076	4,802
C	CRP3	1	2,1680	6,78	9,92	0,376	6,019	3,913	8,367	18,675
C	CRP3	2	2,5260	6,77	9,44	0,378	6,284	4,020	8,606	19,288
C	CRP3	3	2,1460	6,76	9,25	0,396	6,307	4,106	9,014	19,823
C	CRP4	1	1,0600	6,07	20,57	0,067	1,483	0,508	2,345	4,403
C	CRP4	2	1,0600	6,06	18,65	0,062	1,461	0,481	2,270	4,274
C	CRP4	3	1,0600	6,06	18,71	0,065	1,443	0,514	2,297	4,319
D	CRP1	1	0,9951	7,82	51,94	0,031	0,461	0,218	0,664	1,374
D	CRP1	2	0,9907	7,84	51,64	0,034	0,467	0,230	0,713	1,443
D	CRP1	3	0,9074	7,85	51,52	0,034	0,461	0,233	0,726	1,455
D	CRP2	1	1,2429	7,71	54,41	0,160	1,576	0,483	2,007	4,227
D	CRP2	2	1,2457	7,71	54,39	0,166	1,580	0,499	1,975	4,219
D	CRP2	3	1,2460	7,71	54,36	0,160	1,627	0,481	2,024	4,293
D	CRP3	1	2,2183	6,80	8,84	0,412	5,079	4,199	8,839	18,530
D	CRP3	2	2,2049	6,80	8,84	0,424	5,155	4,196	8,911	18,684
D	CRP3	3	2,2088	6,79	8,87	0,397	5,110	4,312	8,824	18,643
D	CRP4	1	1,1032	5,91	22,06	0,057	1,122	0,466	2,196	3,841
D	CRP4	2	1,0922	5,91	21,96	0,061	1,113	0,424	2,067	3,665
D	CRP4	3	1,1255	5,90	21,95	0,065	1,123	0,452	2,178	3,818
E	CRP1	1	1,0500	7,98		<0.03	0,440	0,220	0,560	1,220
E	CRP1	2	1,0300	7,97		<0.03	0,430	0,220	0,540	1,190
E	CRP1	3	1,0600	7,96		<0.03	0,420	0,200	0,530	1,150
E	CRP2	1	1,3700	7,70		0,150	1,980	0,470	1,840	4,440
E	CRP2	2	1,3600	7,71		0,160	1,960	0,490	1,850	4,460
E	CRP2	3	1,3700	7,71		0,150	1,920	0,500	1,890	4,460
E	CRP3	1	2,1900	6,71		0,420	5,570	4,790	8,780	19,560
E	CRP3	2	2,1700	6,73		0,430	5,610	4,680	8,820	19,540
E	CRP3	3	2,0900	6,72		0,450	5,670	4,740	8,910	19,770
E	CRP4	1	1,2300	5,92		0,070	1,240	0,480	1,910	3,700
E	CRP4	2	1,2300	5,91		0,070	1,230	0,460	1,890	3,650
E	CRP4	3	1,2400	5,92		0,060	1,230	0,440	1,920	3,650
F	CRP1	1	1,0180	7,91	51,84	0,039	0,500	0,191	0,616	1,346
F	CRP1	2	0,9000	7,89	51,20	0,036	0,482	0,197	0,633	1,349

Laboratory code	Product	Replicate	Nicotine (%)	pH	Moisture (%)	NAB (ppm)	NAT (ppm)	NNK (ppm)	NNN (ppm)	TSNA Total (ppm)
F	CRP1	3	0,8820	7,88	53,55	0,033	0,481	0,203	0,635	1,352
F	CRP2	1	1,2970	7,66	54,15	0,145	1,678	0,452	1,711	3,987
F	CRP2	2	1,2950	7,66	53,93	0,150	1,695	0,449	1,700	3,995
F	CRP2	3	1,2920	7,65	53,93	0,148	1,674	0,440	1,715	3,978
F	CRP3	1	1,9560	6,74	8,85	0,364	5,391	4,012	7,689	17,456
F	CRP3	2	2,2460	6,74	8,75	0,356	5,352	4,006	7,686	17,400
F	CRP3	3	2,2120	6,75	8,76	0,364	5,364	4,029	7,689	17,446
F	CRP4	1	1,3090	5,99	20,54	0,065	1,084	0,392	1,895	3,437
F	CRP4	2	1,3750	6,06	21,52	0,063	1,049	0,400	1,869	3,382
F	CRP4	3	1,2160	5,88	21,80	0,061	1,044	0,399	1,890	3,395
G	CRP1	1	0,9279	7,86	51,18	0,036	0,536	0,236	0,732	1,540
G	CRP1	2	0,8985	7,85	52,88	0,031	0,537	0,232	0,750	1,551
G	CRP1	3	0,9422	7,84	53,20	0,043	0,566	0,247	0,750	1,606
G	CRP2	1	1,2230	7,66	54,79	0,164	1,846	0,522	2,157	4,689
G	CRP2	2	1,1962	7,66	54,74	0,160	1,790	0,489	2,052	4,491
G	CRP2	3	1,2147	7,67	54,68	0,169	1,891	0,491	2,094	4,645
G	CRP3	1	2,1665	6,75	9,33	0,449	6,313	4,888	9,776	21,426
G	CRP3	2	2,1561	6,75	9,38	0,455	6,299	5,003	9,816	21,574
G	CRP3	3	2,1414	6,74	9,36	0,456	6,526	4,953	9,689	21,623
G	CRP4	1	1,1332	5,99	21,44	0,075	1,318	0,559	2,276	4,227
G	CRP4	2	1,1231	5,88	21,49	0,071	1,375	0,579	2,266	4,291
G	CRP4	3	1,1299	5,89	21,51	0,058	1,306	0,606	2,252	4,222
H	CRP1	1	0,9446	7,70	50,78	0,040	0,630	0,219	0,702	1,590
H	CRP1	2	0,9813	7,72	50,93	0,037	0,572	0,236	0,702	1,548
H	CRP1	3	0,8514	8,00	50,34	0,031	0,590	0,200	0,668	1,489
H	CRP2	1	1,2436	7,60	54,40	0,155	1,905	0,443	1,780	4,283
H	CRP2	2	1,2486	7,74	54,35	0,147	1,873	0,421	1,740	4,180
H	CRP2	3	1,2795	7,71	54,60	0,152	1,967	0,449	1,811	4,378
H	CRP3	1	2,2577	6,82	8,17	0,399	6,209	3,638	8,224	18,469
H	CRP3	2	2,2510	6,81	8,12	0,385	5,929	3,839	8,374	18,526
H	CRP3	3	2,2847	6,93	8,23	0,433	6,285	3,670	8,168	18,556
H	CRP4	1	1,0633	5,84	20,30	0,060	1,441	0,378	2,032	3,911
H	CRP4	2	1,0540	5,74	20,03	0,052	1,313	0,390	1,828	3,583
H	CRP4	3	1,0715	5,69	19,87	0,054	1,284	0,427	1,967	3,732
I	CRP1	1	0,9700	7,99	51,85	0,033	0,568	0,218	0,685	1,504
I	CRP1	2	0,9800	7,98	50,93	0,033	0,579	0,228	0,692	1,532
I	CRP1	3	0,9600	8,00	50,13	0,032	0,545	0,214	0,681	1,472
I	CRP2	1	1,2300	7,65	53,03	0,151	1,860	0,448	1,840	4,299
I	CRP2	2	1,3200	7,65	53,95	0,148	1,910	0,441	1,870	4,369
I	CRP2	3	1,2600	7,65	54,23	0,148	1,840	0,437	1,880	4,305
I	CRP3	1	2,1700	6,87	8,82	0,395	5,960	3,960	8,280	18,595
I	CRP3	2	2,1900	6,87	8,40	0,397	5,880	4,070	8,490	18,837
I	CRP3	3	2,1900	6,89	8,72	0,396	5,750	4,000	8,520	18,666

Laboratory code	Product	Replicate	Nicotine (%)	pH	Moisture (%)	NAB (ppm)	NAT (ppm)	NNK (ppm)	NNN (ppm)	TSNA Total (ppm)
I	CRP4	1	1,1300	5,95	21,64	0,056	1,290	0,429	1,980	3,755
I	CRP4	2	1,1400	5,94	21,50	0,055	1,310	0,417	1,950	3,732
I	CRP4	3	1,1600	5,95	21,50	0,057	1,290	0,409	1,940	3,696
J	CRP1	1	0,9400	7,93	49,90					
J	CRP1	2	0,9320	7,87	51,60					
J	CRP1	3	0,9480	7,88	50,91					
J	CRP2	1	1,2480	7,67	53,82					
J	CRP2	2	1,2640	7,66	53,65					
J	CRP2	3	1,2280	7,65	53,68					
J	CRP3	1	2,2160	6,79	7,30					
J	CRP3	2	2,2520	6,77	8,68					
J	CRP3	3	2,2440	6,76	8,15					
J	CRP4	1	1,3040	5,65	20,70					
J	CRP4	2	1,3040	5,66	21,69					
J	CRP4	3	1,3080	5,66	20,50					

## 5. Data – Statistical Analysis

The statistical analysis of the 2010 and 2011 CRP data was provided by Oscar Camacho (BAT) following ISO 5725-2 (1994). The repeatability and reproducibility results for each parameter are given in the table below and the full statistical report is included in Appendix A<sup>5</sup>. The statistical report refers to time points 1 and 2 which correspond to the 2010 and 2011 WG4 studies, respectively.

### 5.1 Exclusion of Outliers

Numerical outlier detection was conducted following ISO 5725-2 (1994). The decisions on straggling (0.95) and outlying (0.99) data were made using GRUBBS' single outlier and COCHRAN's tests.

Graphical outlier detection was also performed. ISO 5725-2 (1994) proposes MANDEL's h to assess the inter-laboratory consistency and MANDEL's k to assess the within laboratory consistency. The MANDEL's h plots and the MANDEL's k plots can be found in the statistical report, given in Appendix A<sup>5</sup>. No decision on removing outlying data was made based upon the results of MANDEL's k and MANDEL's h plots because these analyses are more likely to detect outliers than the above mentioned methods, which can lead to excessive data exclusion.

The results for the numerical outlier detection for the 2010 and 2011 WG4 studies are shown in Table 5.

### 5.2 Calculation of r & R

After removal of outlier data based on numerical data consistency methods (GRUBBS' test, COCHRAN's test), repeatability standard deviation (r SD); reproducibility standard deviation (R SD); repeatability (r) and reproducibility (R) for each sample and analyte were calculated for the 2010 and 2011 WG4 studies (straggler data were retained). These data are shown in Table 6.

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<sup>5</sup> Appendix A: Statistical Report: CORESTA Smokeless Tobacco Inter-laboratory Study: Analysis of CORESTA Reference Products for pH, nicotine, moisture, NAB, NAT, NNK, NNN and total TSNAs, 2010 & 2011 is available in a separate document.

**Table 5: Numerical Outlier Results for 2010 and 2011 WG4 Studies**

	2010 WG4				2011 WG4			
	Cochran's		Grubbs'		Cochran's		Grubbs'	
	Straggler	Outlier	Straggler	Outlier	Straggler	Outlier	Straggler	Outlier
	0.05	0.01	0.05	0.01	0.05	0.01	0.05	0.01
	<b>CRP-1</b>				<b>CRP-1</b>			
Nicotine								
pH				N		H		
Moisture				E				
NAB								
NAT								
NNK								
NNN	A						E	
Total TSNAs	N						E	
	<b>CRP-2</b>				<b>CRP-2</b>			
Nicotine								
pH				N		H		
Moisture				E				
NAB								
NAT								
NNK								
NNN	A							
Total TSNAs								
	<b>CRP-3</b>				<b>CRP-3</b>			
Nicotine	D					C		
pH						H		
Moisture								
NAB	N							
NAT								
NNK								
NNN							A	
Total TSNAs					A			
	<b>CRP-4</b>				<b>CRP-4</b>			
Nicotine						F		
pH		L						
Moisture								
NAB					C			A
NAT								
NNK						H		
NNN								
Total TSNAs		L						

**Table 6: Calculation of Repeatability (r) and Reproducibility (R) for the CRPs for the 2010 and 2011 WG4 Studies**

Parameter	2010 WG4 Analysis						2011 WG4 Analysis					
	Mean	r SD	R SD	r	R	Number of Labs	Mean	r SD	R SD	r	R	Number of Labs
<b>CRP-1</b>												
Nicotine	0.985	0.014	0.080	0.039	0.224	7	0.956	0.039	0.052	0.109	0.146	10
pH	7.999	0.019	0.051	0.052	0.143	4	7.910	0.020	0.057	0.057	0.159	9
Moisture	51.513	0.353	0.353	0.988	0.988	5	51.505	0.795	1.001	2.225	2.803	8
NAB	0.031	0.003	0.020	0.007	0.056	6	0.031	0.003	0.010	0.009	0.027	9
NAT	0.550	0.029	0.103	0.080	0.289	6	0.525	0.021	0.056	0.060	0.158	9
NNK	0.218	0.010	0.021	0.027	0.060	6	0.219	0.010	0.014	0.027	0.039	9
NNN	0.672	0.025	0.132	0.070	0.370	6	0.683	0.016	0.063	0.044	0.177	9
Total TSNAs	1.471	0.036	0.260	0.101	0.729	6	1.457	0.038	0.125	0.108	0.350	9
<b>CRP-2</b>												
Nicotine	1.278	0.027	0.085	0.077	0.237	8	1.252	0.022	0.063	0.062	0.177	10
pH	7.750	0.017	0.050	0.047	0.141	4	7.678	0.006	0.024	0.016	0.068	9
Moisture	54.675	0.101	0.221	0.284	0.618	5	54.230	0.336	0.462	0.942	1.294	8
NAB	0.157	0.005	0.033	0.015	0.091	6	0.157	0.003	0.008	0.010	0.023	9
NAT	1.842	0.067	0.237	0.187	0.663	6	1.854	0.040	0.146	0.112	0.410	9
NNK	0.456	0.027	0.062	0.075	0.173	6	0.467	0.014	0.029	0.039	0.081	9
NNN	1.811	0.078	0.234	0.218	0.654	6	1.913	0.027	0.140	0.076	0.392	9
Total TSNAs	4.266	0.143	0.518	0.402	1.452	6	4.390	0.060	0.236	0.167	0.662	9
<b>CRP-3</b>												
Nicotine	2.124	0.042	0.183	0.116	0.513	8	2.194	0.057	0.063	0.159	0.176	9
pH	6.773	0.030	0.052	0.083	0.145	4	6.771	0.011	0.051	0.031	0.142	9
Moisture	8.206	0.072	0.541	0.201	1.514	6	8.819	0.288	0.579	0.807	1.622	8
NAB	0.398	0.027	0.059	0.076	0.167	6	0.406	0.013	0.029	0.036	0.080	9
NAT	5.587	0.265	0.676	0.743	1.894	6	5.821	0.128	0.474	0.358	1.326	9
NNK	3.877	0.261	0.764	0.730	2.141	6	4.183	0.072	0.410	0.201	1.148	9
NNN	7.891	0.178	1.102	0.498	3.085	6	8.590	0.136	0.618	0.382	1.730	8
Total TSNAs	18.070	0.513	2.241	1.437	6.275	5	19.040	0.310	1.235	0.867	3.459	9
<b>CRP-4</b>												
Nicotine	1.116	0.027	0.125	0.077	0.349	8	1.148	0.016	0.083	0.046	0.232	9
pH	5.947	0.061	0.061	0.170	0.170	8	5.885	0.044	0.120	0.124	0.335	10
Moisture	21.914	0.165	0.752	0.462	2.105	8	21.079	0.529	1.039	1.480	2.910	8
NAB	0.060	0.004	0.013	0.011	0.037	8	0.062	0.004	0.006	0.012	0.016	8
NAT	1.199	0.042	0.235	0.117	0.658	8	1.253	0.021	0.129	0.058	0.362	8
NNK	0.409	0.030	0.050	0.084	0.141	8	0.458	0.018	0.064	0.052	0.178	9
NNN	1.901	0.072	0.294	0.203	0.824	8	2.069	0.055	0.168	0.153	0.469	9
Total TSNAs	3.569	0.118	0.567	0.329	1.589	8	3.853	0.083	0.299	0.232	0.838	9

## **6. Data - Interpretation**

When comparing the 2010 and 2011 data, increased variability for moisture and decreased variability for TSNA is apparent for both intra-laboratory and inter-laboratory comparisons. In addition, the inter-laboratory variability for nicotine decreased as well. However, the significance of these trends is difficult to interpret considering the fact that participating laboratories may have used different methodology in 2010 and 2011. Furthermore, it is difficult to discern a trend with only two time points.

## **7. Recommendations**

The STS recommends that WG4 continue to monitor stability of the CRPs on an annual basis. As stated in the Introduction, data generated in 2011 will serve as the baseline for future WG4 stability analyses. A formal analysis of product stability should be conducted with data obtained from the next WG4 study.

## APPENDIX A - Statistical Report

### CORESTA Smokeless Tobacco Inter-laboratory Study: Analysis of CORESTA Reference Products for pH, nicotine, moisture, NAB, NAT, NNK, NNN and total TSNAs, 2010 & 2011

Oscar M Camacho, British American Tobacco

The data analysis of the CORESTA Smokeless Tobacco Inter-laboratory Study was performed following the ISO 5725-2 (1994) “**Accuracy (trueness and precision) of measurement methods and results – Part 2: Basic method for the determination of repeatability and reproducibility of a standard measurement method.**”

Four smokeless tobacco products were assessed for their pH and content of nicotine, moisture, NAB, NAT, NNK, NNN and Total TSNAs. Table 1 lists the 4 products tested.

The study consisted of collecting data at 2 time-points and 13 laboratories provided the data specified above at each time-point as shown in Table 2. Laboratories reported 3 repeats for each analyte by product and time-point.

<b>Product</b>	<b>Label</b>	<b>Description</b>
CRP 1	Snus smokeless tobacco	Swedish style snus pouch
CRP 2	Moist smokeless tobacco	US-style moist snuff
CRP 3	Dry smokeless tobacco	US-style dry snuff
CRP 4	Loose leaf smokeless tobacco	US-style loose leaf

**Table 1. Products tested.**

<b>Participating laboratories</b>	
<b>Timepoint 1</b>	<b>Timepoint 2</b>
Altria	Arista
ASC	BAT
BAT	Eurofins
Eurofins	Global Laboratories
ITC	Japan Tobacco
JTI- Ökolab	JTI- Ökolab
Labstat	Labstat
SMNE	Poeschl
	RJRT
	SMNE

**Table 2. Participating laboratories.**

Only 3 of the laboratories submitted data for both time-points for most of the analytes. Nicotine was submitted by 5 laboratories and pH by only 2, at both time-points. Table 3 displays the data submitted by each laboratory by time-point for all 4 products and analytes.



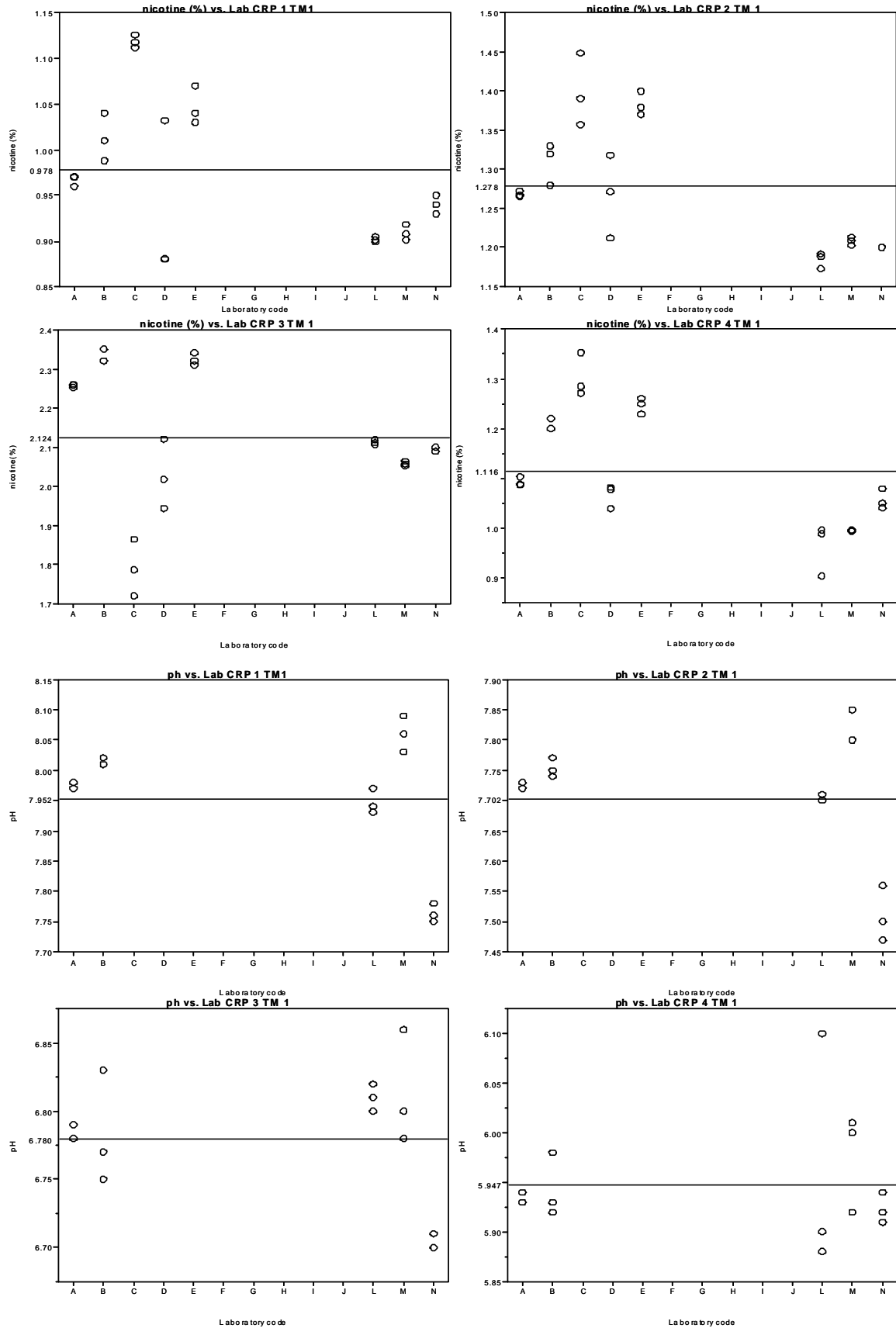
Laboratory	Analyte and Time-Point															
	Nicotine		pH		Moisture		NAB		NAT		NNK		NNN		TSNA Total	
	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2
A	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
B	X	X	X	X			X	X	X	X	X	X	X	X	X	X
C	X	X		X		X		X		X		X		X		X
D	X	X		X	X	X		X		X		X		X		X
E	X	X		X	X		X	X	X	X	X	X	X	X	X	X
F		X		X		X		X		X		X		X		X
G		X		X		X		X		X		X		X		X
H		X		X		X		X		X		X		X		X
I		X		X		X		X		X		X		X		X
J		X		X		X										
K																
L	X		X		X		X		X		X		X		X	
M	X		X		X		X		X		X		X		X	
N	X		X		X		X		X		X		X		X	

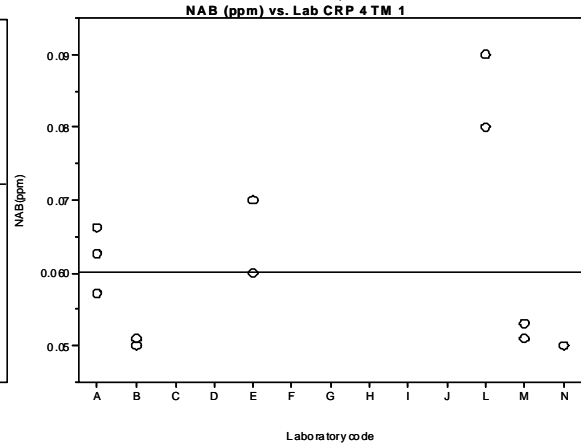
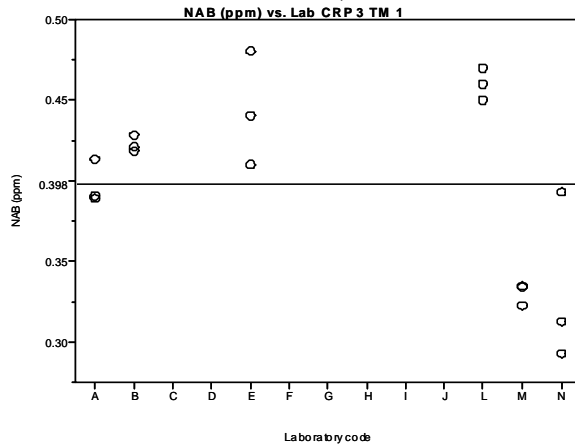
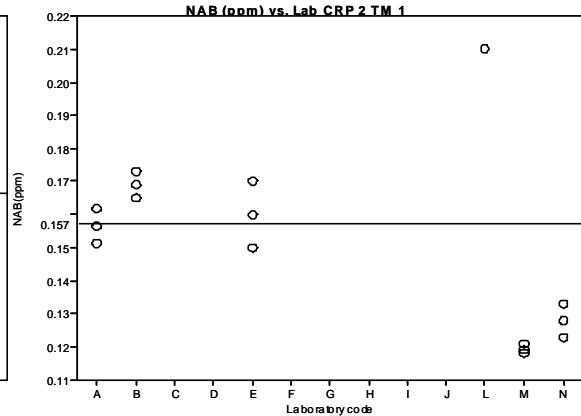
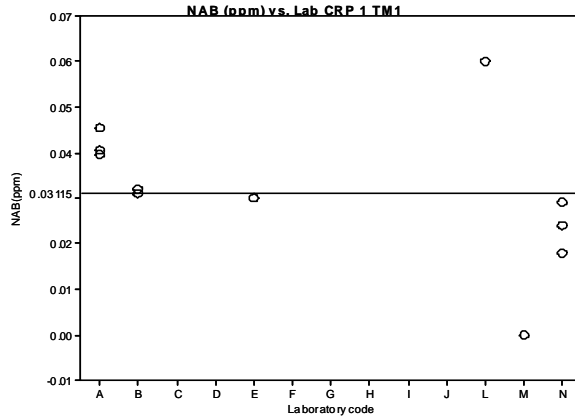
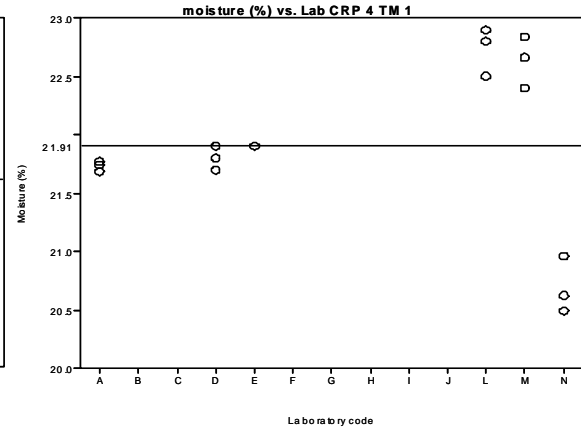
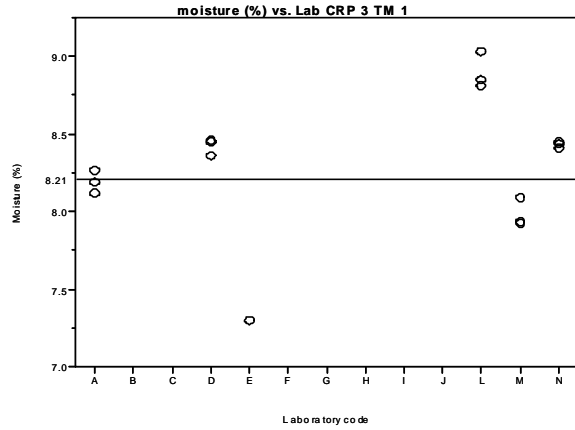
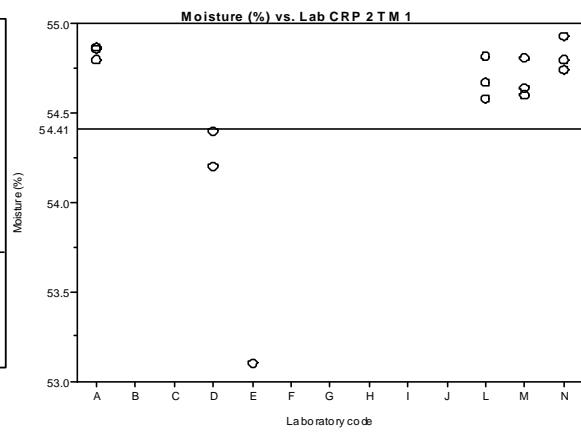
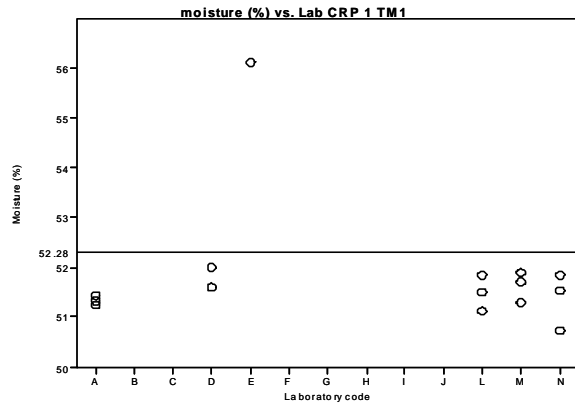
**Table 3. Results submitted by laboratory for the four products. They are disclosed by analyte at each time-point.**

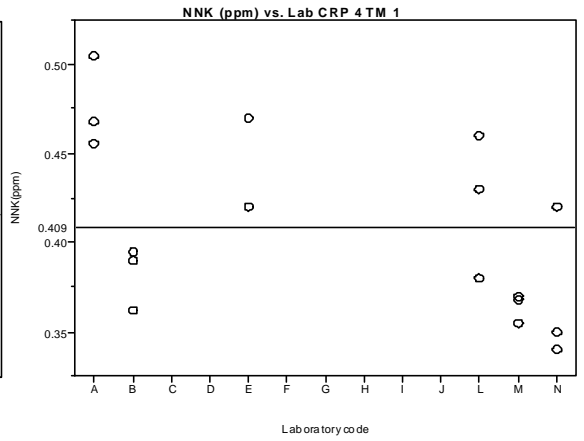
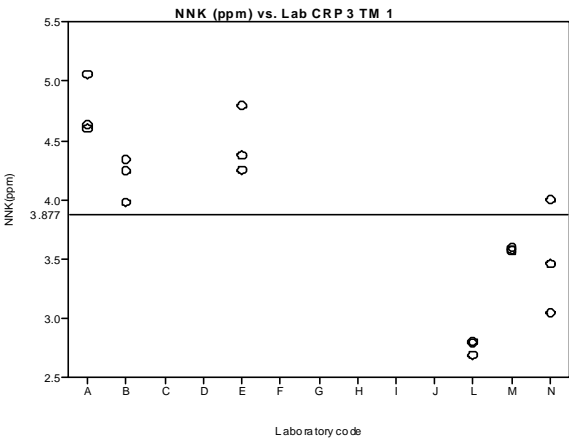
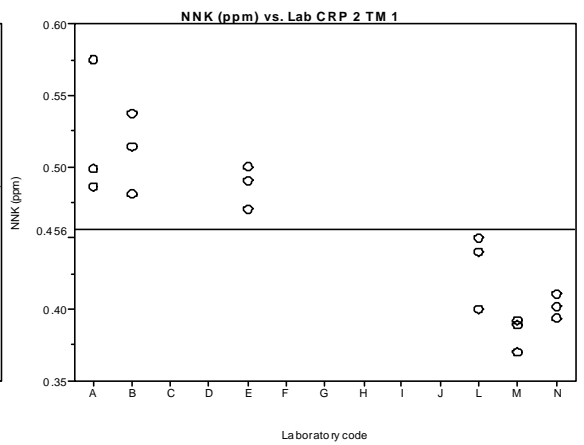
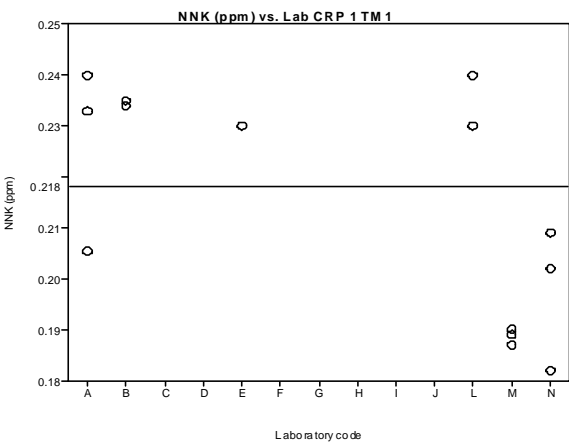
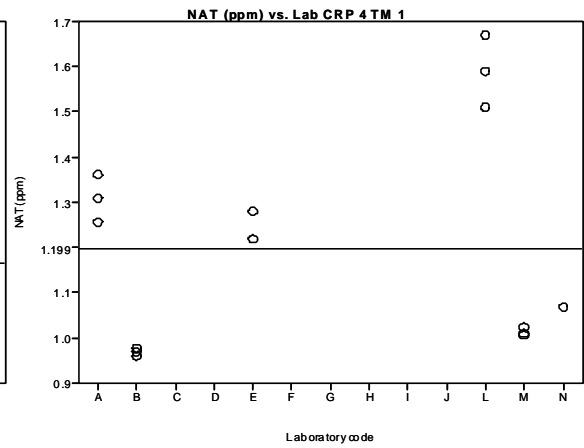
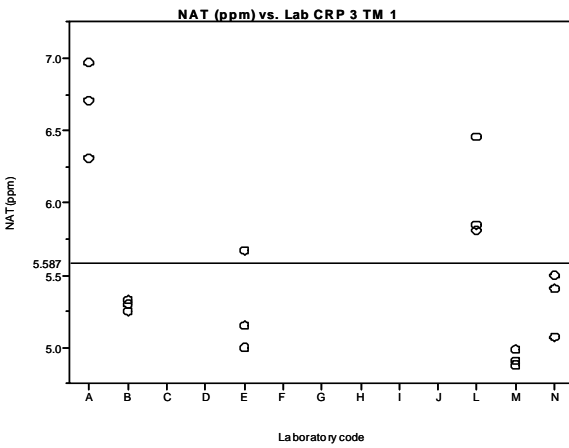
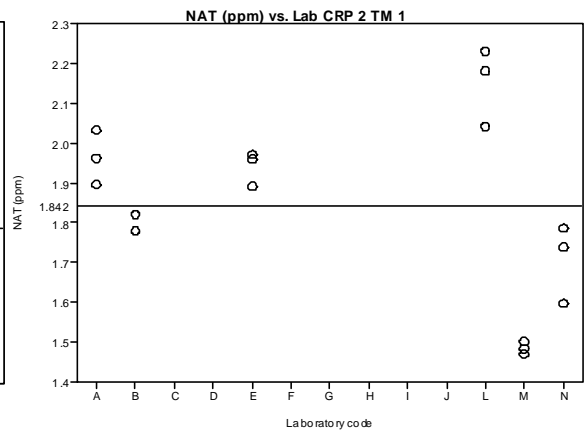
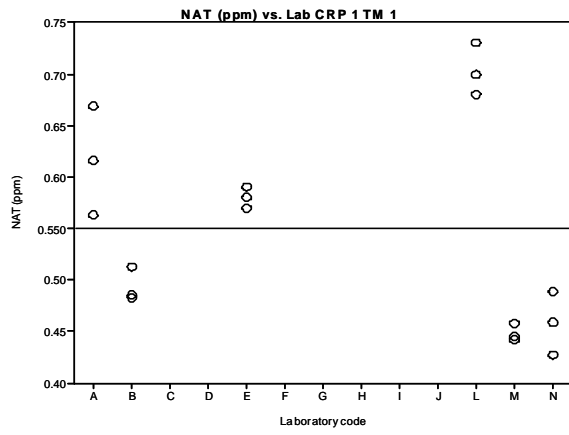
Repeatability and reproducibility (r & R) analysis was performed for each time-point separately and also both time-points together considering only those laboratories reporting data for both time-points.

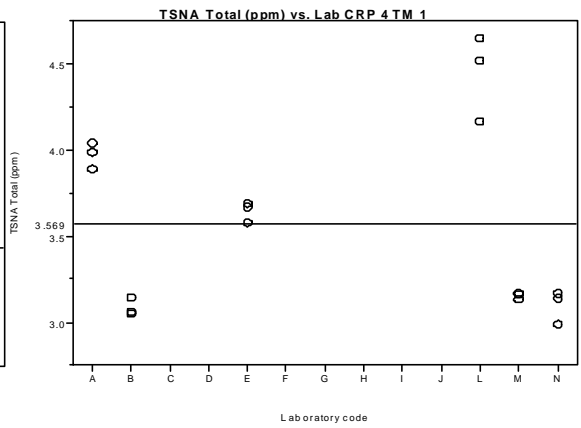
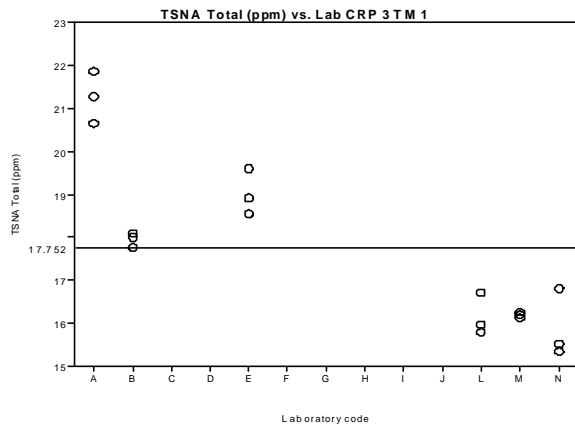
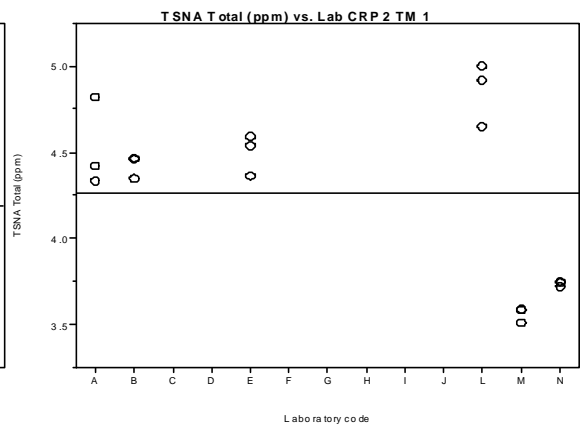
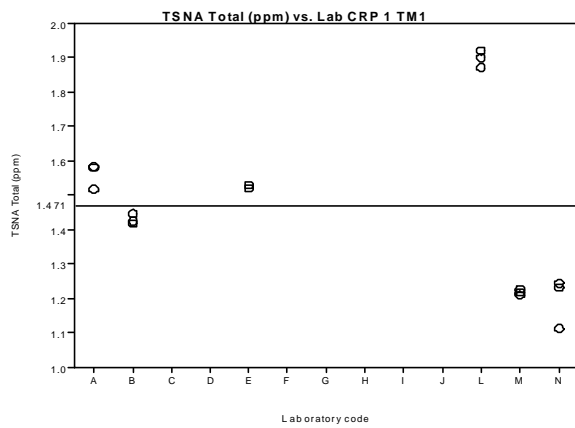
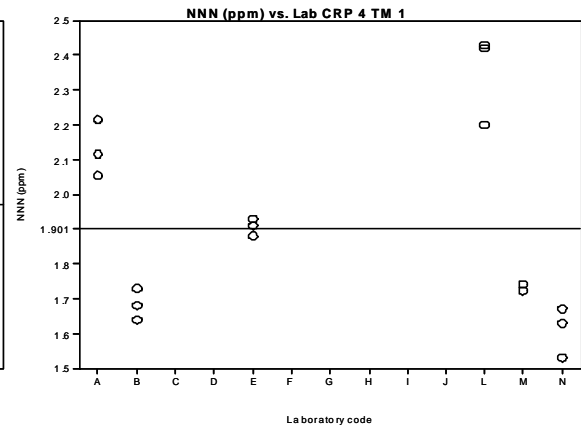
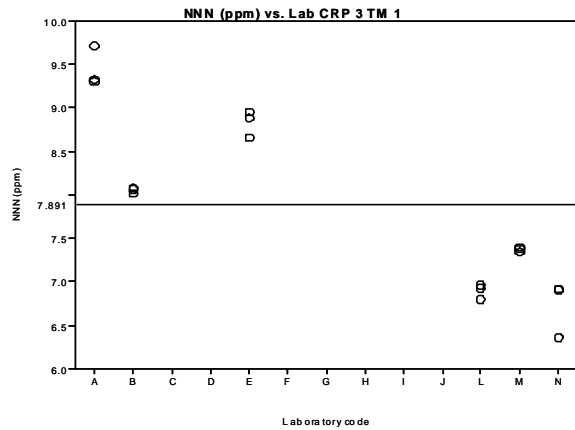
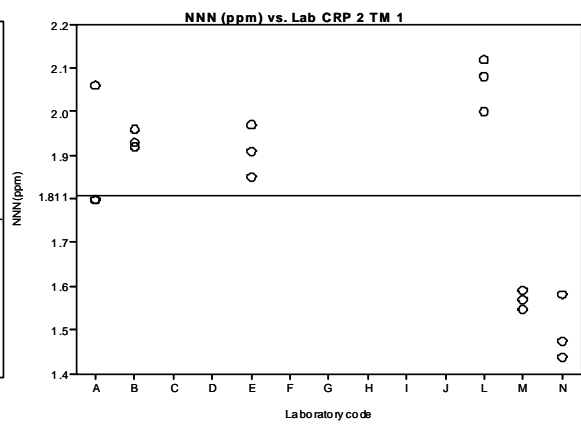
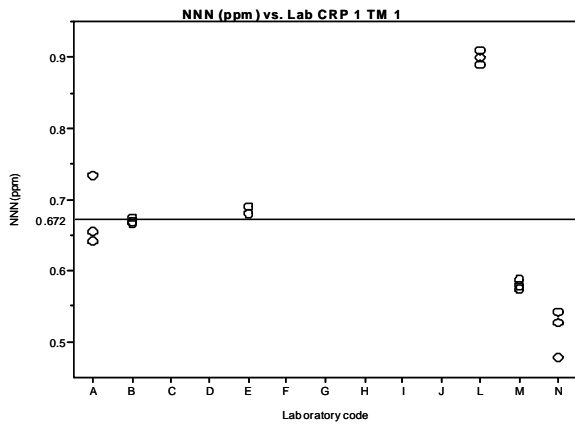
Tests results were reported to a different number of decimal places. Section 5.1.4 of ISO 5725-2 states that ‘results shall be reported to at least one more digit than specified in the standard method’. In this study, results from 2 to 4 digits have been reported. Laboratory E reported all results to 2 decimal places which has led to values of 0 for some standard deviations. This same effect of insufficient decimal places can be seen for laboratory N product CRP 4. Dot-plots of the raw data have been created including a line representing the mean value of the data displayed. All 3 repeats are represented by laboratory, where it appears to be less than 3 this is due to overlapping. The raw data plots start on page 3.

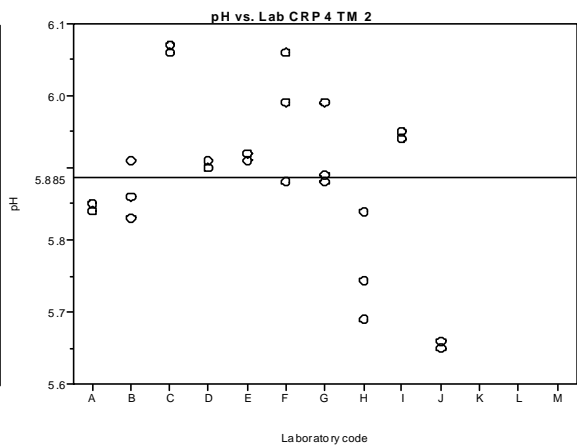
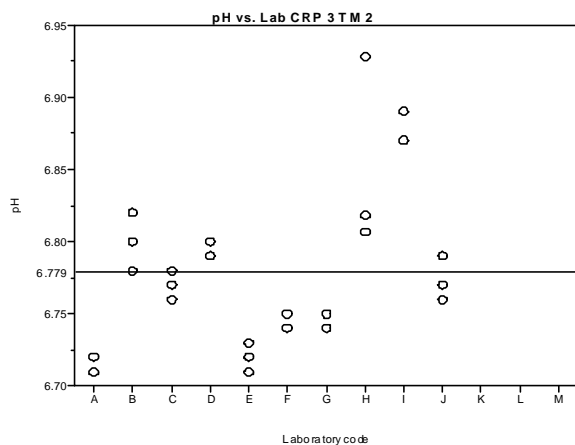
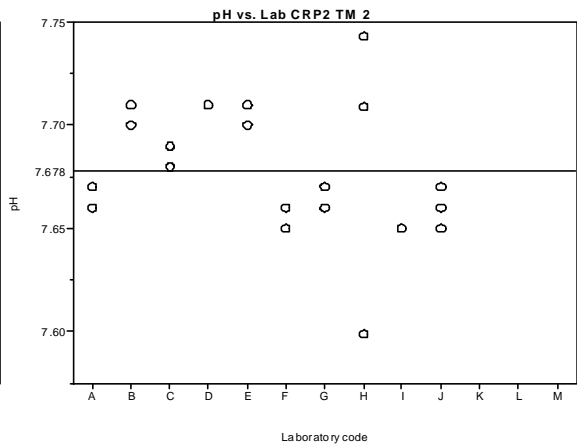
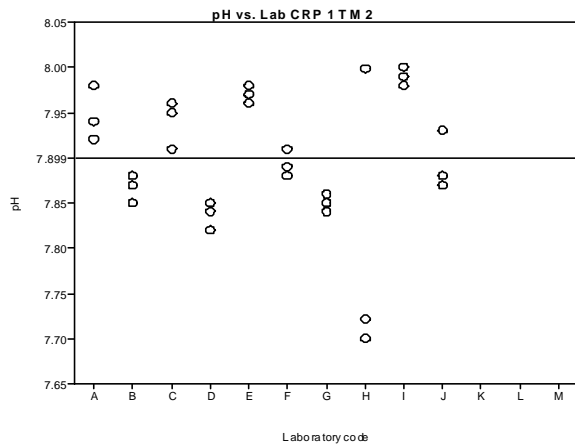
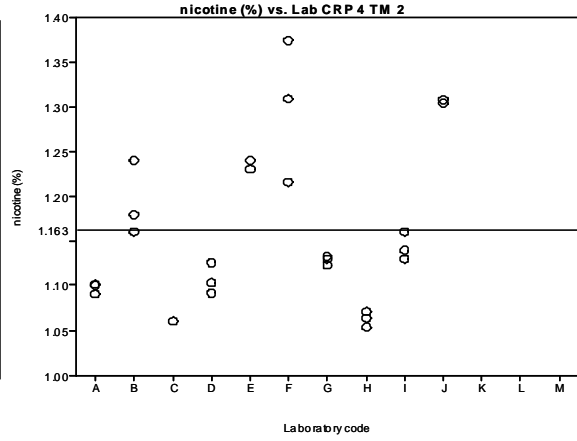
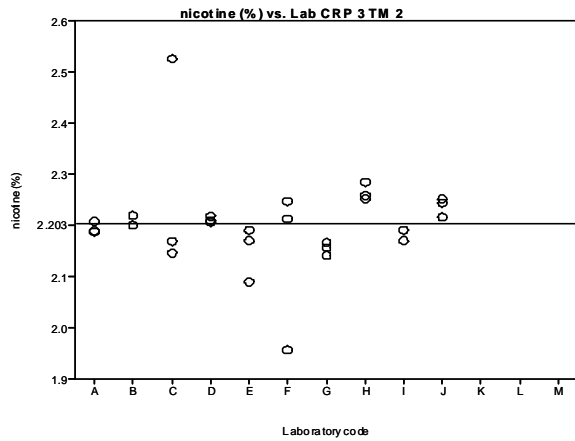
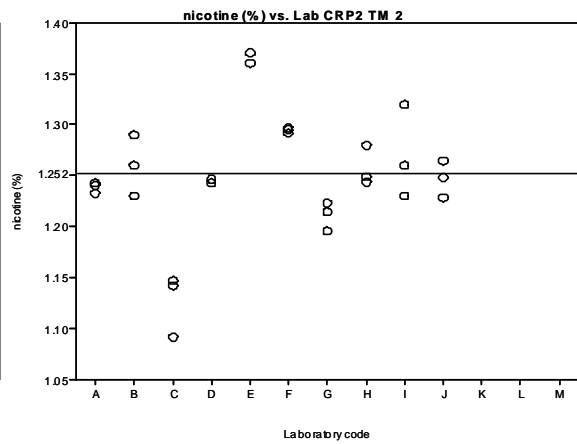
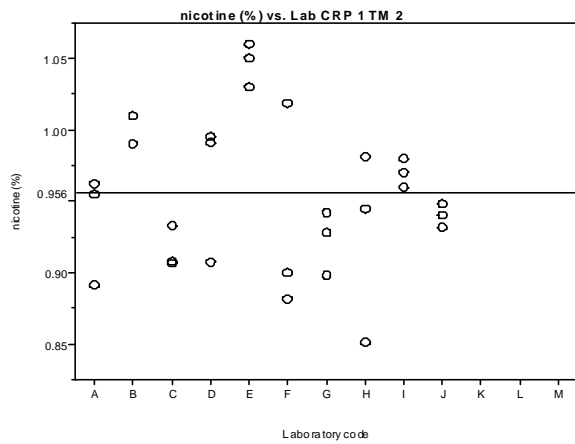
## Charts 1. Raw Data Plots

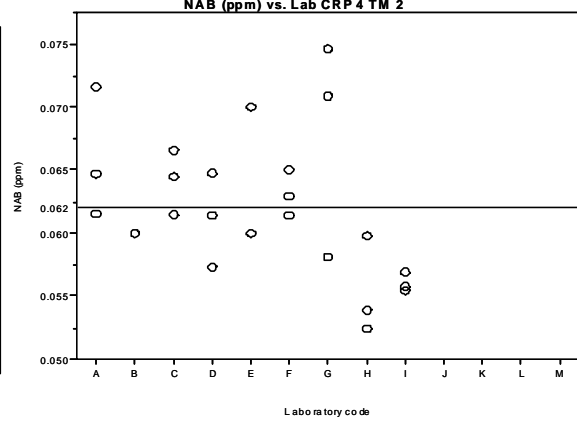
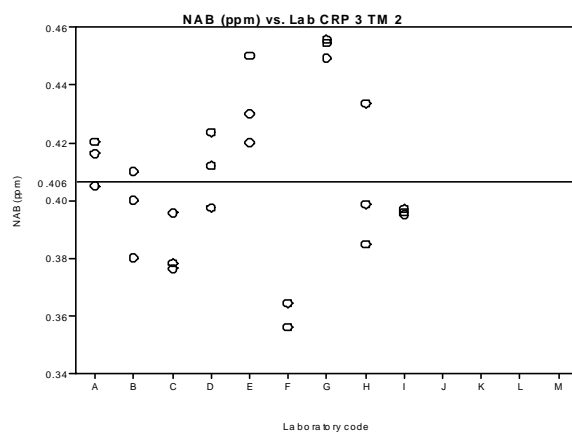
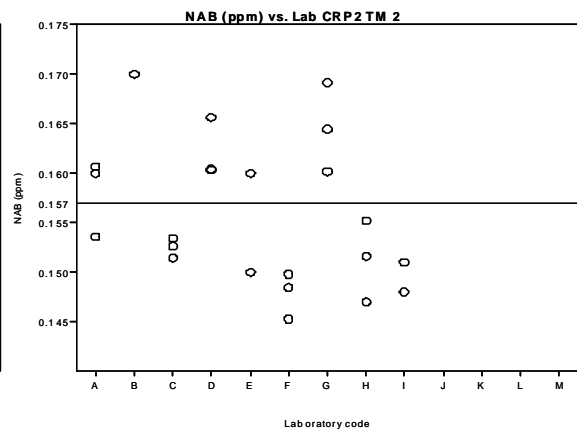
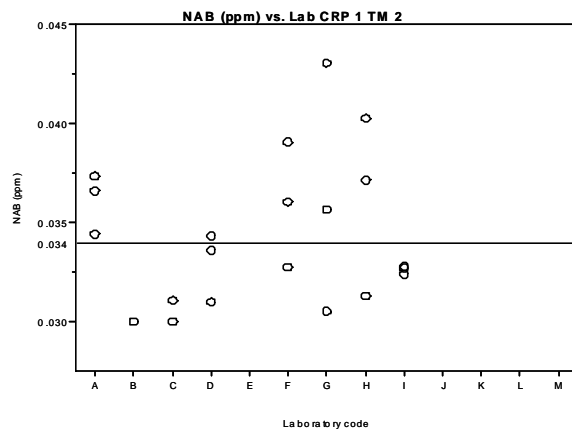
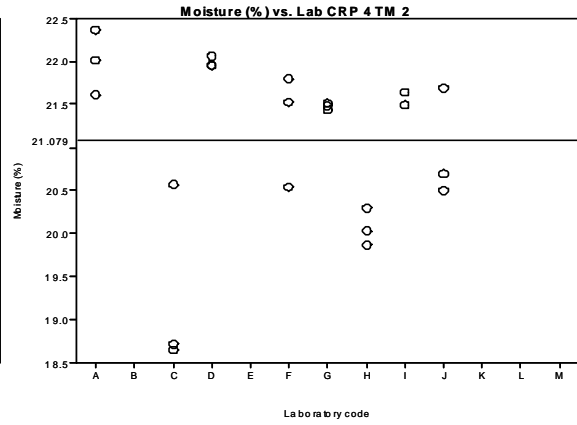
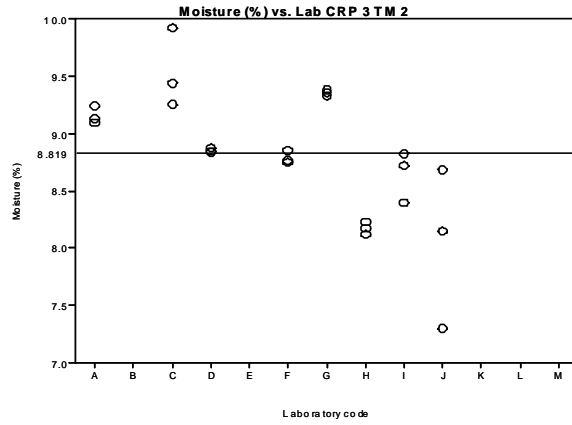
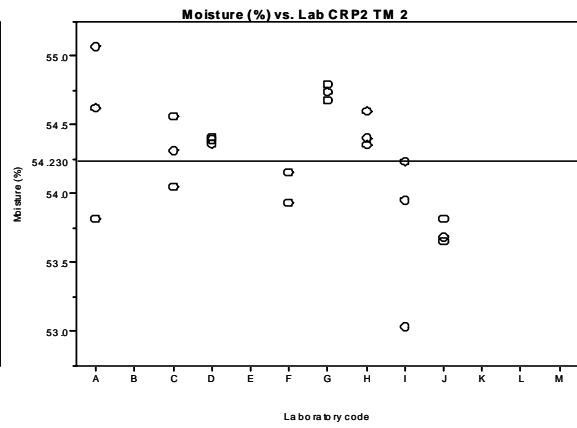
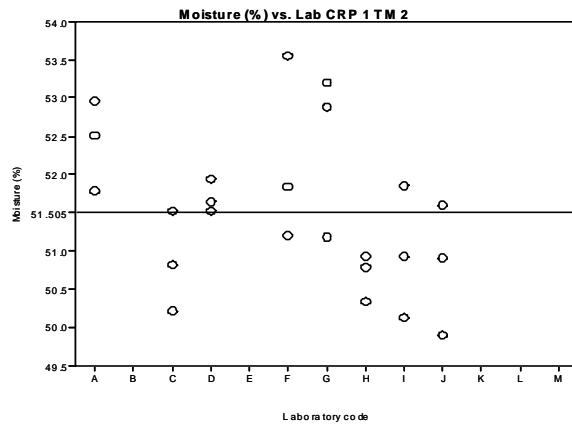


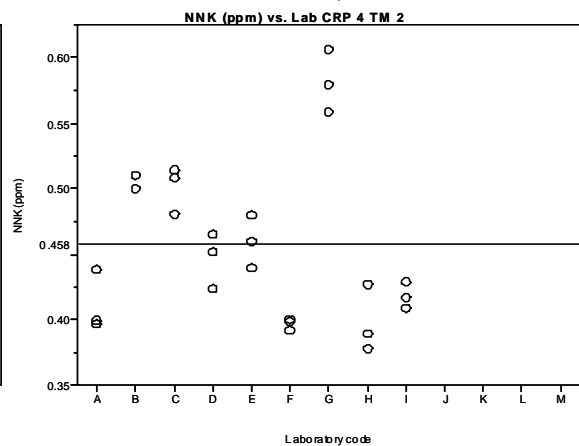
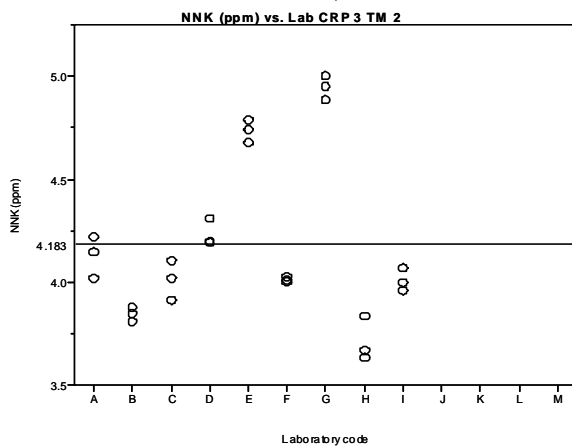
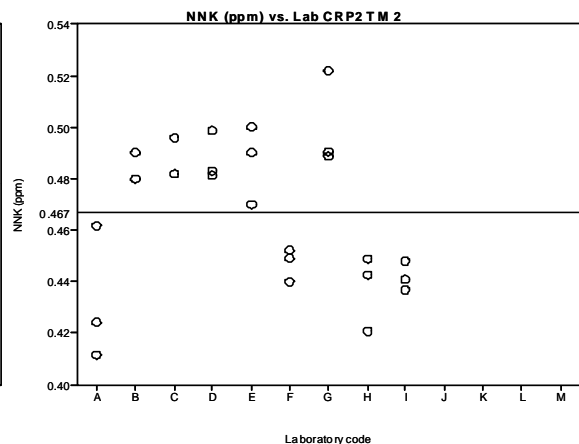
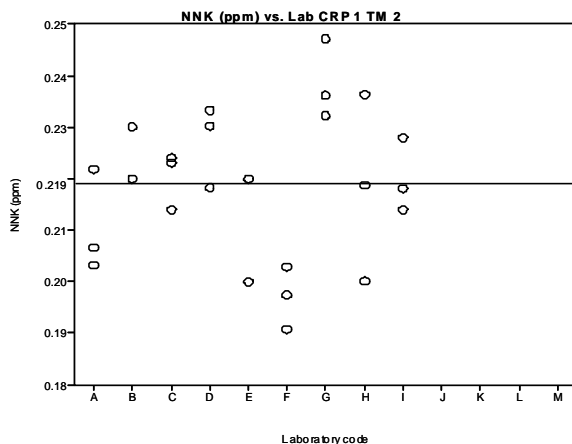
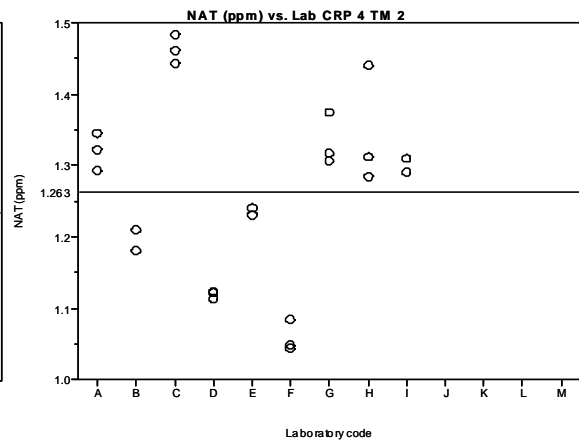
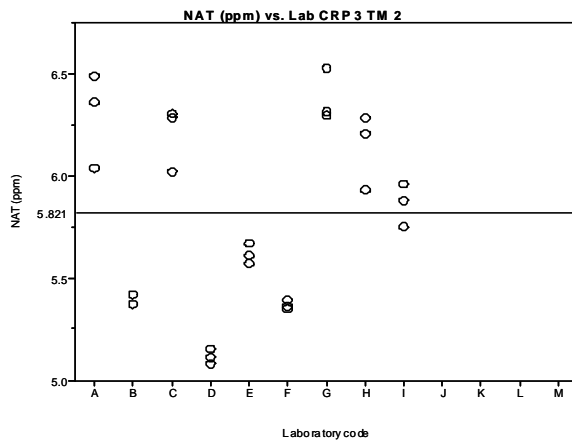
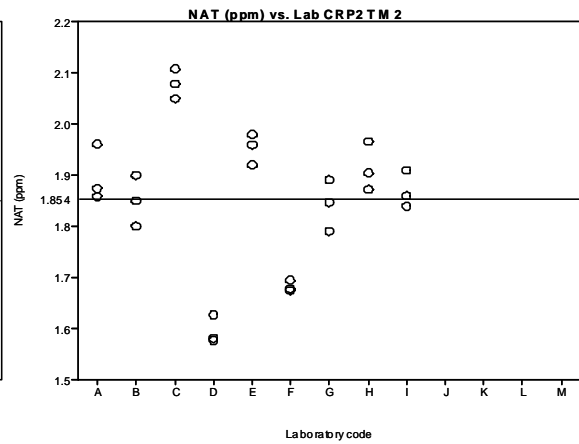
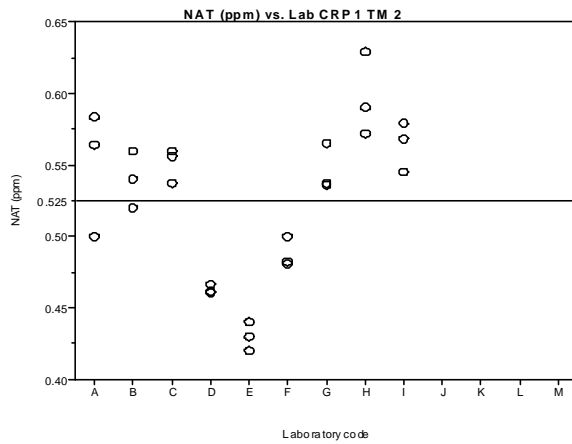




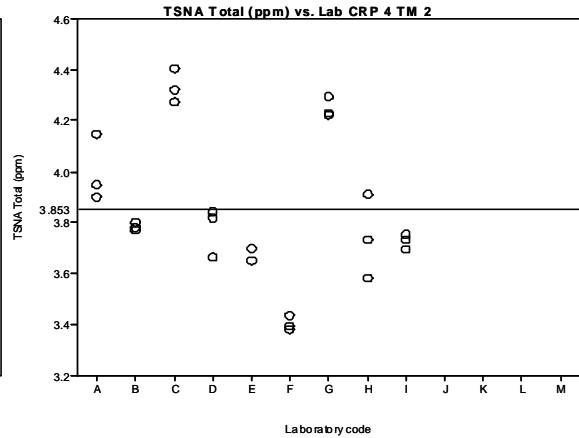
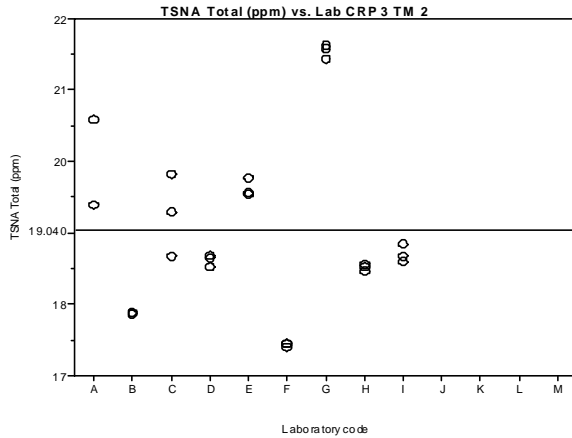
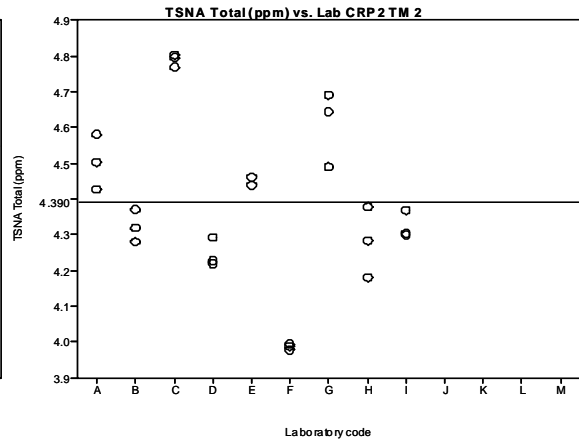
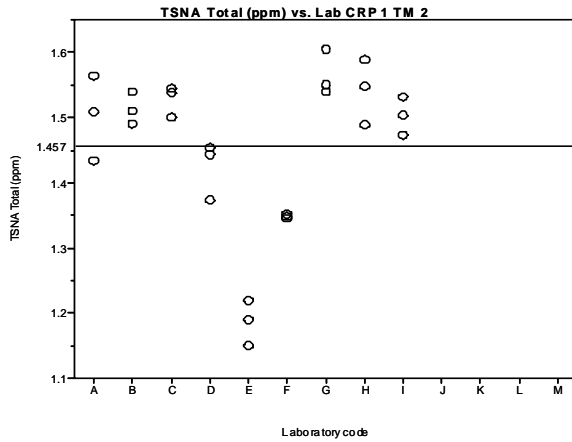
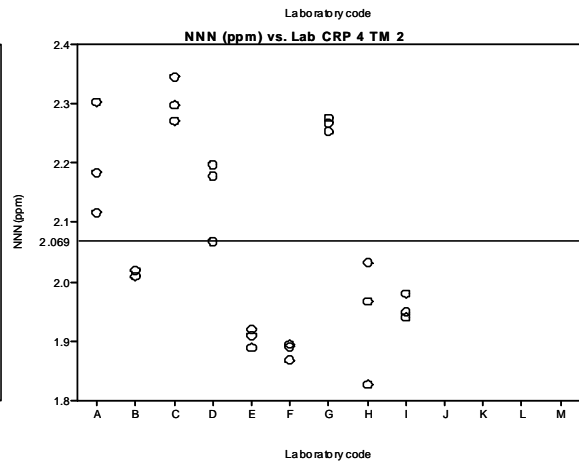
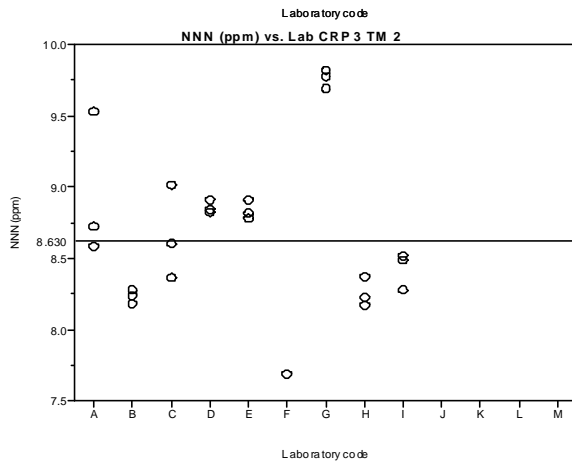
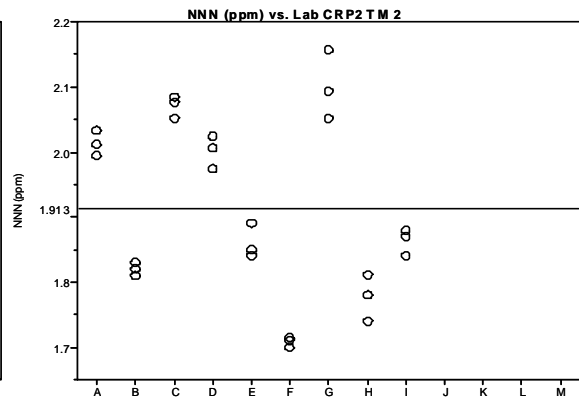
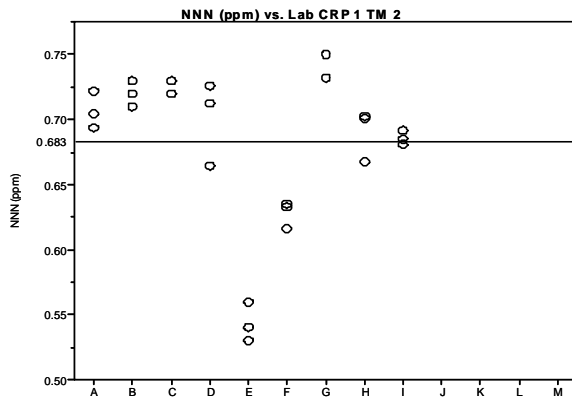












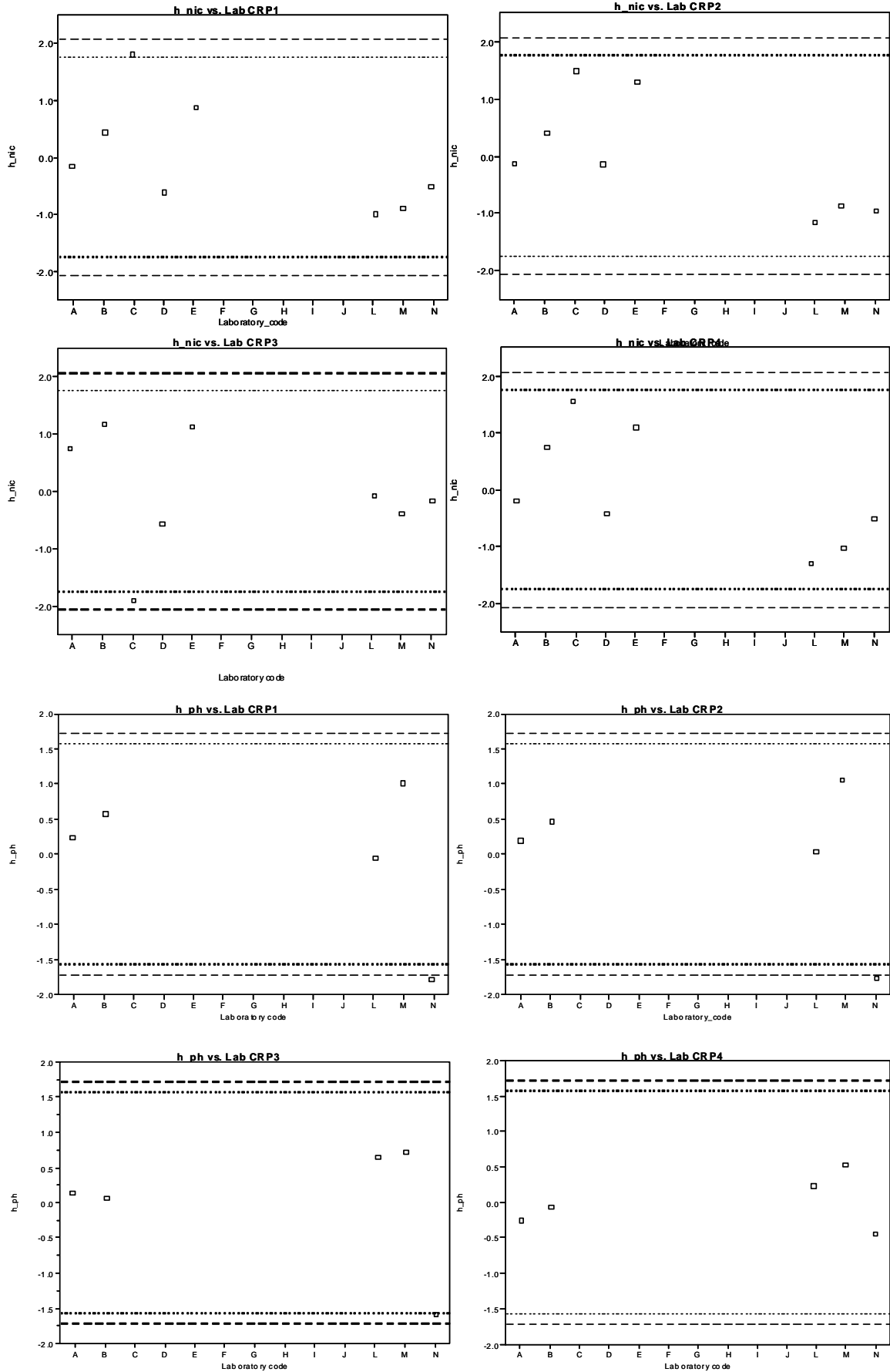
Data analysis has been performed following ISO 5725-2 recommended stages:

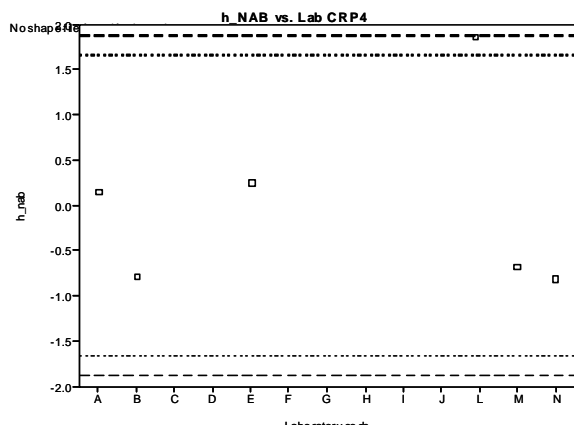
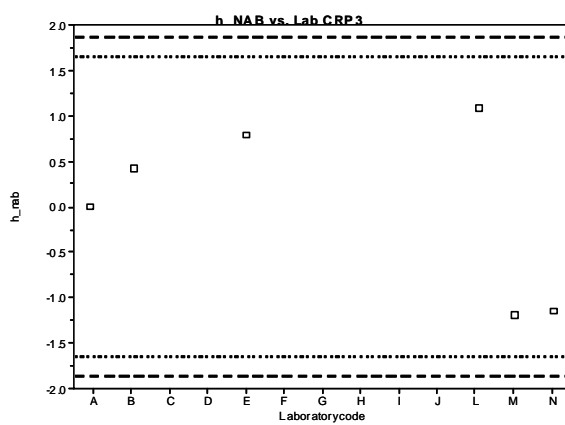
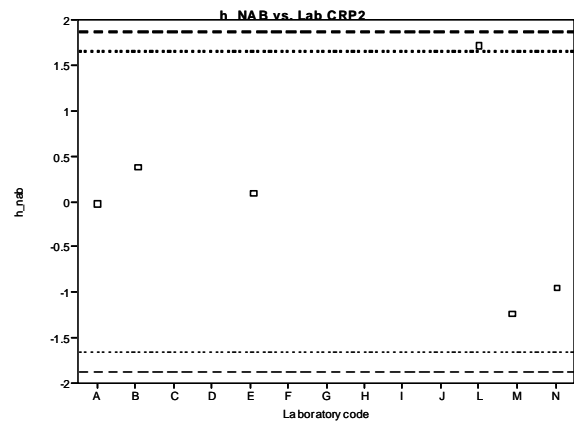
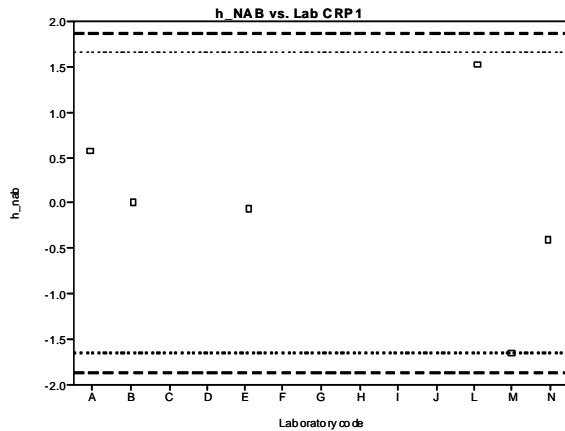
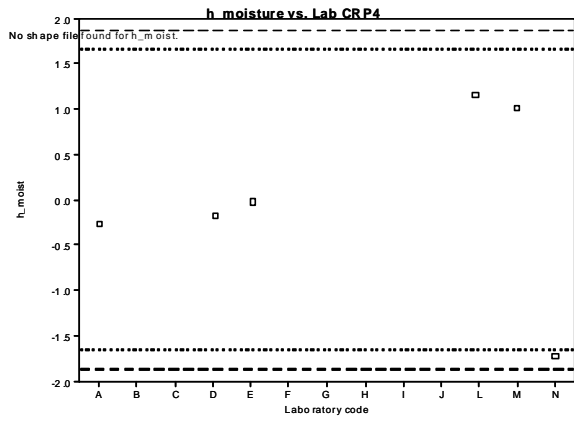
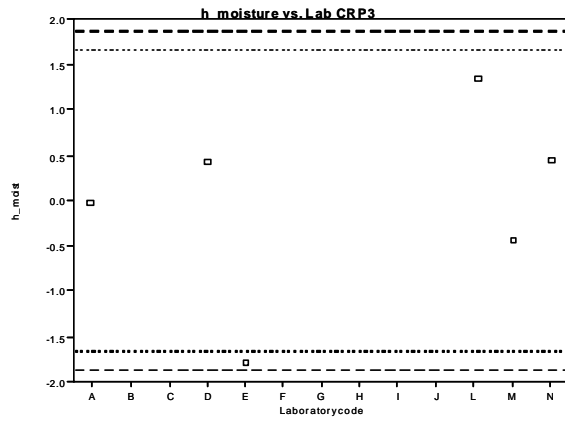
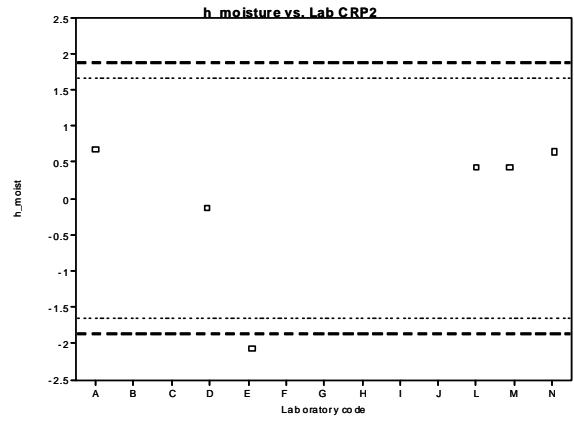
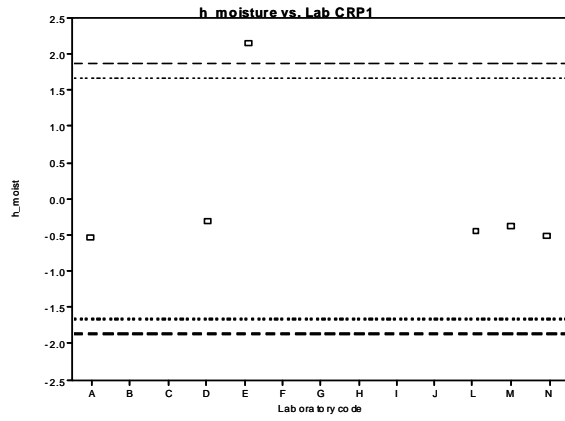
- Critical examination of the data, including the detection of outliers.
- Calculation of precision and means for each level separately.
- Calculation of final values of precision and means.

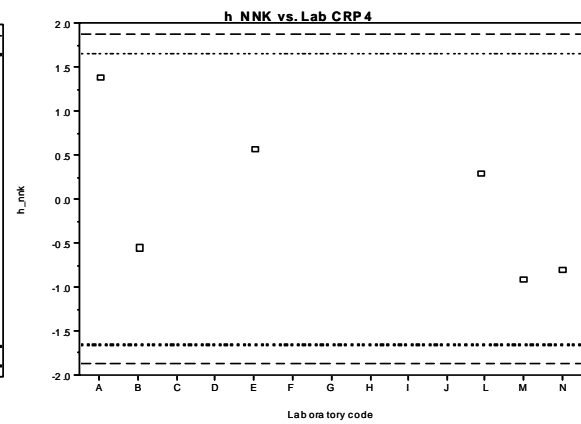
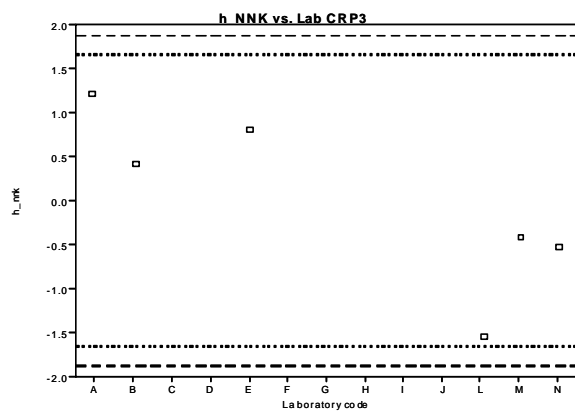
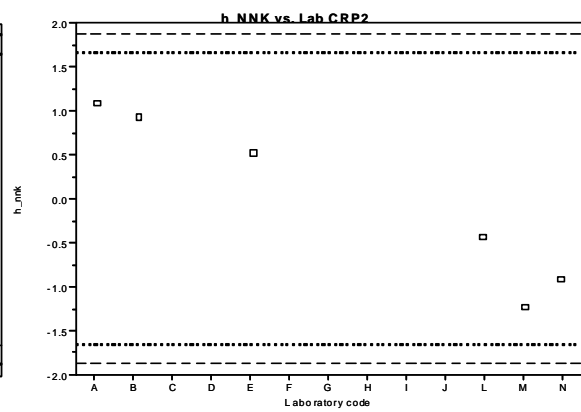
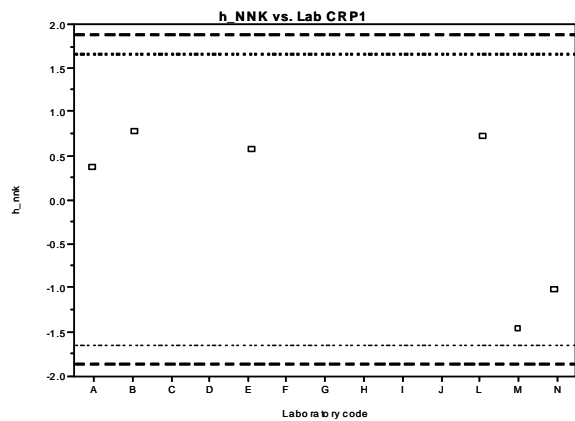
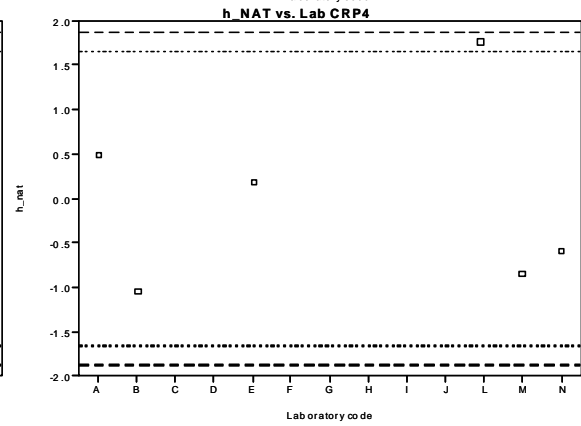
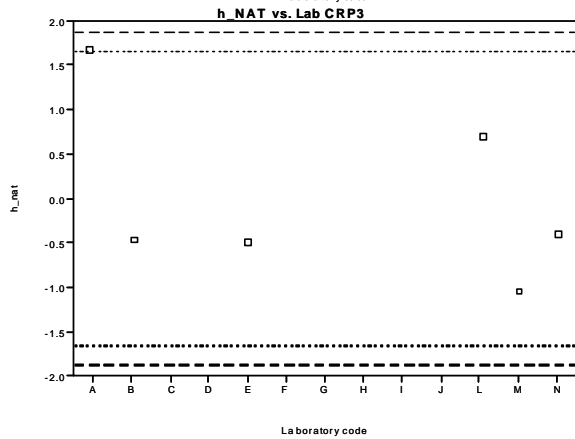
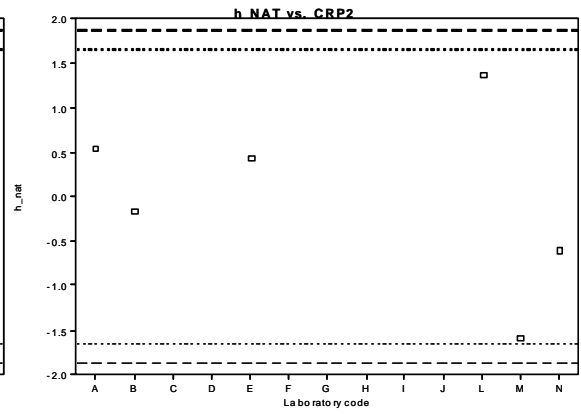
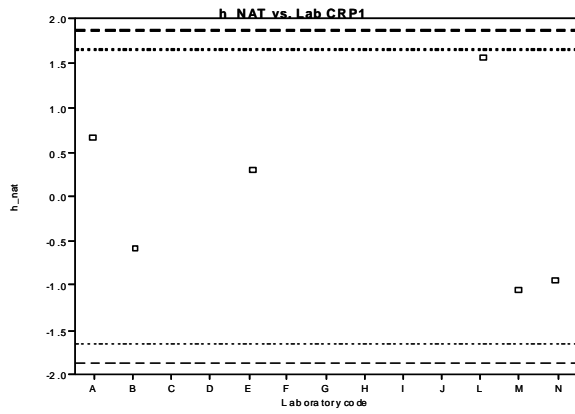
Mandel's  $h$  and  $k$  measurements were used to examine the data graphically. Critical values at 5% and 1% were represented in both types of graphs. Laboratories with scores between 5% critical value and 0 were accepted as correct; between the 5% and 1% critical values were classified as straggler and over 1% critical value is a statistical outlier. Observations were not removed from the study as result of this examination. All plots were created separately by product and time-point for each analyte. Mandel's  $h$  plots are displayed from page 12 while Mandel's  $k$  plots start at page 20.

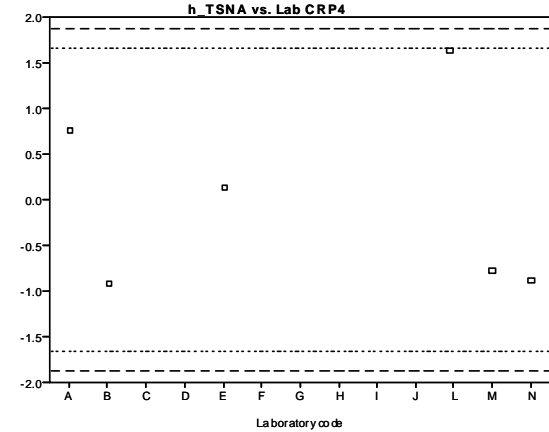
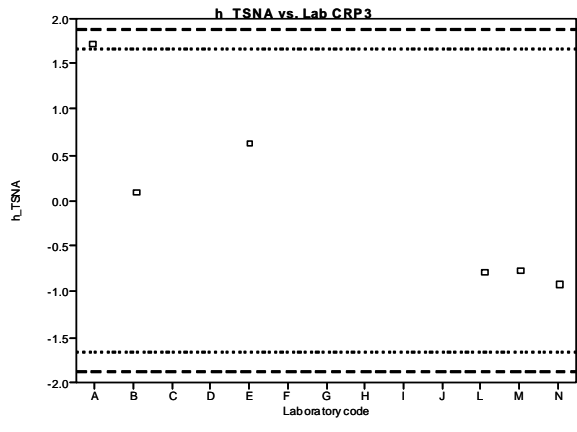
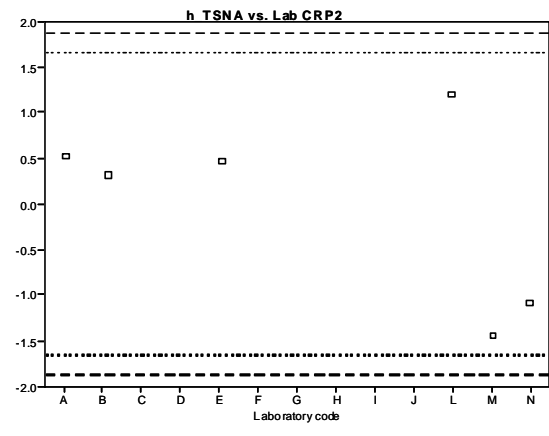
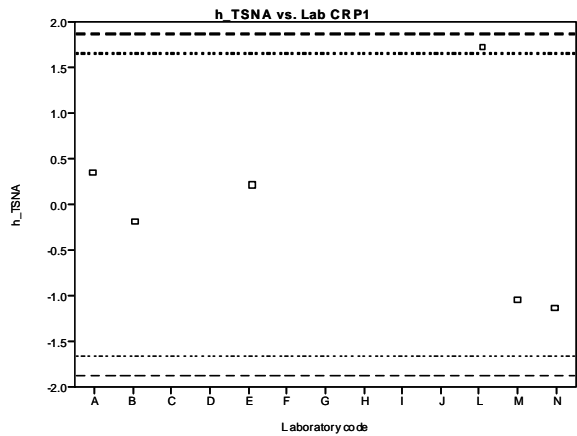
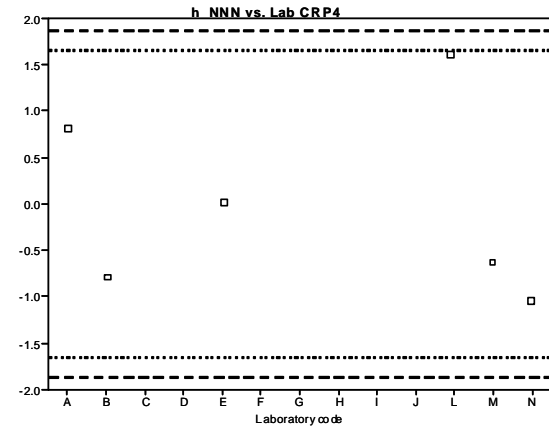
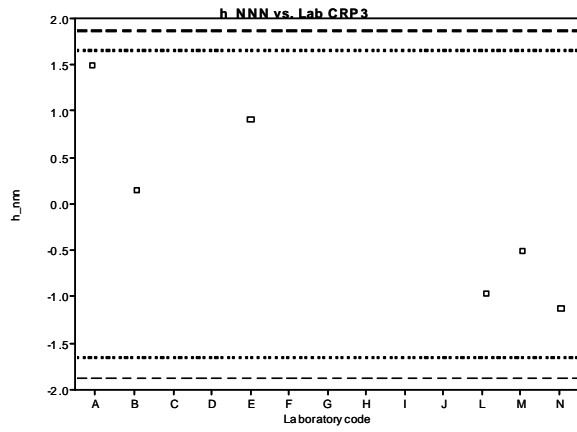
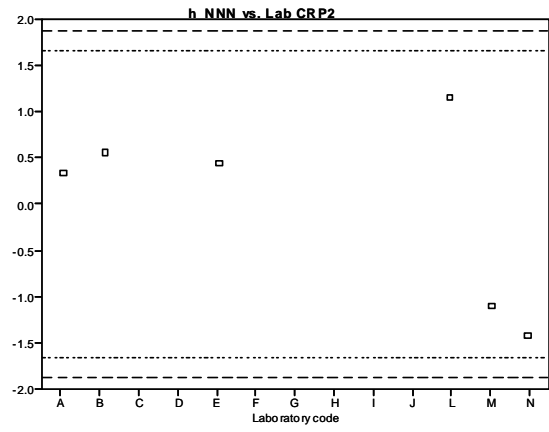
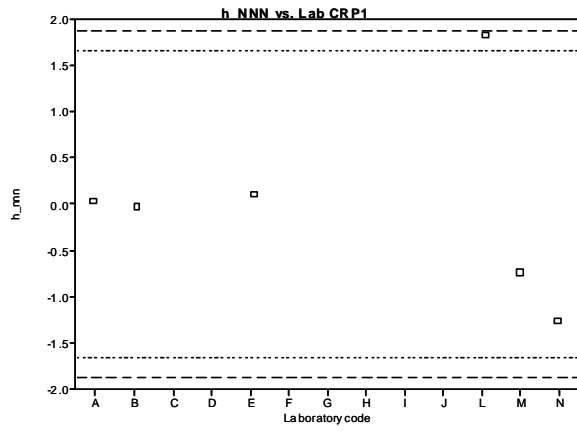
As mentioned before, low  $k$ -scores should be carefully assessed because they could be the result of poor precision on the number of digits reported rather than an indication of better technique.

## Charts 2. Mandel's h Plots – Timepoint 1

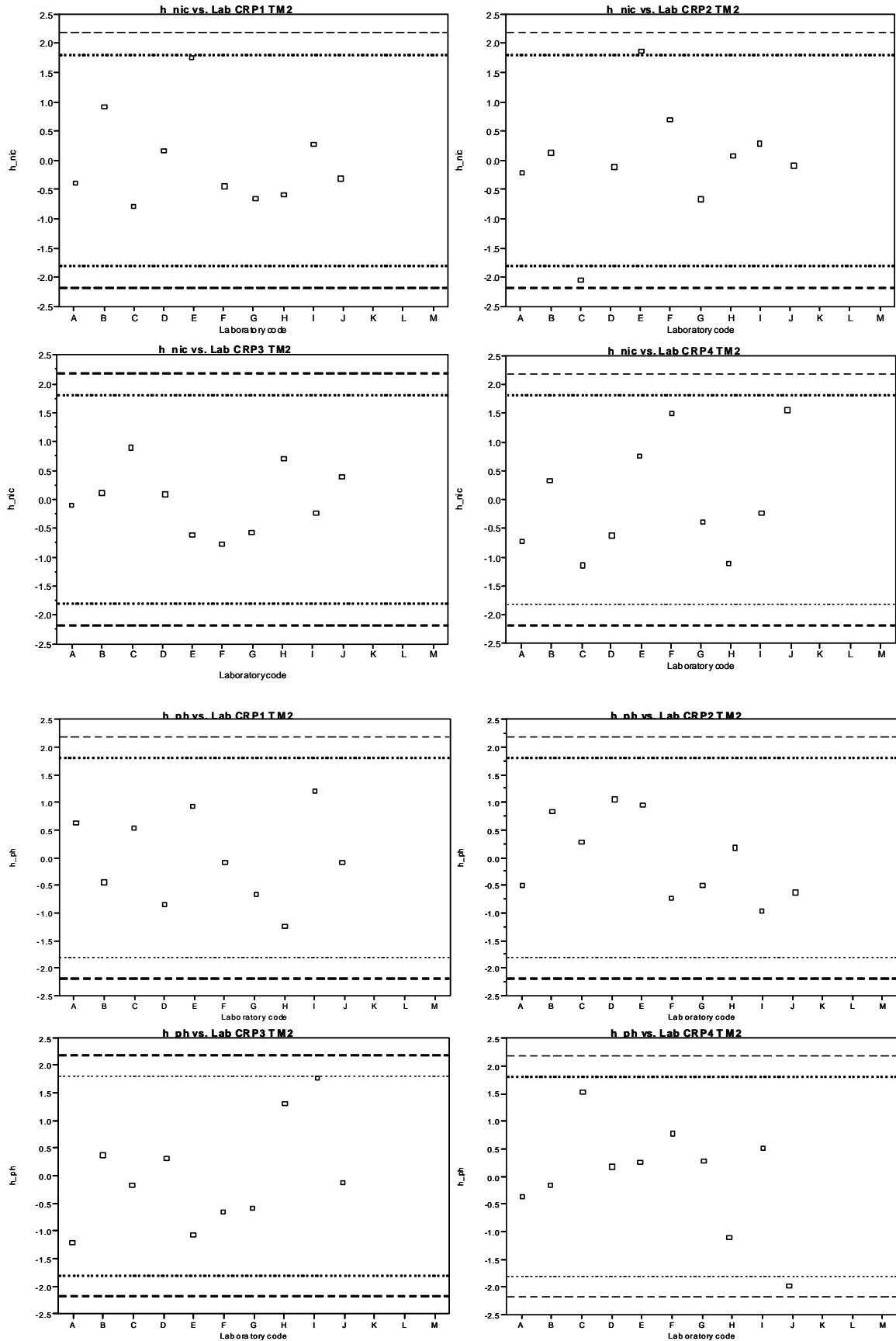


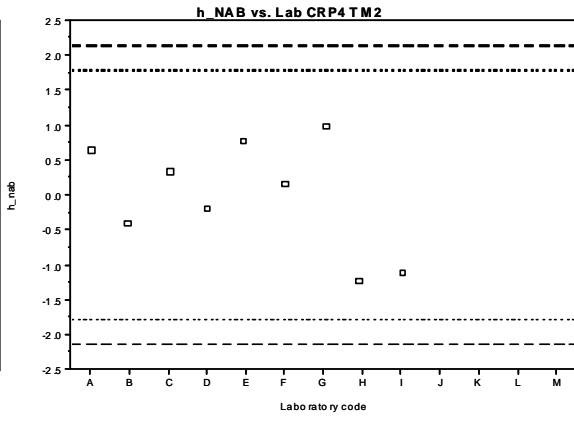
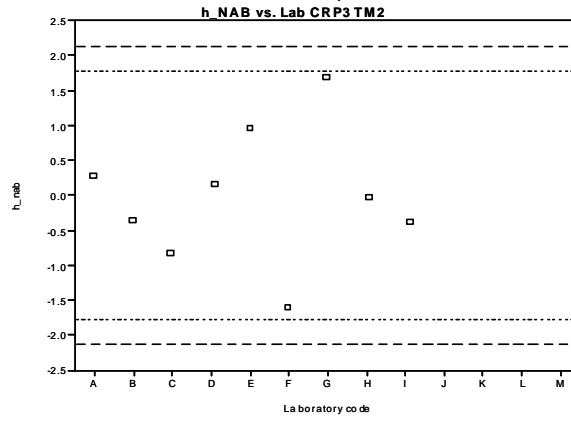
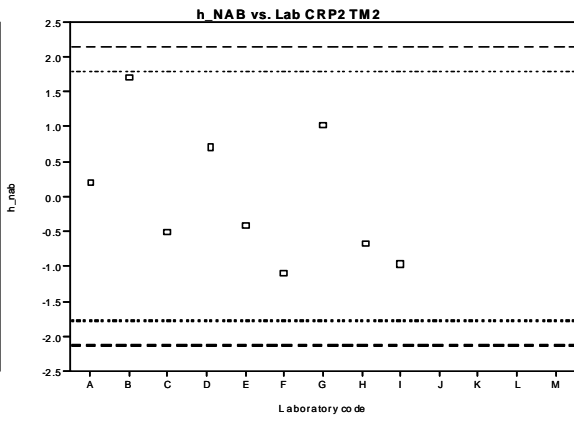
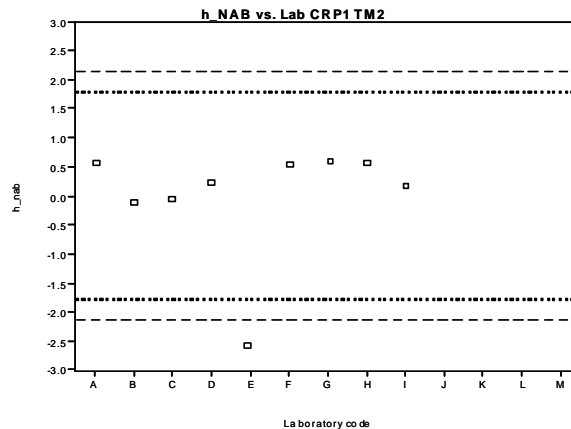
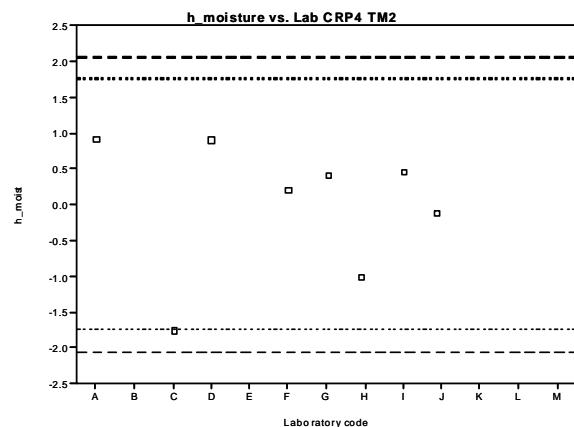
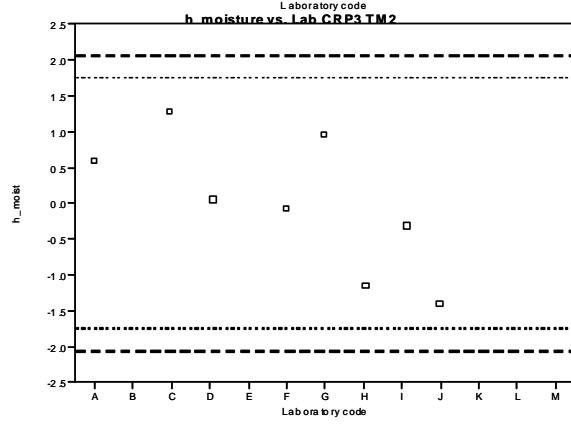
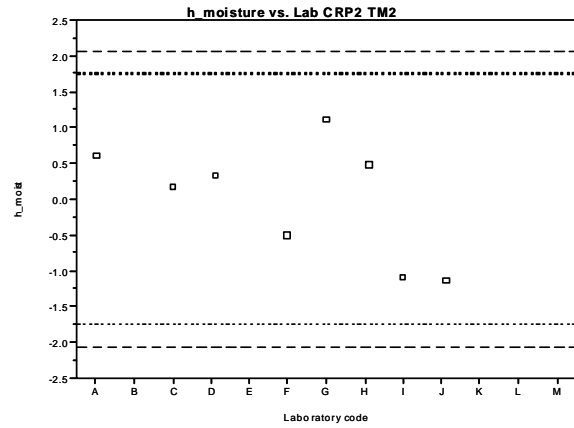
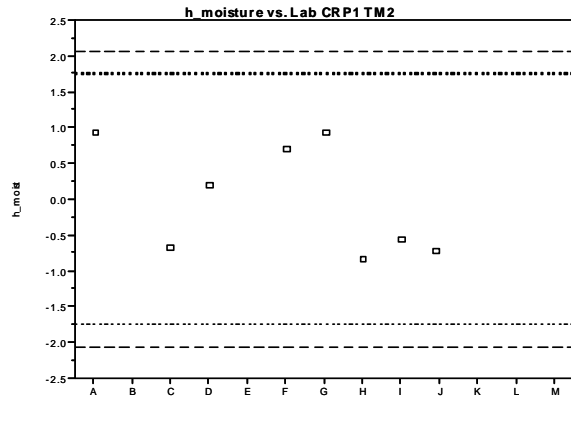




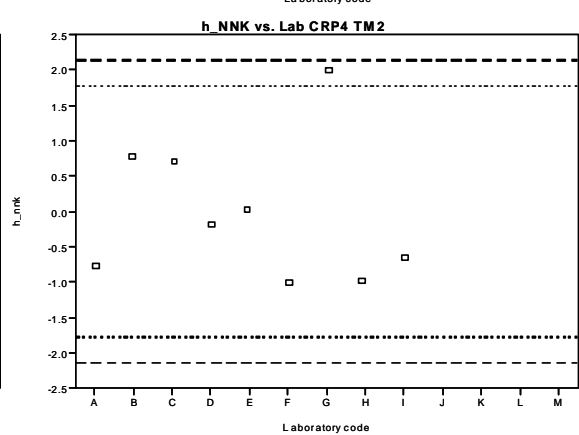
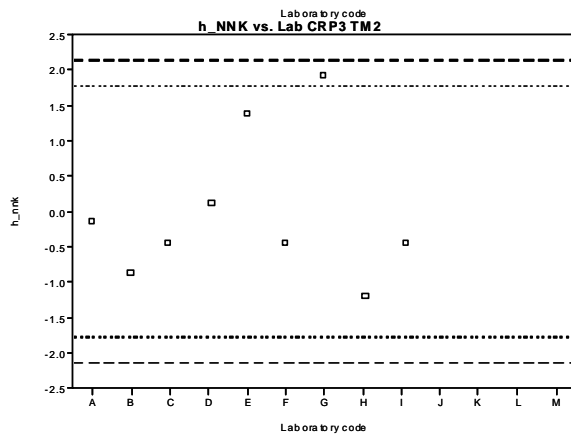
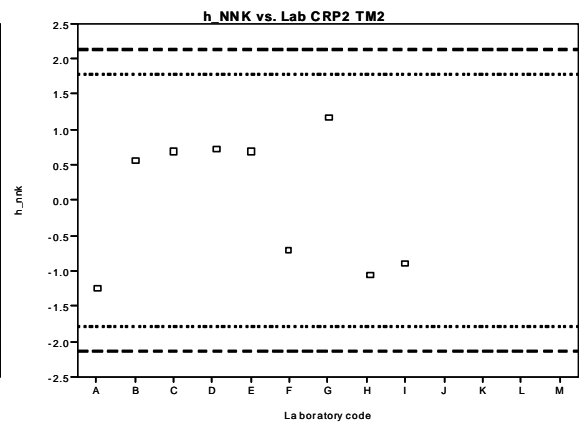
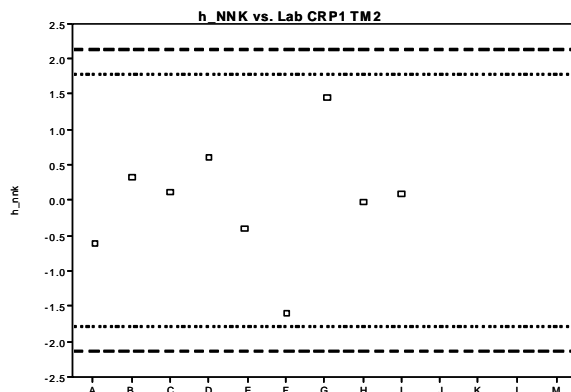
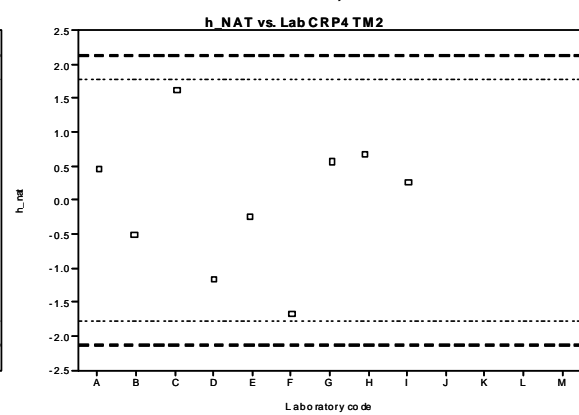
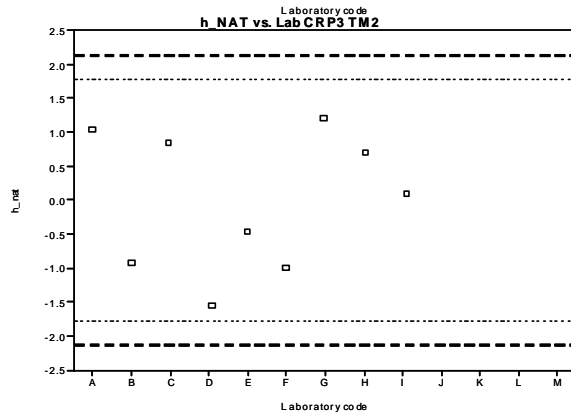
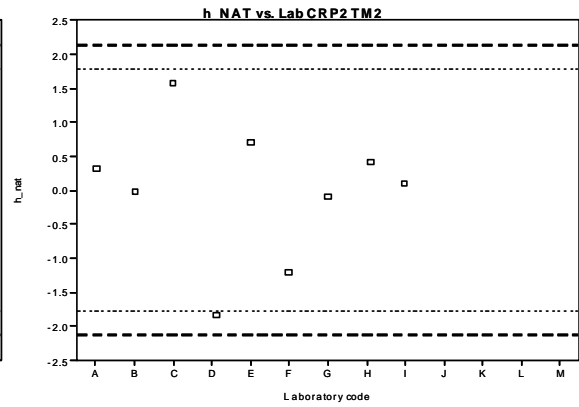
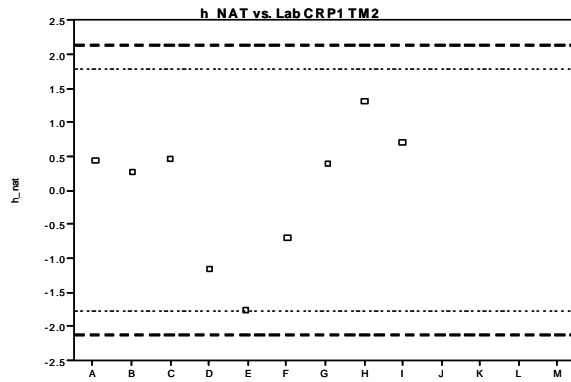


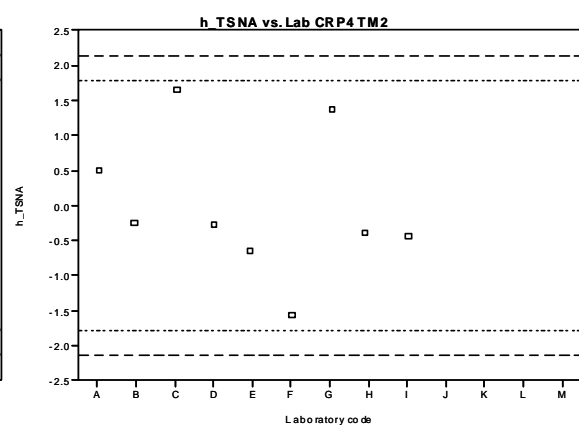
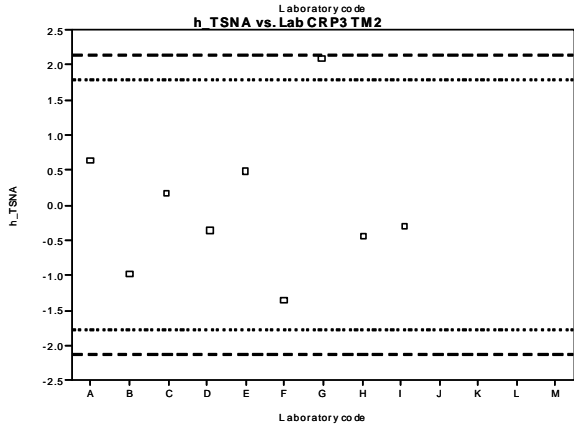
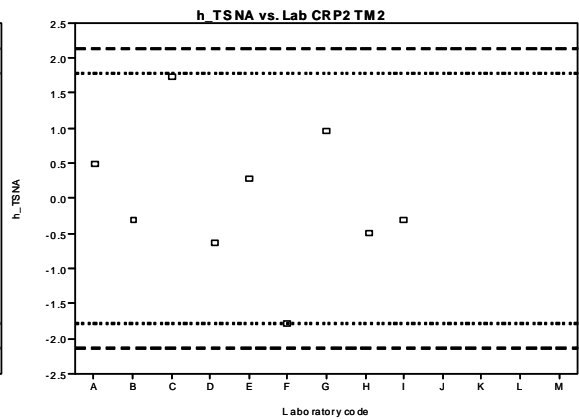
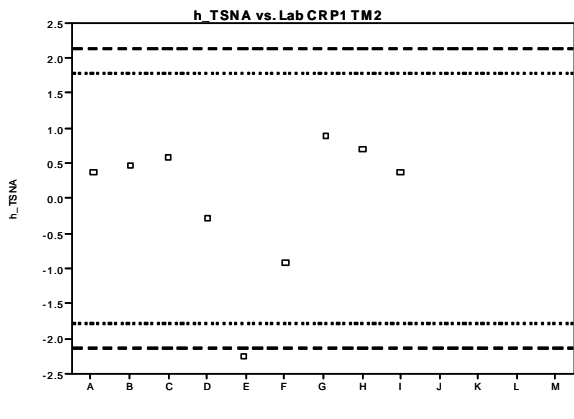
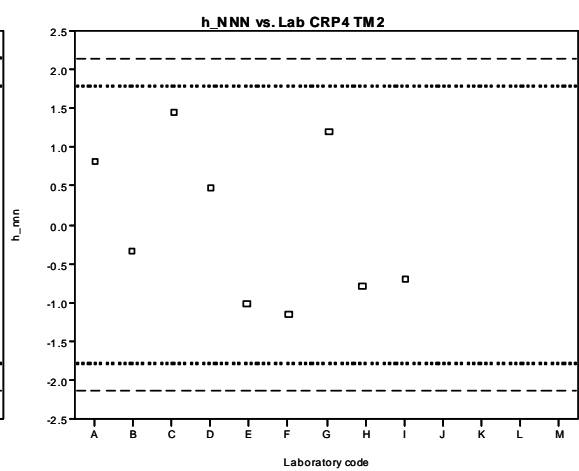
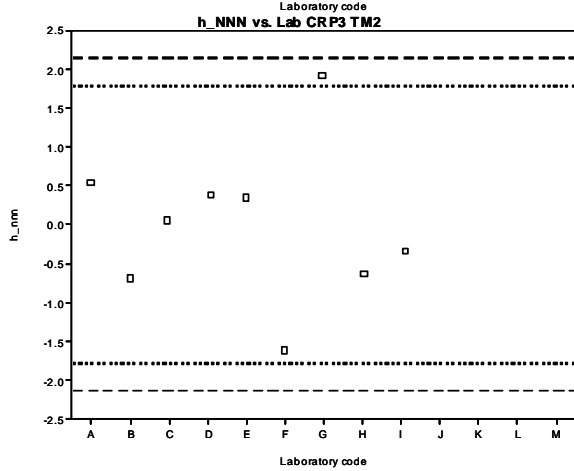
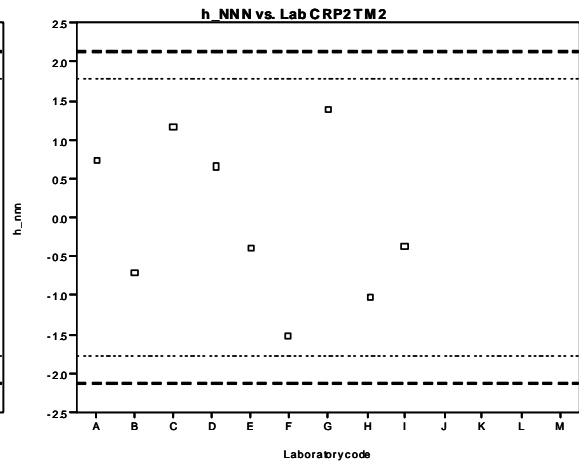
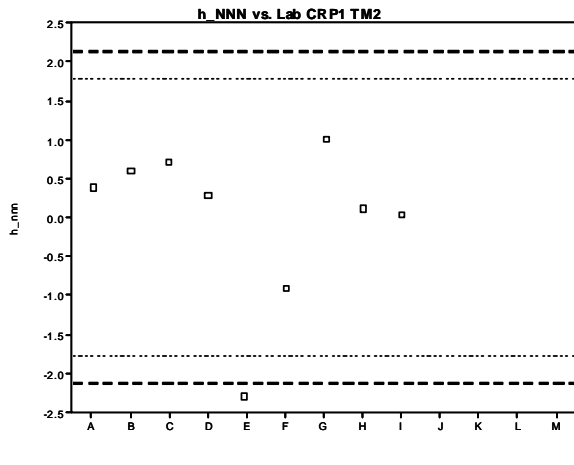
### Charts 3. Mandel's *h* Plots – Timepoint 2



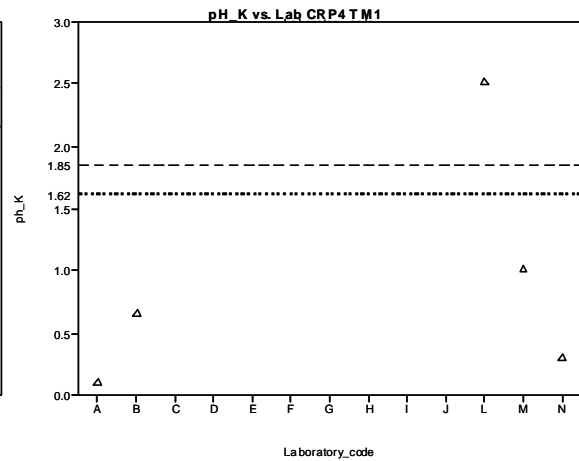
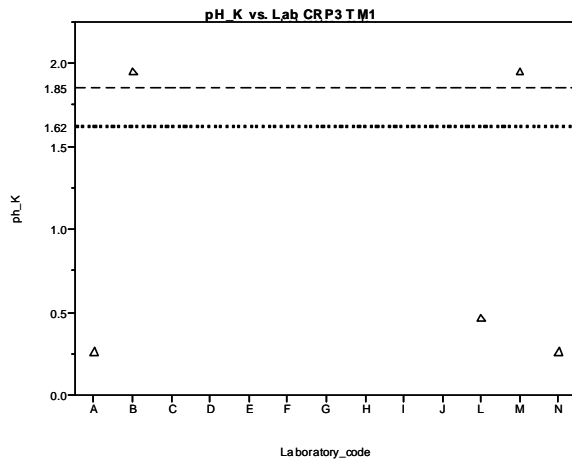
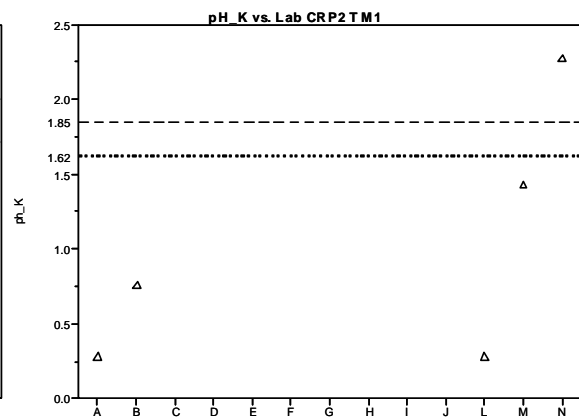
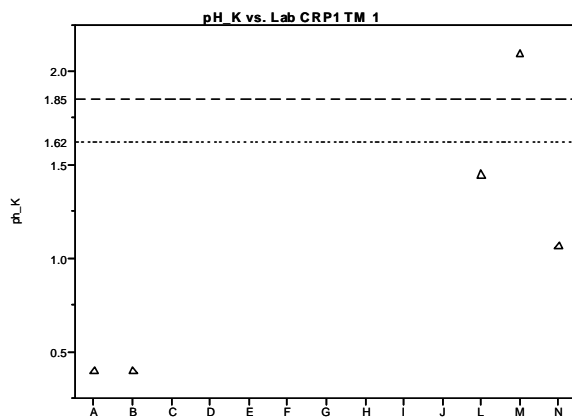
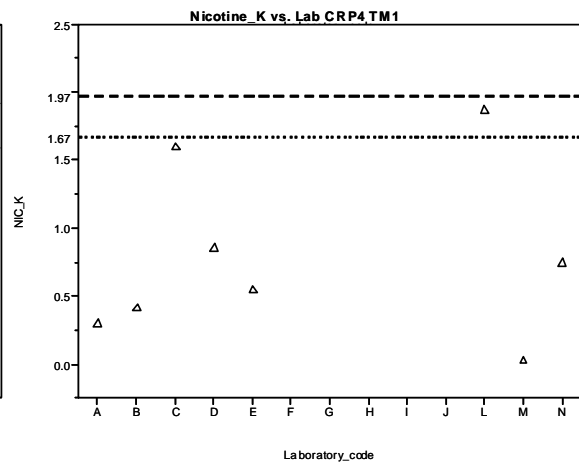
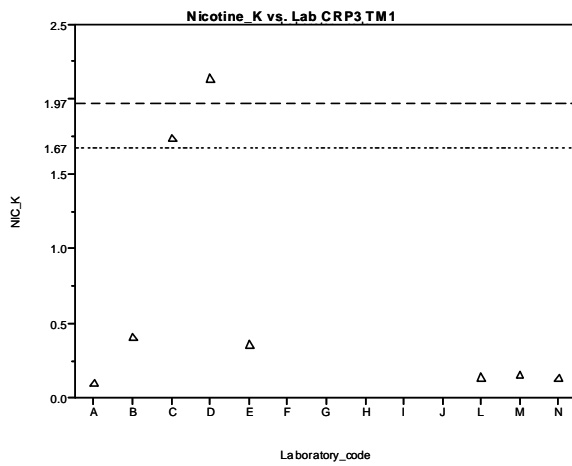
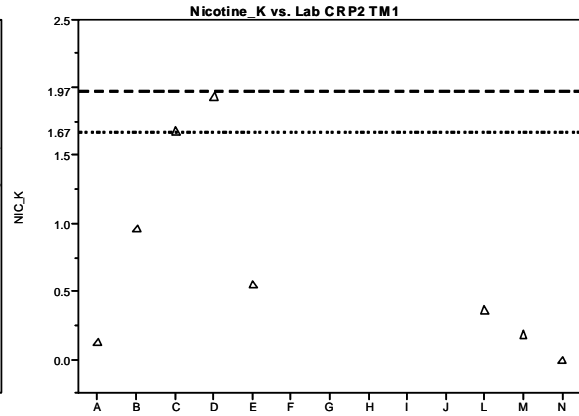
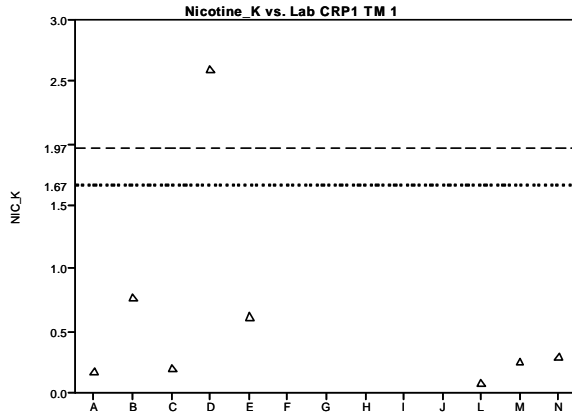


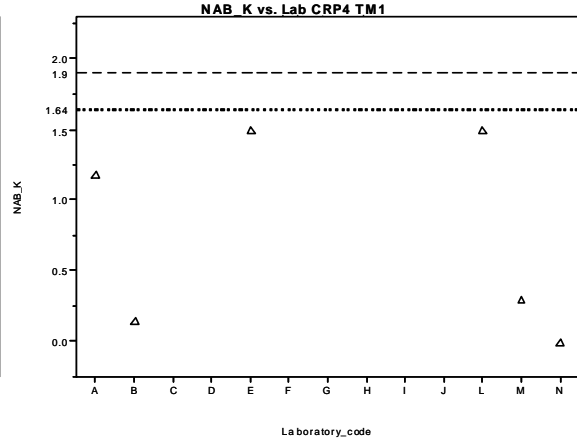
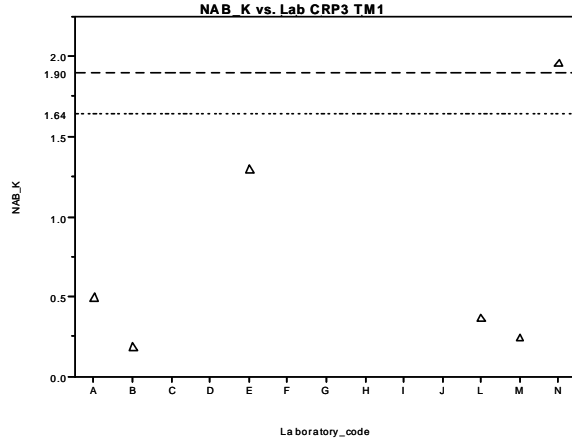
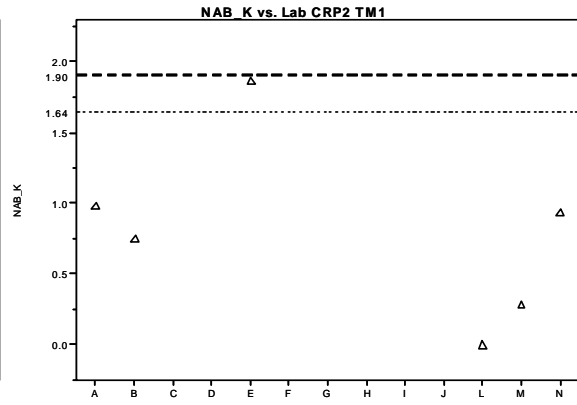
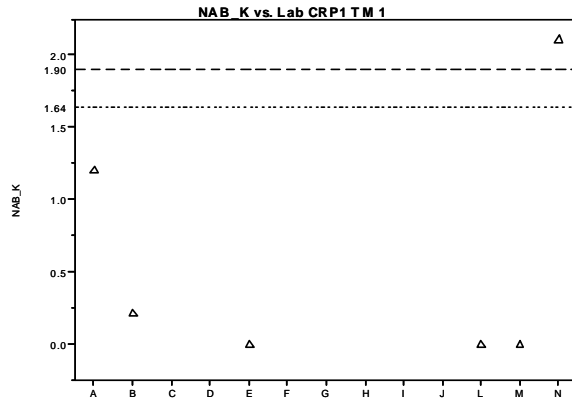
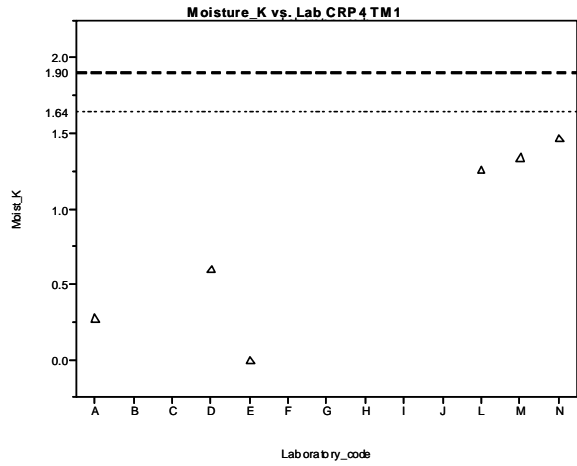
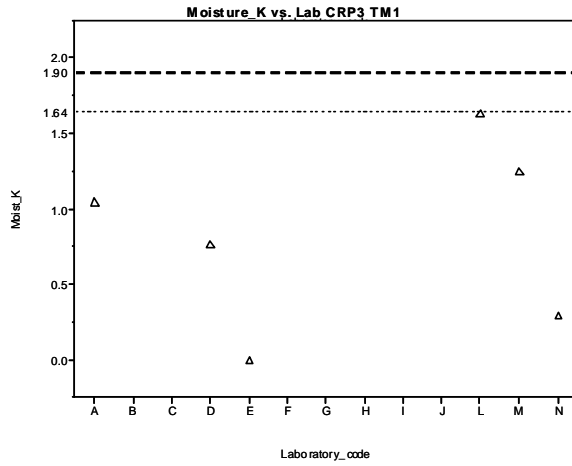
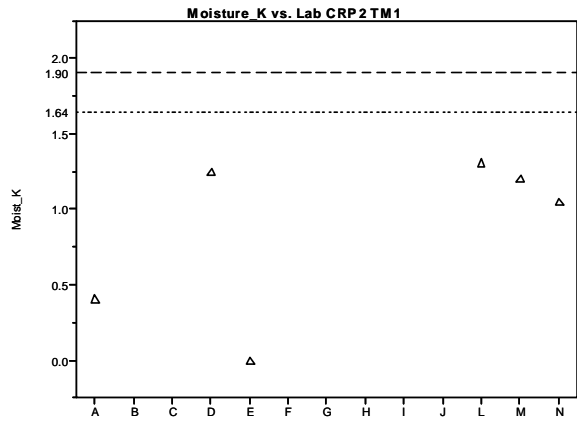
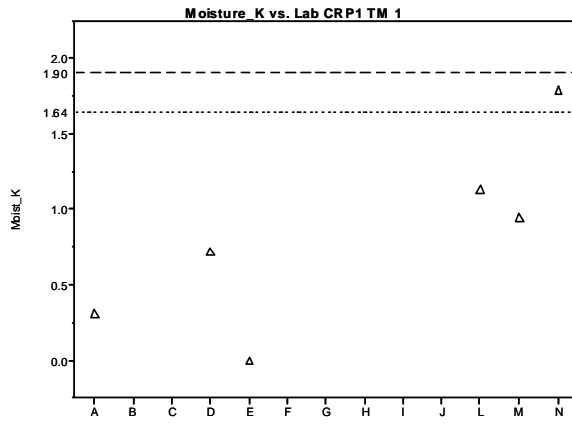


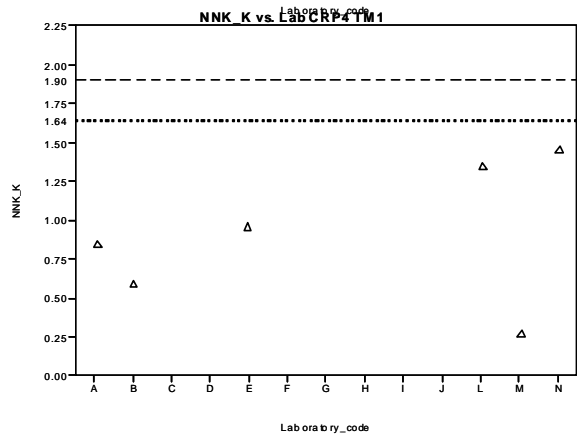
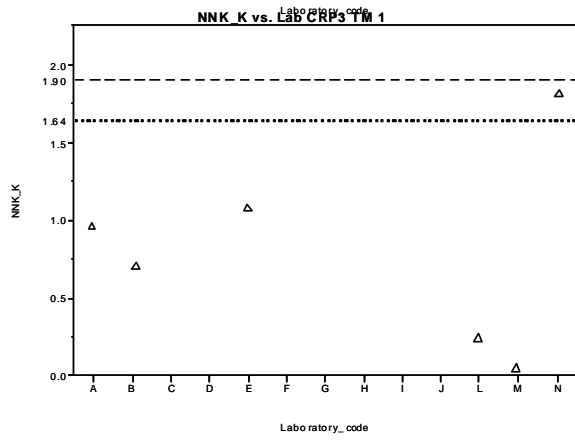
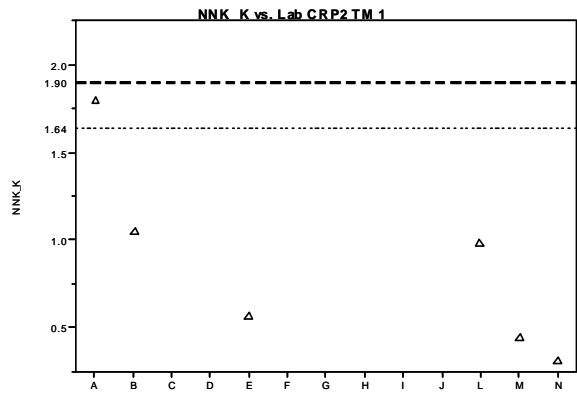
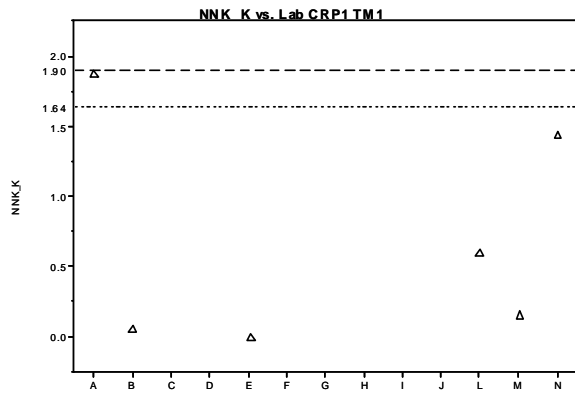
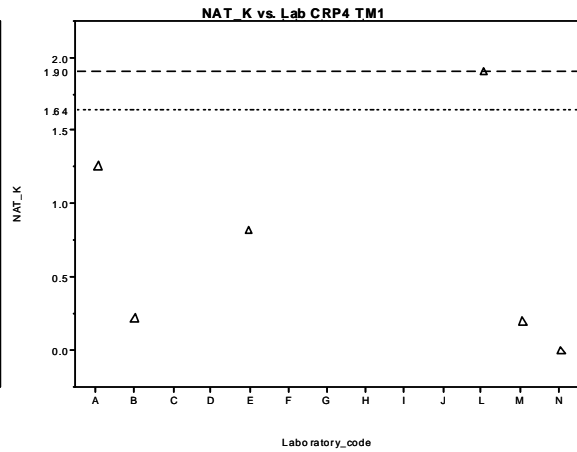
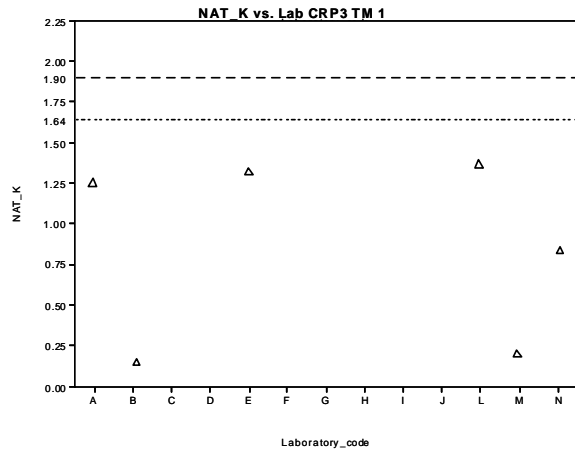
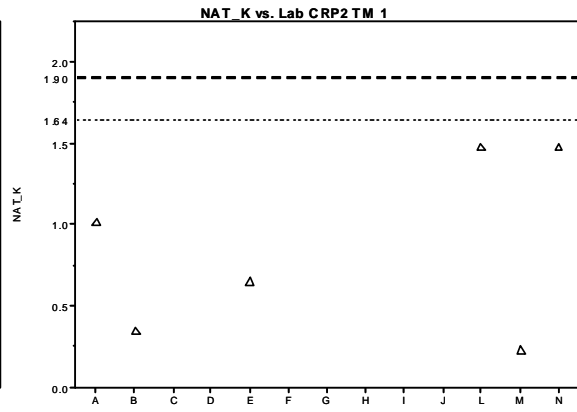
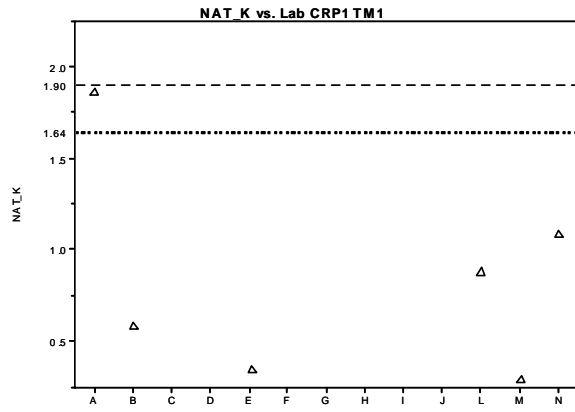


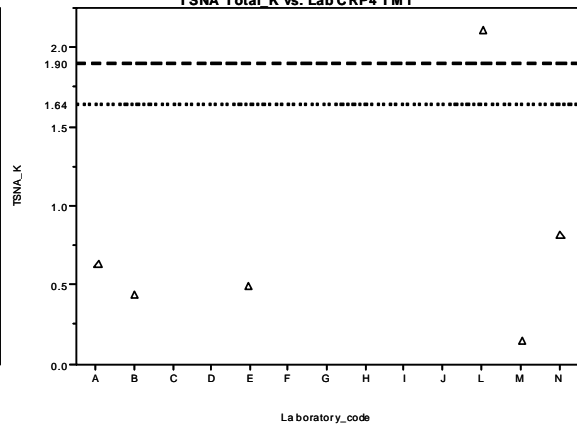
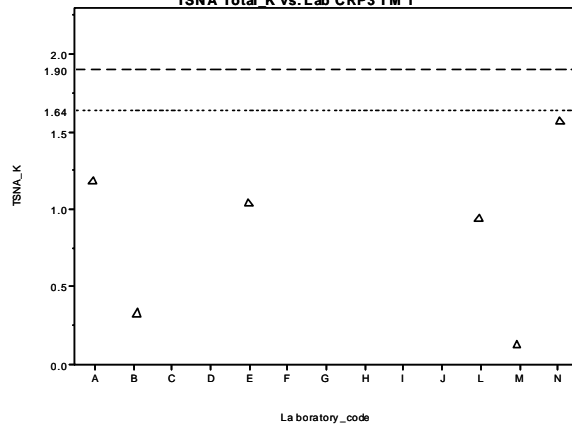
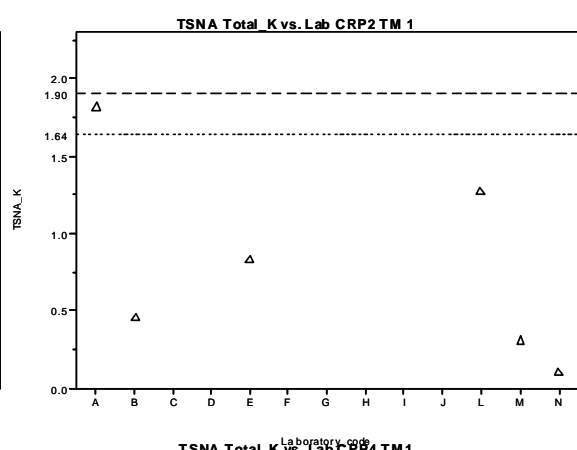
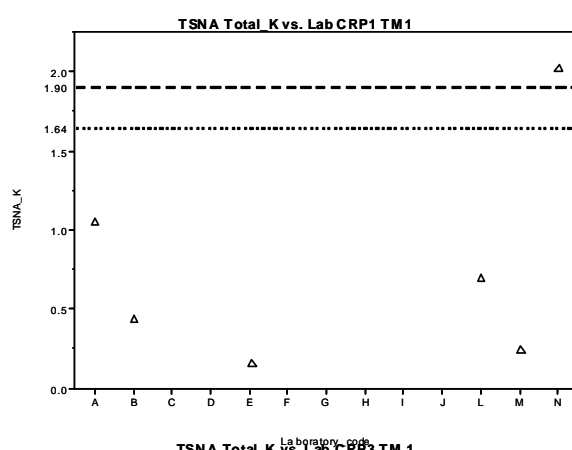
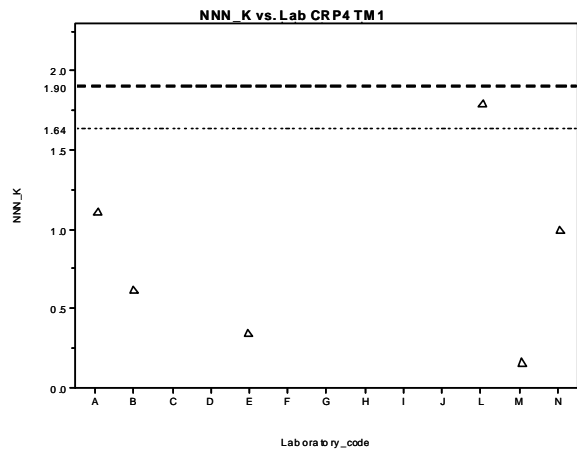
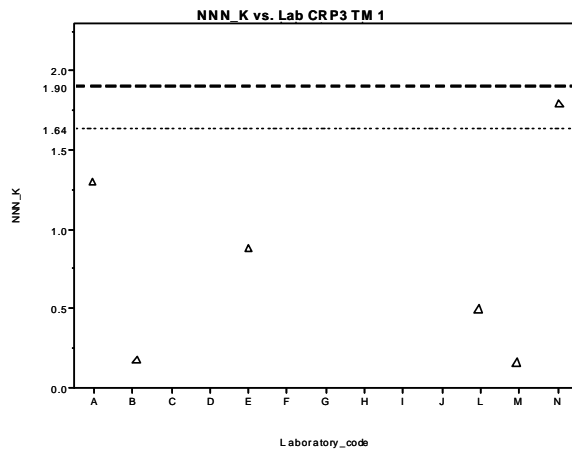
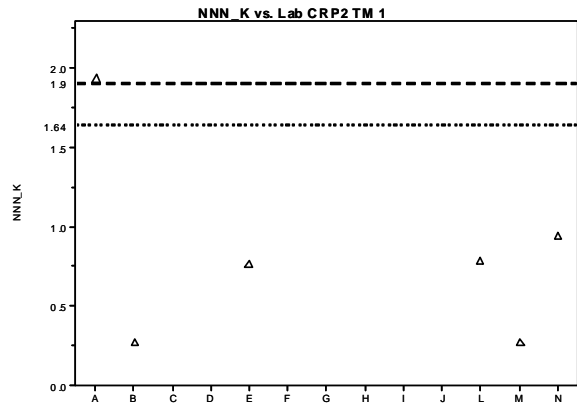
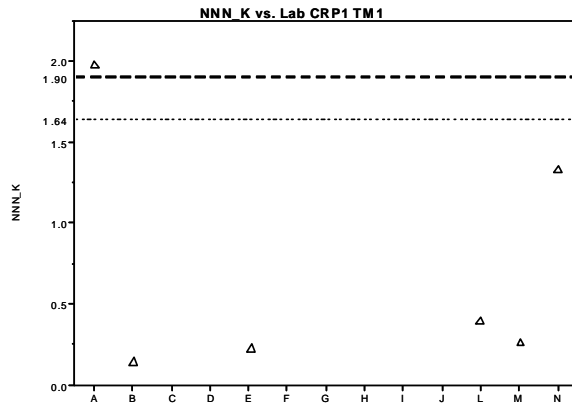


### Charts 4. Mandel's k Plots– Timepoint 1

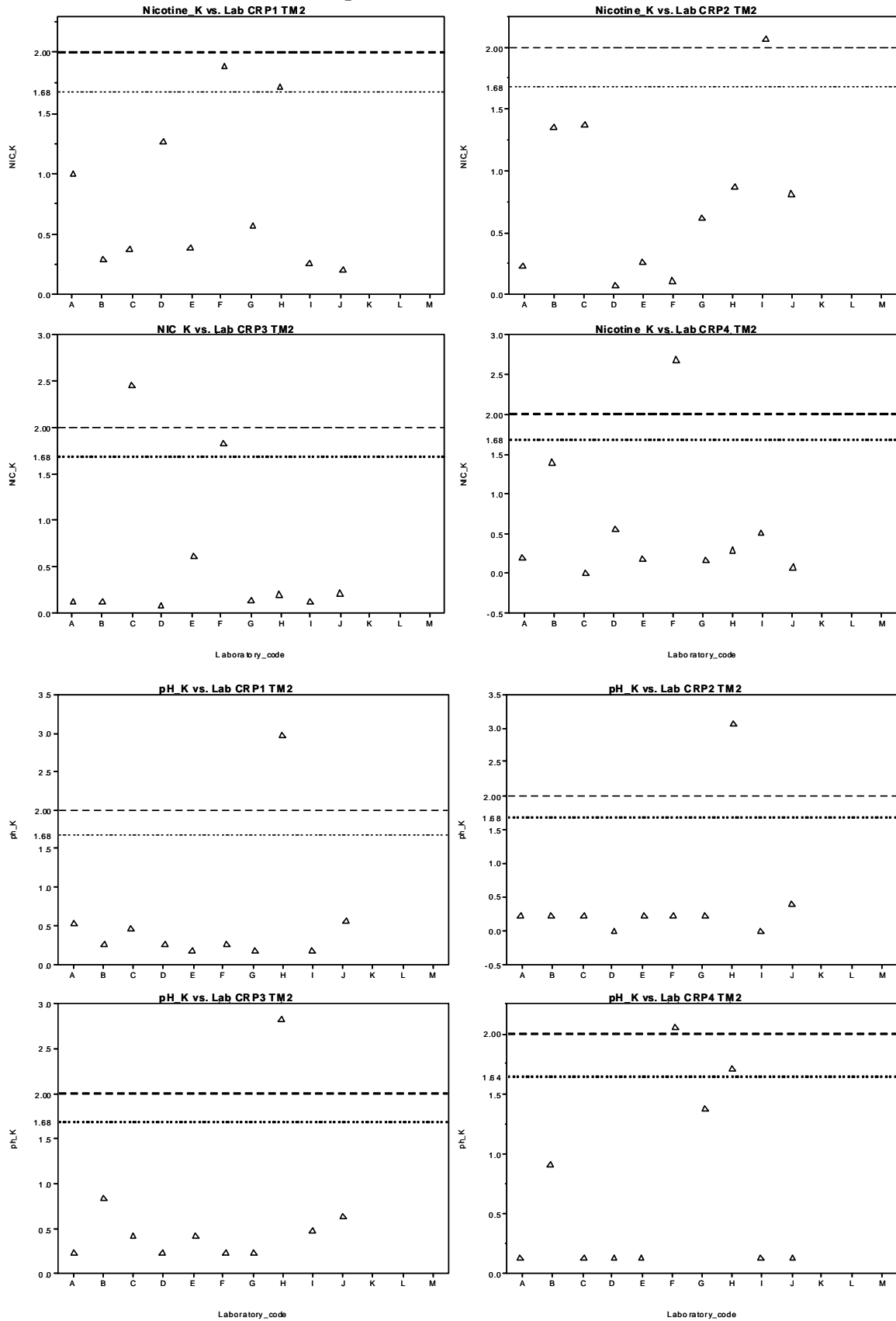


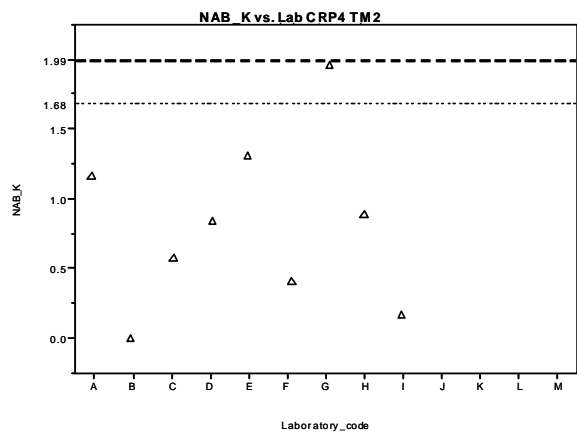
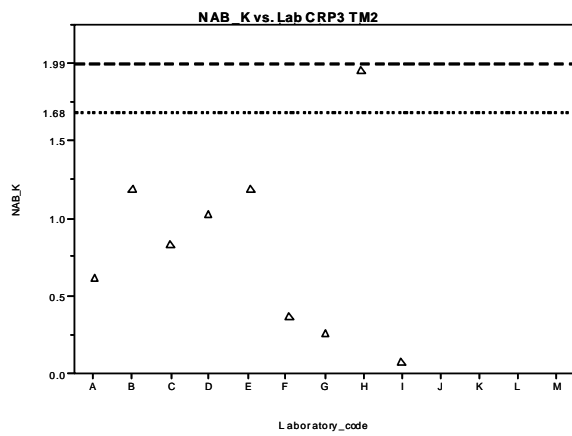
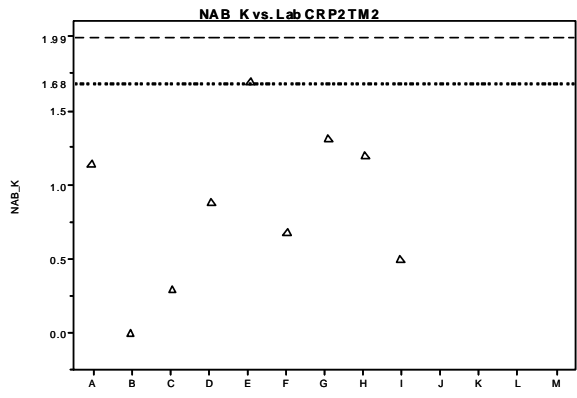
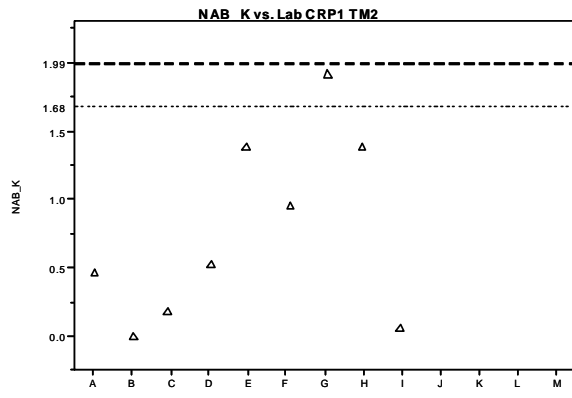
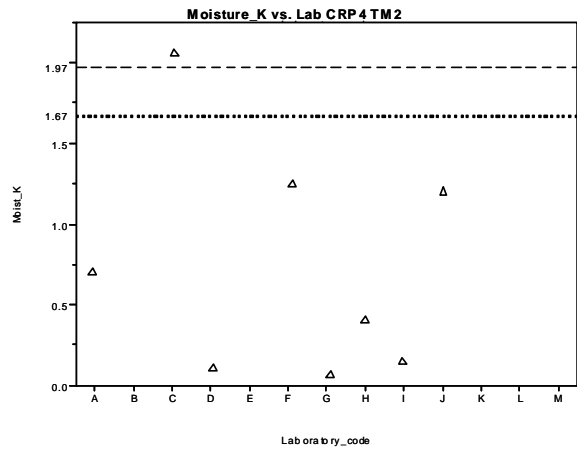
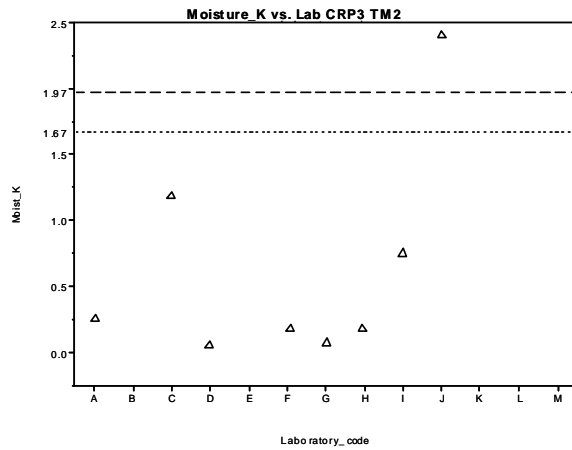
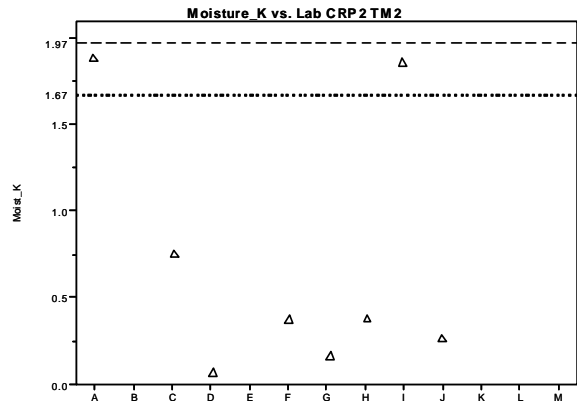
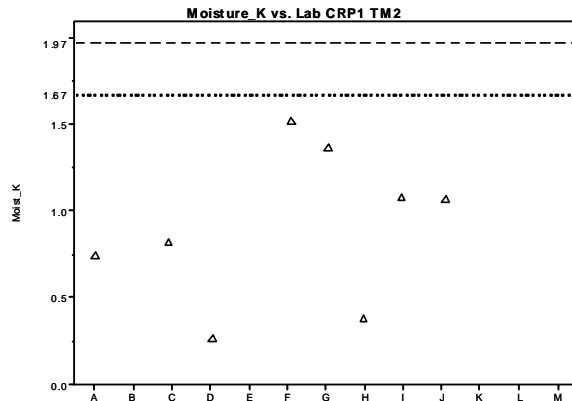




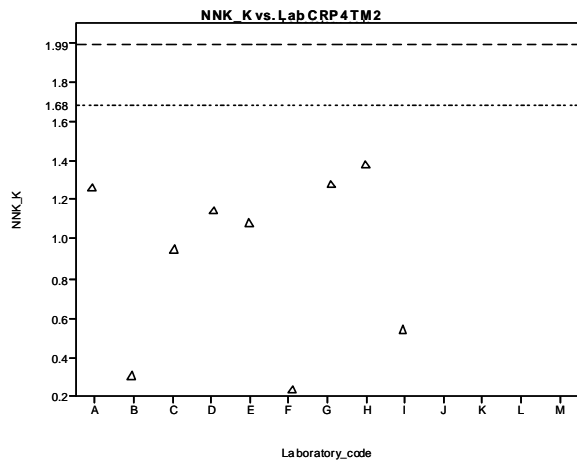
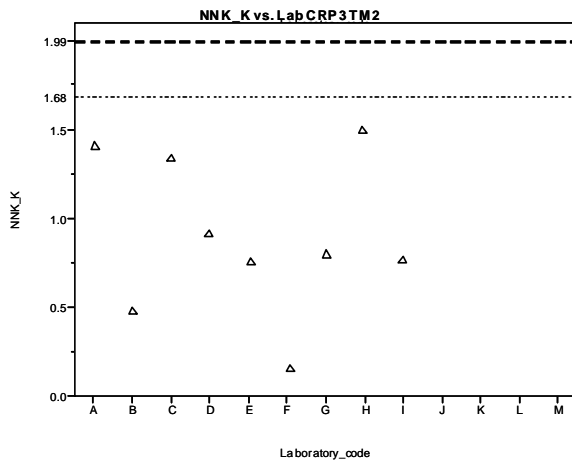
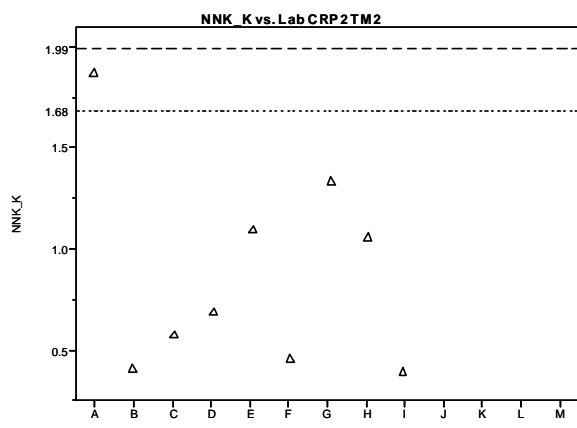
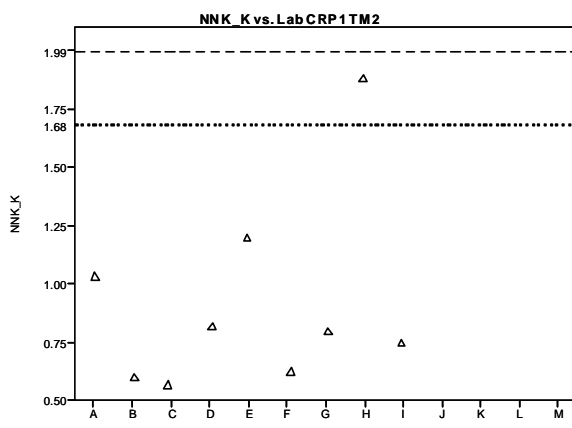
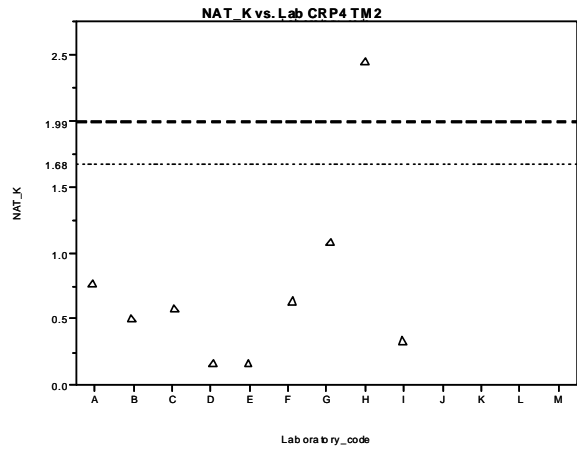
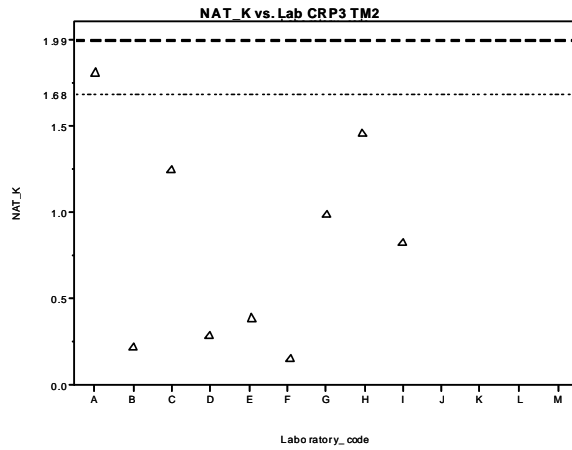
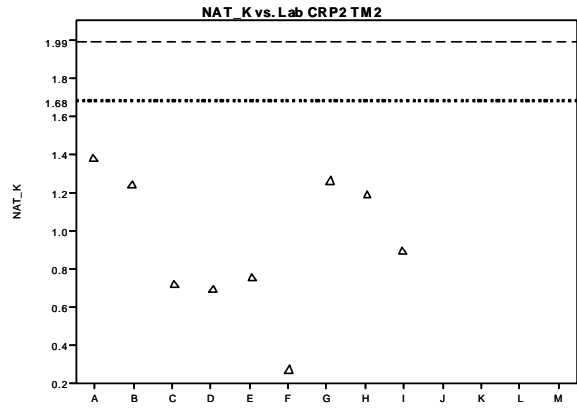
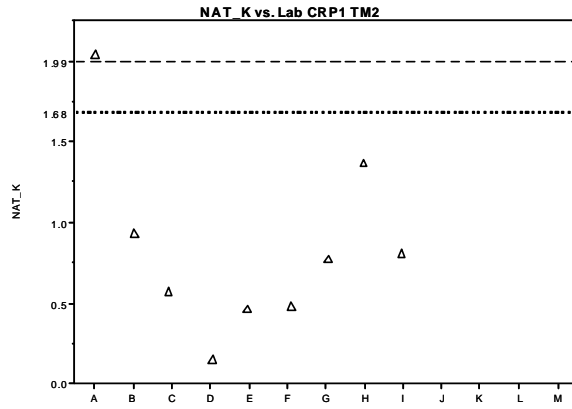


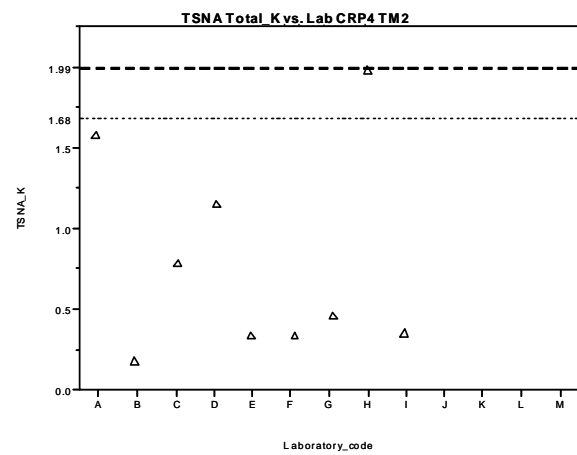
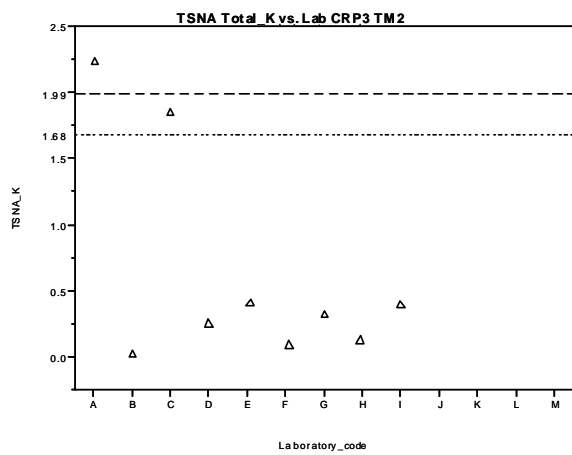
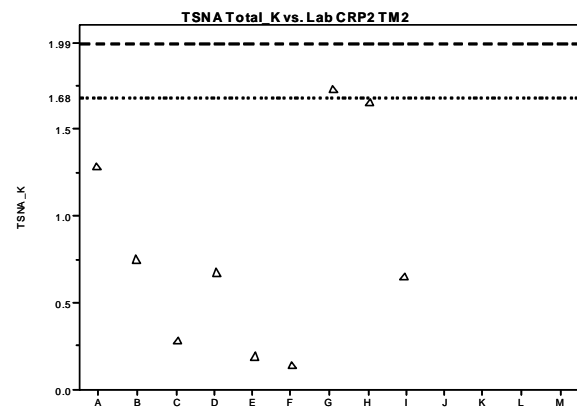
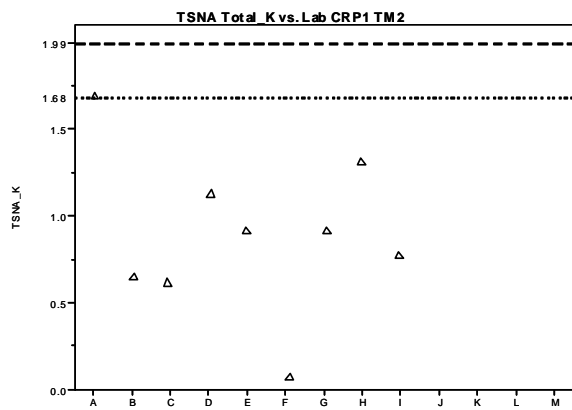
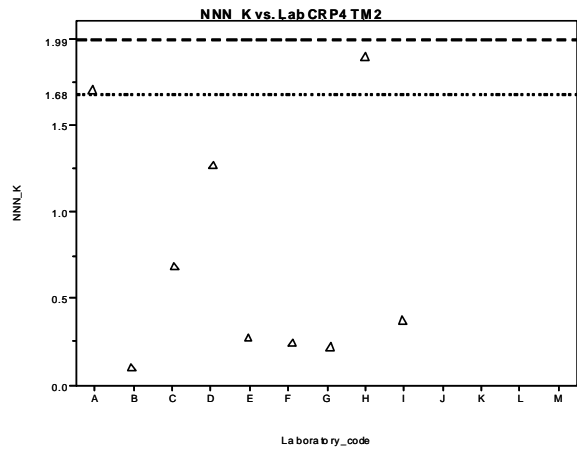
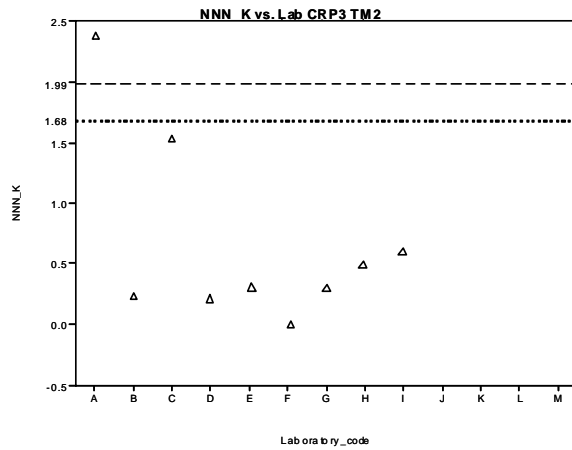
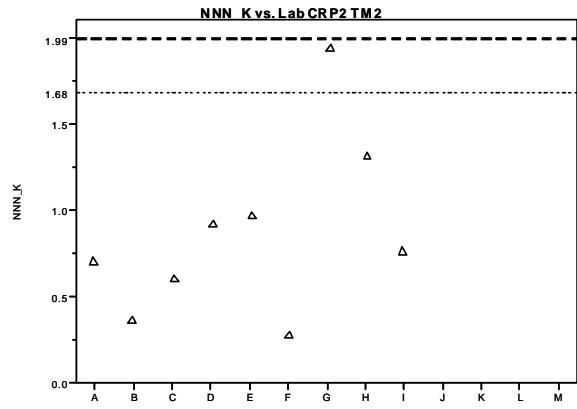
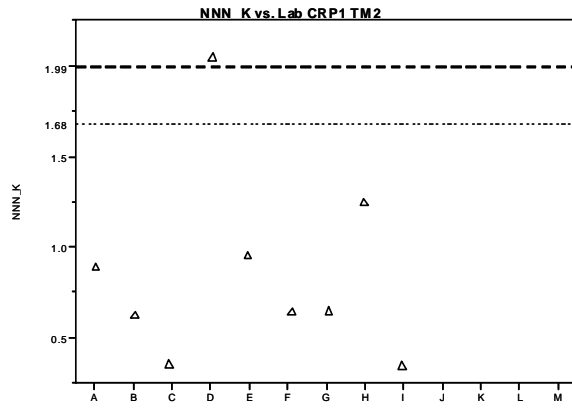
### Charts 5. Mandel's k Plots– Timepoint 2











Numeric consistency tests were also carried out on the data. Cochran's test was applied first. It was applied iteratively until no further outlying data could be detected.

Note that Cochran's test only assesses the highest value of the laboratories' variances. This characteristic makes it a one-sided outlier test. The aim of the test is to evaluate homogeneity of variances and although variances can differ from others because they are small it seems unreasonable to reject data from a laboratory because it performs with higher precision than others.

Subsequently, Grubbs' test was performed. The evaluation of the outlier is now based on the mean of the results of the laboratories by product and time-point.

Outliers detected by either numerical method were excluded from the analysis while all the stragglers found were retained. Table 4 summaries stragglers and outliers detected by graphical and numerical outlier detection methods by time-point.

Outlier methods were not applied before r&R when both time-points analysed in conjunction. There are very few laboratories presenting data for both time-points and therefore exclusion of laboratories could lead to a complete miss-match between the laboratories providing data for the 2 time-points.

**Table 4. Stragglers and outliers detected by graphical and numerical methods by time-point.**

		Time-Point 1							
		Mandel's <i>h</i>		Mandel's <i>k</i>		Cochran's		Grubbs'	
		Straggler	Outlier	Straggler	Outlier	Straggler	Outlier	Straggler	Outlier
		0.05	0.01	0.05	0.01	0.05	0.01	0.05	0.01
CRP 1	Nicotine	C			D				
	pH		N		M		D		N
	Moisture		E	N					E
	NAB				N				
	NAT			A					
	NNK			A					
CRP 2	NNN	L			A	A			
	Total TSNA	L			N	N			
	Nicotine			CD					
	pH		N		N				N
	Moisture		E						E
	NAB	L							
CRP 3	NAT								
	NNK			A					
	NNN			A	A	A			
	Total TSNA			A					
	Nicotine	C		C	D	D			
	pH	N			B				
CRP 4	Moisture	E			M				
	NAB				N	N			
	NAT	A							
	NNK			N					
	NNN			N					
	Total TSNA	A							

		Time-Point 2							
		Mandel's <i>h</i>		Mandel's <i>k</i>		Cochran's		Grubbs'	
		Straggler	Outlier	Straggler	Outlier	Straggler	Outlier	Straggler	Outlier
		0.05	0.01	0.05	0.01	0.05	0.01	0.05	0.01
CRP 1	Nicotine			F	H		H		
	pH								
	Moisture		E	G					
	NAB				A				
	NAT			H					
	NNK				D				
CRP 2	NNN		E					E	
	Total TSNA		E	A				E	
	Nicotine	C	E		I				
	pH				H		H		
	Moisture			A					
	NAB	D							
CRP 3	NAT								
	NNK			A					
	NNN			G					
	Total TSNA			G					
	Nicotine			F	C		C		
	pH				H		H		
CRP 4	Moisture				J				
	NAB				C				
	NAT								
	NNK	G							
	NNN	G			A	A	A		
	Total TSNA	G		C	A	A			

After the removal of the data identified as outlier, repeatability standard deviation (r SD); reproducibility standard deviation (R SD); repeatability (r) and reproducibility (R) for each sample and analyte yield were calculated by time-point.

The repeatability, reproducibility, their standards deviations are displayed in tables 5 and 6. The means of these analytes by product and time-point and the number of observations used to calculate these results have also been included.

**Table 5. Repeatability and reproducibility by product and time-point.**

Product CRP 1	Time-Point 1						Time-Point 2					
	Mean	r SD	R SD	r	R	N	Mean	r SD	R SD	r	R	N
Nicotine	0.985	0.014	0.080	0.039	0.224	21	0.956	0.039	0.052	0.109	0.146	30
pH	7.999	0.019	0.051	0.052	0.143	12	7.910	0.020	0.057	0.057	0.159	27
Moisture	51.513	0.353	0.334	0.988	0.936	15	51.505	0.795	1.001	2.225	2.803	24
NAB	0.031	0.003	0.020	0.007	0.056	18	0.031	0.003	0.010	0.009	0.027	27
NAT	0.550	0.029	0.103	0.080	0.289	18	0.525	0.021	0.056	0.060	0.158	27
NNK	0.218	0.010	0.021	0.027	0.060	18	0.219	0.010	0.014	0.027	0.039	27
NNN	0.672	0.025	0.132	0.070	0.370	18	0.683	0.016	0.063	0.044	0.177	27
Total TSNAs	1.471	0.036	0.260	0.101	0.729	18	1.457	0.038	0.125	0.108	0.350	27
<b>Product CRP 2</b>												
Parameter	Mean	r SD	R SD	r	R	N	Mean	r SD	R SD	r	R	N
Nicotine	1.278	0.027	0.085	0.077	0.237	24	1.252	0.022	0.063	0.062	0.177	30
pH	7.750	0.017	0.050	0.047	0.141	12	7.678	0.006	0.024	0.016	0.068	27
Moisture	54.675	0.101	0.221	0.284	0.618	15	54.230	0.336	0.462	0.942	1.294	24
NAB	0.157	0.005	0.033	0.015	0.091	18	0.157	0.003	0.008	0.010	0.023	27
NAT	1.842	0.067	0.237	0.187	0.663	18	1.854	0.040	0.146	0.112	0.410	27
NNK	0.456	0.027	0.062	0.075	0.173	18	0.467	0.014	0.029	0.039	0.081	27
NNN	1.811	0.078	0.234	0.218	0.654	18	1.913	0.027	0.140	0.076	0.392	27
Total TSNAs	4.266	0.143	0.518	0.402	1.452	18	4.390	0.060	0.236	0.167	0.662	27
<b>Product CRP 3</b>												
Parameter	Mean	r SD	R SD	r	R	N	Mean	r SD	R SD	r	R	N
Nicotine	2.124	0.042	0.183	0.116	0.513	24	2.194	0.057	0.063	0.159	0.176	27
pH	6.773	0.030	0.052	0.083	0.145	12	6.771	0.011	0.051	0.031	0.142	27
Moisture	8.206	0.072	0.541	0.201	1.514	18	8.819	0.288	0.579	0.807	1.622	24
NAB	0.398	0.027	0.059	0.076	0.167	18	0.406	0.013	0.029	0.036	0.080	27
NAT	5.587	0.265	0.676	0.743	1.894	18	5.821	0.128	0.474	0.358	1.326	27
NNK	3.877	0.261	0.764	0.730	2.141	18	4.183	0.072	0.410	0.201	1.148	27
NNN	7.891	0.178	1.102	0.498	3.085	18	8.590	0.136	0.618	0.382	1.730	24
Total TSNAs	18.070	0.513	2.241	1.437	6.275	15	19.040	0.310	1.235	0.867	3.459	27
<b>Product CRP 4</b>												
Parameter	Mean	r SD	R SD	r	R	N	Mean	r SD	R SD	r	R	N
Nicotine	1.116	0.027	0.125	0.077	0.349	24	1.148	0.016	0.083	0.046	0.232	27
pH	5.947	0.061	0.054	0.170	0.151	15	5.885	0.044	0.120	0.124	0.335	30
Moisture	21.914	0.165	0.752	0.462	2.105	18	21.079	0.529	1.039	1.480	2.910	24
NAB	0.060	0.004	0.013	0.011	0.037	18	0.062	0.004	0.006	0.012	0.016	24
NAT	1.199	0.042	0.235	0.117	0.658	18	1.253	0.021	0.129	0.058	0.362	24
NNK	0.409	0.030	0.050	0.084	0.141	18	0.458	0.018	0.064	0.052	0.178	27
NNN	1.901	0.072	0.294	0.203	0.824	18	2.069	0.055	0.168	0.153	0.469	27
Total TSNAs	3.569	0.118	0.567	0.329	1.589	18	3.853	0.083	0.299	0.232	0.838	27

**Table 6. . Repeatability and reproducibility by product.**

Common Laboratories for Both Time-Points						
<b>Product CRP 1</b>						
Parameter	Mean	r SD	R SD	r	R	N
Nicotine	0.994	0.060	0.070	0.169	0.196	30
pH	7.951	0.060	0.057	0.168	0.159	12
Moisture	51.797	0.518	0.486	1.449	1.360	12
NAB	0.035	0.003	0.006	0.008	0.018	12
NAT	0.535	0.060	0.069	0.169	0.194	18
NNK	0.223	0.012	0.012	0.034	0.034	18
NNN	0.667	0.053	0.066	0.148	0.185	18
Total TSNAs	1.453	0.117	0.139	0.327	0.389	18
<b>Product CRP 2</b>						
Parameter	Mean	r SD	R SD	r	R	N
Nicotine	1.286	0.073	0.084	0.204	0.235	30
pH	7.711	0.031	0.038	0.088	0.106	12
Moisture	54.516	0.318	0.365	0.890	1.023	12
NAB	0.161	0.006	0.009	0.015	0.025	18
NAT	1.902	0.049	0.078	0.138	0.220	18
NNK	0.487	0.038	0.036	0.105	0.100	18
NNN	1.904	0.084	0.086	0.234	0.240	18
Total TSNAs	4.454	0.118	0.130	0.331	0.364	18
<b>Product CRP 3</b>						
Parameter	Mean	r SD	R SD	r	R	N
Nicotine	2.177	0.156	0.173	0.437	0.484	30
pH	6.771	0.036	0.044	0.101	0.123	12
Moisture	8.656	0.411	0.376	1.150	1.053	12
NAB	0.418	0.019	0.025	0.053	0.070	18
NAT	5.758	0.256	0.669	0.717	1.873	18
NNK	4.355	0.290	0.403	0.812	1.128	18
NNN	8.727	0.273	0.591	0.765	1.655	18
Total TSNAs	19.257	0.643	1.432	1.800	4.009	18
<b>Product CRP 4</b>						
Parameter	Mean	r SD	R SD	r	R	N
Nicotine	1.157	0.066	0.088	0.184	0.246	29
pH	5.897	0.051	0.048	0.144	0.135	12
Moisture	21.878	0.217	0.200	0.608	0.559	12
NAB	0.061	0.005	0.007	0.014	0.021	17
NAT	1.212	0.076	0.142	0.213	0.397	17
NNK	0.447	0.050	0.046	0.140	0.128	17
NNN	1.979	0.118	0.205	0.330	0.573	17
Total TSNAs	3.699	0.228	0.359	0.640	1.006	17

Z-scores quantify the distance of a laboratory result from 0. The score uses the standard deviation as reference of this distance from 0. Scores are calculated after removing outlier detected with Cochran's and Grubbs' tests. However, there is lack of parallelism between time-points with respect to the laboratories submitting results. In order to create a complete data set, both time-points data sets have been merged by taking the data set corresponding to time-point 2 and completing this with the time-point 1 data set.

Table 7 shows the origin of laboratory data with respect to the time-points.

**Table 7. Origin of data used to calculate z-scores.**

		Analyte							
		Nicotine	pH	Moisture	NAB	NAT	NNK	NNN	TSNA Total
Laboratory	A	TP2	TP2	TP2	TP2	TP2	TP2	TP2	TP2
	B	TP2	TP2		TP2	TP2	TP2	TP2	TP2
	C	TP2	TP2	TP2	TP2	TP2	TP2	TP2	TP2
	D	TP2	TP2	TP2	TP2	TP2	TP2	TP2	TP2
	E	TP2	TP2	TP1	TP2	TP2	TP2	TP2	TP2
	F	TP2	TP2	TP2	TP2	TP2	TP2	TP2	TP2
	G	TP2	TP2	TP2	TP2	TP2	TP2	TP2	TP2
	I	TP2	TP2	TP2	TP2	TP2	TP2	TP2	TP2
	J	TP2	TP2	TP2	TP2	TP2	TP2	TP2	TP2
	L	TP1	TP1	TP1	TP1	TP1	TP1	TP1	TP1
	M	TP1	TP1	TP1	TP1	TP1	TP1	TP1	TP1
	N	TP1	TP1	TP1	TP1	TP1	TP1	TP1	TP1

From the z-scores each laboratory overall performance is derived. The overall performance is calculated as the sum of z-scores divided by the square root of the number of z-scores of a laboratory for a certain analyte.

The limits set to evaluate the laboratories performances are:

- +4 < Overall performance → Unsatisfactory high
- +3 < Overall performance < +4 → Questionable high
- +2 < Overall performance < +3 → Satisfactory (high)
- 2 < Overall performance < +2 → Good
- 3 < Overall performance < -2 → Satisfactory (low)
- 4 < Overall performance < -3 → Questionable (low)
- Overall performance < -4 → Unsatisfactory low

Tables numbered as 8 display the z-scores and calculated laboratory performances.

**Table 8. Z-Scores and overall laboratory performance**

<b>Nicotine</b>						
Lab Code	CRP1	CRP2	CRP3	CRP4	Performance	
A	-0.219	-0.005	0.445	-0.150	0.036	GOOD
B	1.159	0.355	0.602	0.843	1.480	GOOD
C	-0.634	-1.919	-2.807	-0.542	-2.950	SATISFACTORY
D	0.360	0.096	0.580	-0.054	0.491	GOOD
E	2.049	2.179	0.092	1.259	2.789	SATISFACTORY
F	-0.278	0.948	-0.004		0.384	GOOD
G	-0.493	-0.477	0.130	0.172	-0.334	GOOD
H	-0.433	0.308	1.013	-0.511	0.188	GOOD
I	0.475	0.526	0.360	0.324	0.843	GOOD
J	-0.141	0.127	0.795	2.007	1.394	GOOD
L	-0.928	-0.939	-0.213	-1.556	-1.818	GOOD
M	-0.777	-0.528	-0.656	-1.217	-1.589	GOOD
N	-0.141	-0.671	-0.337	-0.576	-0.862	GOOD

<b>pH</b>						
Lab Code	CRP1	CRP2	CRP3	CRP4	Performance	
A	0.299	-0.641	-1.093	-0.524	-0.980	GOOD
B	-0.897	0.222	0.606	-0.312	-0.190	GOOD
C	0.199	-0.137	0.018	1.472	0.776	GOOD
D	-1.345	0.366	0.541	0.050	-0.194	GOOD
E	0.647	0.294	-0.962	0.141	0.060	GOOD
F	-0.498	-0.785	-0.505	0.686	-0.551	GOOD
G	-1.146	-0.641	-0.440	0.171	-1.027	GOOD
H				-1.301		GOOD
I	0.946	-0.929	2.109	0.413	1.270	GOOD
J	-0.498	-0.713	0.083	-2.218	-1.673	GOOD
L	0.299	0.294		0.534	0.651	GOOD
M	1.992	2.668	0.867	0.686	3.107	QUESTIONABLE HIGH
N			-1.224	0.202	-0.723	GOOD

<b>Moisture</b>						
Lab Code	CRP1	CRP2	CRP3	CRP4	Performance	
A	0.469	0.428	0.517	0.385	0.899	GOOD
B	-2.313	-2.314	-3.289	-3.369	-5.642	UNSATISFACTORY LOW
C	0.386	0.418	0.684	-0.074	0.707	GOOD
D	0.431	0.422	0.385	0.385	0.811	GOOD
E	-2.313	-2.315	-0.291	0.369	-2.275	SATISFACTORY
F	0.457	0.402	0.357	0.264	0.740	GOOD
G	0.469	0.439	0.604	0.297	0.905	GOOD
H	0.377	0.425	0.090	0.055	0.474	GOOD
I	0.392	0.389	0.296	0.309	0.693	GOOD
J	0.383	0.388	0.033	0.209	0.507	GOOD
L	0.420	0.437	0.405	0.512	0.887	GOOD
M	0.427	0.437	0.008	0.495	0.683	GOOD
N	0.413	0.444	0.203	0.162	0.611	GOOD

<b>NAB</b>						
Lab Code	CRP1	CRP2	CRP3	CRP4	Performance	
A	0.402	0.118	0.361		0.508	GOOD
B	-0.006	0.662	-0.034	-0.185	0.219	GOOD
C	0.018	-0.138	-0.342	0.255	-0.103	GOOD
D	0.191	0.301	0.295	-0.065	0.361	GOOD
E	-1.554	-0.099	0.813	0.513	-0.164	GOOD
F	0.390	-0.348	-0.848	0.142	-0.332	GOOD
G	0.420	0.413	1.269	0.640	1.371	GOOD
H	0.409	-0.193	0.171	-0.670	-0.141	GOOD
I	0.169	-0.297	-0.050	-0.600	-0.389	GOOD
J					0.000	GOOD
L	1.990	2.488	1.429	2.257	4.082	UNSATISFACTORY HIGH
M	-2.002	-1.651	-1.559	-1.057	-3.135	QUESTIONABLE LOW
N	-0.427	-1.256	-1.505	-1.231	-2.210	SATISFACTORY



<b>NAT</b>						
<b>Lab Code</b>	<b>CRP1</b>	<b>CRP2</b>	<b>CRP3</b>	<b>CRP4</b>	<b>Performance</b>	
A	0.273	0.326	1.147	0.427	1.087	GOOD
B	0.154	0.075	-0.641	-0.259	-0.336	GOOD
C	0.297	1.270	0.961	1.243	1.886	GOOD
D	-0.850	-1.262	-1.218	-0.721	-2.026	SATISFACTORY
E	-1.279	0.616	-0.213	-0.068	-0.472	GOOD
F	-0.526	-0.800	-0.709	-1.065	-1.550	GOOD
G	0.236	0.036	1.314	0.502	1.044	GOOD
H	0.899	0.415	0.836		1.241	GOOD
I	0.466	0.180	0.280	0.294	0.610	GOOD
J						GOOD
L	2.280	1.645	0.634	1.975	3.267	QUESTIONABLE HIGH
M	-1.040	-1.829	-1.600	-1.323	-2.896	SATISFACTORY
N	-0.910	-0.671	-0.792	-1.004	-1.689	GOOD

<b>NNK</b>						
<b>Lab Code</b>	<b>CRP1</b>	<b>CRP2</b>	<b>CRP3</b>	<b>CRP4</b>	<b>Performance</b>	
A	-0.308	-0.500	0.303	-0.435	-0.470	GOOD
B	0.460	0.827	-0.197	1.032	1.061	GOOD
C	0.279	0.915	0.097	0.944	1.118	GOOD
D	0.695	0.939	0.491	0.109	1.117	GOOD
E	-0.143	0.915	1.376	0.310	1.229	GOOD
F	-1.124	-0.119	0.102	-0.664	-0.902	GOOD
G	1.372	1.274	1.750	2.187	3.291	QUESTIONABLE HIGH
H	0.163	-0.370	-0.428	-0.641	-0.638	GOOD
I	0.259	-0.252	0.092	-0.334	-0.118	GOOD
J						GOOD
L	1.062	-0.565	-2.111	-0.257	-0.936	GOOD
M	-1.629	-1.775	-0.670	-1.169	-2.622	SATISFACTORY
N	-1.086	-1.288	-0.805	-1.082	-2.130	SATISFACTORY

<b>NNN</b>						
<b>Lab Code</b>	<b>CRP1</b>	<b>CRP2</b>	<b>CRP3</b>	<b>CRP4</b>	<b>Performance</b>	
A	0.281	0.772	1.277	0.755	1.542	GOOD
B	0.412	-0.218	-0.034	-0.040	0.060	GOOD
C	0.478	1.066	0.428	1.201	1.587	GOOD
D	0.221	0.713	0.638	0.524	1.048	GOOD
E	-1.344	-0.013	0.616	-0.515	-0.628	GOOD
F	-0.503	-0.787	-0.621	-0.609	-1.259	GOOD
G	0.654	1.218	1.610	1.031	2.256	SATISFACTORY
H	0.119	-0.439	-0.010	-0.360	-0.345	GOOD
I	0.074	0.004	0.178	-0.299	-0.022	GOOD
J						GOOD
L	2.200	1.043	-1.468	1.399	1.587	GOOD
M	-0.973	-1.497	-0.959	-1.290	-2.359	SATISFACTORY
N	-1.618	-1.863	-1.655	-1.796	-3.466	QUESTIONABLE LOW

<b>Total TSNAs</b>						
<b>Lab Code</b>	<b>CRP1</b>	<b>CRP2</b>	<b>CRP3</b>	<b>CRP4</b>	<b>Performance</b>	
A	0.259	0.512	0.806	0.509	1.043	GOOD
B	0.313	0.047	-0.385	0.004	-0.011	GOOD
C	0.389	1.258	0.478	1.293	1.709	GOOD
D	-0.143	-0.154	0.076	-0.016	-0.119	GOOD
E	-1.352	0.385	0.703	-0.270	-0.267	GOOD
F	-0.526	-0.830	-0.663	-0.887	-1.453	GOOD
G	0.579	0.788	1.900	1.093	2.180	SATISFACTORY
H	0.461	-0.065	0.013	-0.093	0.158	GOOD
I	0.258	0.049	0.127	-0.127	0.154	GOOD
J						GOOD
L	2.266	1.434		1.564	3.039	QUESTIONABLE HIGH
M	-1.194	-1.942	-1.428	-1.467	-3.016	QUESTIONABLE LOW
N	-1.308	-1.482	-1.626	-1.603	-3.010	QUESTIONABLE LOW

*Anexxes with tables of means and SDs*

**Table 9. Means and SDs of the raw data (outliers included by analyte)**

**Nicotine**

Nicotine - Mean								
Time-Point and Product								
Lab Code	CRP1		CRP2		CRP3		CRP4	
	TP 1	TP2	TP 1	TP2	TP 1	TP2	TP 1	TP2
A	0.967	0.936	1.268	1.239	2.257	2.194	1.093	1.098
B	1.013	1.003	1.310	1.260	2.330	2.213	1.207	1.193
C	1.118	0.916	1.399	1.127	1.790	2.280	1.303	1.060
D	0.931	0.964	1.267	1.245	2.027	2.211	1.066	1.107
E	1.047	1.047	1.383	1.367	2.323	2.150	1.247	1.233
F		0.933		1.295		2.138		1.300
G		0.923		1.211		2.155		1.129
H		0.926		1.257		2.264		1.063
I		0.970		1.270		2.183		1.143
J		0.940		1.247		2.237		1.305
K								
L	0.902		1.184		2.112		0.962	
M	0.909		1.208		2.057		0.995	
N	0.940		1.200		2.097		1.057	

Nicotine - SD								
Time-Point and Product								
Lab Code	CRP1		CRP2		CRP3		CRP4	
	TP 1	TP2	TP 1	TP2	TP 1	TP2	TP 1	TP2
A	0.006	0.039	0.004	0.005	0.004	0.011	0.008	0.006
B	0.026	0.012	0.026	0.030	0.017	0.012	0.012	0.042
C	0.007	0.015	0.046	0.030	0.073	0.213	0.044	0.000
D	0.087	0.049	0.053	0.002	0.089	0.007	0.024	0.017
E	0.021	0.015	0.015	0.006	0.015	0.053	0.015	0.006
F		0.074		0.003		0.159		0.080
G		0.022		0.014		0.013		0.005
H		0.067		0.019		0.018		0.009
I		0.010		0.046		0.012		0.015
J		0.008		0.018		0.019		0.002
K								
L	0.003		0.010		0.006		0.052	
M	0.009		0.005		0.007		0.001	
N	0.010		0.000		0.006		0.021	

*pH*

**pH - Mean**

Time-Point and Product								
Lab Code	CRP1		CRP2		CRP3		CRP4	
	TP 1	TP2	TP 1	TP2	TP 1	TP2	TP 1	TP2
A	7.977	7.947	7.723	7.663	6.787	6.713	5.933	5.843
B	8.013	7.867	7.753	7.703	6.783	6.800	5.943	5.867
C		7.940		7.687		6.770		6.063
D		7.837		7.710		6.797		5.907
E		7.970		7.707		6.720		5.917
F		7.893		7.657		6.743		5.977
G		7.850		7.663		6.747		5.920
H		7.806		7.684		6.851		5.758
I		7.990		7.650		6.877		5.947
J		7.893		7.660		6.773		5.657
K								
L	7.947		7.707		6.810		5.960	
M	8.060		7.817		6.813		5.977	
N	7.763		7.510		6.707		5.923	

**pH - SD**

Time-Point and Product								
Lab Code	CRP1		CRP2		CRP3		CRP4	
	TP 1	TP2	TP 1	TP2	TP 1	TP2	TP 1	TP2
A	0.006	0.031	0.006	0.006	0.006	0.006	0.006	0.006
B	0.006	0.015	0.015	0.006	0.042	0.020	0.032	0.040
C		0.026		0.006		0.010		0.006
D		0.015		0.000		0.006		0.006
E		0.010		0.006		0.010		0.006
F		0.015		0.006		0.006		0.091
G		0.010		0.006		0.006		0.061
H		0.166		0.075		0.067		0.075
I		0.010		0.000		0.012		0.006
J		0.032		0.010		0.015		0.006
K								
L	0.021		0.006		0.010		0.122	
M	0.030		0.029		0.042		0.049	
N	0.015		0.046		0.006		0.015	

**Moisture**

**Moisture - Mean**

Time-Point and Product								
Lab Code	CRP1		CRP2		CRP3		CRP4	
	TP 1	TP2	TP 1	TP2	TP 1	TP2	TP 1	TP2
A	51.34	52.42	54.84	54.50	8.19	9.15	21.73	21.99
B								
C		50.85		54.31		9.54		19.31
D	51.73	51.70	54.33	54.38	8.42	8.85	21.80	21.99
E	56.10		53.10		7.30		21.90	
F		52.20		54.00		8.79		21.29
G		52.42		54.74		9.35		21.48
H		50.68		54.45		8.18		20.06
I		50.97		53.74		8.65		21.55
J		50.80		53.72		8.04		20.96
K								
L	51.49		54.69		8.90		22.73	
M	51.63		54.68		7.99		22.63	
N	51.37		54.82		8.43		20.69	

**Moisture - SD**

Time-Point and Product								
Lab Code	CRP1		CRP2		CRP3		CRP4	
	TP 1	TP2	TP 1	TP2	TP 1	TP2	TP 1	TP2
A	0.100	0.596	0.038	0.633	0.075	0.078	0.046	0.375
B								
C		0.656		0.255		0.345		1.092
D	0.231	0.213	0.115	0.024	0.055	0.019	0.100	0.062
E	0.000		0.000		0.000		0.000	
F		1.215		0.127		0.055		0.662
G		1.086		0.057		0.025		0.038
H		0.307		0.129		0.055		0.217
I		0.861		0.628		0.219		0.081
J		0.855		0.091		0.696		0.637
K								
L	0.365		0.121		0.117		0.208	
M	0.306		0.112		0.090		0.221	
N	0.577		0.097		0.021		0.243	

**NAB**

**NAB - Mean**

Time-Point and Product								
Lab Code	CRP1		CRP2		CRP3		CRP4	
	TP 1	TP2	TP 1	TP2	TP 1	TP2	TP 1	TP2
A	0.042	0.036	0.156	0.158	0.398	0.414	0.062	0.066
B	0.031	0.030	0.169	0.170	0.422	0.397	0.050	0.060
C		0.030		0.152		0.383		0.064
D		0.033		0.162		0.411		0.061
E	0.030		0.160	0.153	0.443	0.433	0.063	0.067
F		0.036		0.148		0.361		0.063
G		0.036		0.165		0.453		0.068
H		0.036		0.151		0.406		0.055
I		0.033		0.149		0.396		0.056
J								
K								
L	0.060		0.210		0.460		0.083	
M	0.000		0.119		0.331		0.052	
N	0.024		0.128		0.333		0.050	

**NAB - SD**

Time-Point and Product								
Lab Code	CRP1		CRP2		CRP3		CRP4	
	TP 1	TP2	TP 1	TP2	TP 1	TP2	TP 1	TP2
A	0.003	0.002	0.005	0.004	0.014	0.008	0.005	0.005
B	0.001	0.000	0.004	0.000	0.005	0.015	0.001	0.000
C		0.001		0.001		0.011		0.003
D		0.002		0.003		0.013		0.004
E	0		0.010	0.006	0.035	0.015	0.006	0.006
F		0.003		0.002		0.005		0.002
G		0.006		0.004		0.003		0.009
H		0.005		0.004		0.025		0.004
I		0		0.002		0.001		0.001
J								
K								
L	0		0		0.010		0.006	
M	0		0.002		0.007		0.001	
N	0.006		0.005		0.053		0	

**NAT**

**NAT - Mean**

Time-Point and Product								
Lab Code	CRP1		CRP2		CRP3		CRP4	
	TP 1	TP2	TP 1	TP2	TP 1	TP2	TP 1	TP2
A	0.053	0.044	0.068	0.056	0.333	0.232	0.053	0.026
B	0.017	0.020	0.023	0.050	0.040	0.029	0.010	0.017
C		0.012		0.029		0.160		0.020
D		0.003		0.028		0.038		0.006
E	0.010	0.010	0.044	0.031	0.352	0.050	0.035	0.006
F		0.010		0.011		0.020		0.022
G		0.017		0.051		0.127		0.037
H		0.029		0.048		0.188		0.084
I		0.017		0.036		0.106		0.012
J								
K								
L	0.025		0.098		0.364		0.080	
M	0.009		0.016		0.055		0.009	
N	0.031		0.098		0.225		0.000	

**NAT - SD**

Time-Point and Product								
Lab Code	CRP1		CRP2		CRP3		CRP4	
	TP 1	TP2	TP 1	TP2	TP 1	TP2	TP 1	TP2
A	0.053	0.044	0.068	0.056	0.333	0.232	0.053	0.026
B	0.017	0.020	0.023	0.050	0.040	0.029	0.010	0.017
C		0.012		0.029		0.160		0.020
D		0.003		0.028		0.038		0.006
E	0.010	0.010	0.044	0.031	0.352	0.050	0.035	0.006
F		0.010		0.011		0.020		0.022
G		0.017		0.051		0.127		0.037
H		0.029		0.048		0.188		0.084
I		0.017		0.036		0.106		0.012
J								
K								
L	0.025		0.098		0.364		0.080	
M	0.009		0.016		0.055		0.009	
N	0.031		0.098		0.225		0	

**NNK**

**NNK - Mean**

Time-Point and Product								
Lab Code	CRP1		CRP2		CRP3		CRP4	
	TP 1	TP2	TP 1	TP2	TP 1	TP2	TP 1	TP2
A	0.226	0.211	0.520	0.432	4.759	4.129	0.476	0.412
B	0.234	0.223	0.511	0.483	4.187	3.847	0.382	0.507
C		0.220		0.487		4.013		0.501
D		0.227		0.488		4.236		0.447
E	0.230	0.213	0.487	0.487	4.470	4.737	0.437	0.460
F		0.197		0.447		4.016		0.397
G		0.238		0.500		4.948		0.581
H		0.218		0.437		3.716		0.398
I		0.220		0.442		4.010		0.418
J								
K								
L	0.233		0.430		2.763		0.423	
M	0.189		0.384		3.579		0.364	
N	0.198		0.402		3.502		0.370	

**NNK - SD**

Time-Point and Product								
Lab Code	CRP1		CRP2		CRP3		CRP4	
	TP 1	TP2	TP 1	TP2	TP 1	TP2	TP 1	TP2
A	0.050	0.014	0.151	0.019	0.231	0.510	0.081	0.094
B	0.004	0.010	0.021	0.010	0.032	0.050	0.045	0.006
C		0.006		0.017		0.327		0.038
D		0.032		0.025		0.046		0.070
E	0.006	0.015	0.060	0.026	0.157	0.067	0.025	0.015
F		0.010		0.008		0.002		0.014
G		0.010		0.053		0.065		0.012
H		0.020		0.036		0.107		0.104
I		0.006		0.021		0.131		0.021
J								
K								
L	0.010		0.061		0.089		0.130	
M	0.007		0.022		0.029		0.012	
N	0.033		0.074		0.319		0.072	

NNN

NNN - Mean

Time-Point and Product								
Lab Code	CRP1		CRP2		CRP3		CRP4	
	TP 1	TP2	TP 1	TP2	TP 1	TP2	TP 1	TP2
A	0.677	0.707	1.886	2.014	9.451	8.948	2.127	2.201
B	0.670	0.720	1.937	1.820	8.057	8.233	1.683	2.017
C		0.727		2.071		8.662		2.304
D		0.701		2.002		8.858		2.147
E	0.687	0.543	1.910	1.860	8.837	8.837	1.907	1.907
F		0.628		1.709		7.688		1.885
G		0.744		2.101		9.760		2.265
H		0.691		1.777		8.255		1.943
I		0.686		1.863		8.430		1.957
J								
K								
L	0.900		2.067		6.900		2.350	
M	0.581		1.570		7.373		1.727	
N	0.516		1.498		6.727		1.610	

NNN - SD

Time-Point and Product								
Lab Code	CRP1		CRP2		CRP3		CRP4	
	TP 1	TP2	TP 1	TP2	TP 1	TP2	TP 1	TP2
A	0.050	0.014	0.151	0.019	0.231	0.510	0.081	0.094
B	0.004	0.010	0.021	0.010	0.032	0.050	0.045	0.006
C		0.006		0.017		0.327		0.038
D		0.032		0.025		0.046		0.070
E	0.006	0.015	0.060	0.026	0.157	0.067	0.025	0.015
F		0.010		0.008		0.002		0.014
G		0.010		0.053		0.065		0.012
H		0.020		0.036		0.107		0.104
I		0.006		0.021		0.131		0.021
J								
K								
L	0.010		0.061		0.089		0.130	
M	0.007		0.022		0.029		0.012	
N	0.033		0.074		0.319		0.072	



## Total TSNAs

TSNAs - Mean								
Time-Point and Product								
Lab Code	CRP1		CRP2		CRP3		CRP4	
	TP 1	TP2	TP 1	TP2	TP 1	TP2	TP 1	TP2
A	1.560	1.503	4.525	4.502	21.271	19.788	3.975	3.998
B	1.429	1.513	4.423	4.323	17.959	17.880	3.086	3.783
C		1.528		4.789		19.262		4.332
D		1.424		4.246		18.619		3.775
E	1.527	1.187	4.497	4.453	19.023	19.623	3.647	3.667
F		1.349		3.986		17.434		3.404
G		1.566		4.608		21.541		4.247
H		1.542		4.280		18.517		3.742
I		1.503		4.324		18.699		3.728
J								
K								
L	1.897		4.857		16.163		4.447	
M	1.218		3.559		16.207		3.158	
N	1.195		3.736		15.890		3.100	

TSNAs - SD								
Time-Point and Product								
Lab Code	CRP1		CRP2		CRP3		CRP4	
	TP 1	TP2	TP 1	TP2	TP 1	TP2	TP 1	TP2
A	0.038	0.065	0.262	0.077	0.603	0.694	0.075	0.131
B	0.016	0.025	0.067	0.045	0.172	0.010	0.052	0.015
C		0.024		0.017		0.574		0.066
D		0.044		0.040		0.080		0.095
E	0.006	0.035	0.121	0.012	0.533	0.127	0.059	0.029
F		0.003		0.008		0.030		0.029
G		0.035		0.104		0.103		0.038
H		0.051		0.099		0.044		0.164
I		0.030		0.039		0.124		0.030
J								
K								
L	0.025		0.183		0.482		0.248	
M	0.009		0.045		0.068		0.018	
N	0.073		0.016		0.798		0.096	