

Birmingham Quality

Previously known as the *Wolfson EQA Laboratory*, Birmingham Quality provides primarily UK NEQAS External Quality Assessment Services in Clinical Chemistry



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Innovations from Birmingham Quality [UK NEQAS Birmingham] for Newborn Screening EQA

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Anne Green's July 2007 Meeting

There was agreement that Quality Assurance needed to funded by commissioners and that there was support for a higher profile for Quality Assurance.

The group agreed the following:-

- That generic criteria should apply to all newborn screening schemes.
- New schemes should be established or current ones adapted to ensure that they meet all the generic criteria.
- There is a need to establish a multi professional group which focuses on newborn screening schemes and to oversee laboratory quality.

Activities of such a Quality group would include:-

- Provide input to existing EQA schemes.
- Set standards, provide criteria for new schemes.
- Co-ordinate and work with external QA providers for the five disorders including molecular testing.
- Report performance to the screening programme directors
- Provide information/guidance about EQA schemes and Lab procedures to CPA
- Advise on risks associated with Lab screening procedures.





UK NBS LQADG

This group transmogrified into the

UK Newborn Blood Spot Laboratory Quality Assurance Development Group [UK NBS LQADG]

Venue: Government Office for the West Midlands, Birmingham

Chair: Rowena Clayton, UKNSC and NHS SHA Screening Leads

Independent Chair, Terms of Reference etc etc

I took it that **my** role was to have in place, by April 2010, a fully functional EQA Scheme for Newborn Screening which built on the existing Scheme for CHT and PKU, but would now include Tyrosine and cover MCADD and also include IRT for CF.

Business Plans were submitted, funding agreed and the work started.....





Birmingham Quality's master plan

The key decision was that BQ put forward a case to run effective EQA for all the new analytes wef 1st April 2010.

The poisoned chalice was IRT, but the other analytes were not going to be without their problems.

Birmingham Childrens had already been successfully running an 'EQA-lite" programme for Acyl Carnitines

We had good co-operation from Birmingham, Liverpool and Manchester





Birmingham Quality's Pre-Pilot master plan

We looked at the basic recoveries of added material We looked at PCVs and spot sizes We looked at different types of base material We sourced C8 and C10 from the Netherlands We sourced two suppliers of IRT from the USA We spoke in a conference call with CDC, Atlanta [Joanne Mei, Harry Hannon and Jesus?] We looked at protease inhibitors We looked at frozen reagents and frozen cards. We added specimens directly to the PE Delfia wells, to bypass elution concerns, at Alder Hey





Birmingham Quality's Pre-Pilot master plan

We essentially thought of most things and with help from Birmingham, Liverpool and Manchester we think we got the basics sorted out.

Even the liquid plasma Phenylalanine results from Edinburgh and Sheffield that we use as a cross-check gave conflicting data.

The proof of the pudding was in the between-lab picture, as the results coming back from the pre-pilot were internally consistent, but did exhibit marked biases between centres.

We ran with a couple of Pilots, looking at the numerical analytes, leaving the interpretations until we were happy with the numbers and until the Programs Centre's Protocols were in place.

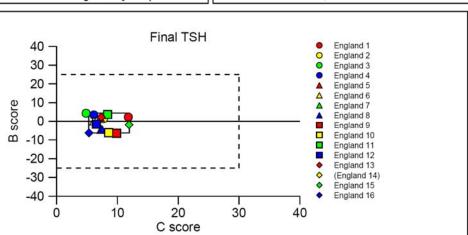




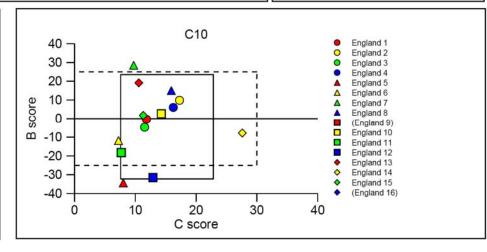
Network Reports Penalty Box Plot immediately identifies issues



Birmingham Quality ~	Birmingham Quality ~ Newborn British Isles			
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Penalty Box Plots



The Best versus The Worst ~ TSH and C10 this is the only slide you will ever need!







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Update from Birmingham Quality: Paper 7 for 7 September 2009

We are very slightly behind our notional proposed times-scale, but given the episodic intensive nature of our work we believe we are on schedule to go live with the 'established scheme' in April 2010.

1.1. Proposed timescale

Phase	Start	End
Obtain (initial) funding	July 2009	
Fact-finding trip	Aug 2009	
Pre-pilot phase	Aug 2009	Sept 2009
Pilot	Oct 2009	Dec 2009
Evaluation of pilot data	Jan 2010	Mar 2010
'Established scheme' launch	April 2010	
First interim report	October 2010	

The tasks already completed include:

- Finalised and submitted Business Case and received approval
- Agreed with BCH, LCH and MCH to undertake analysis
- Spoken to CDC to obtain materials against which to cross check our own materials
- Agreed in principle with Perkin Elmer to check against their spots, where applicable
- Gleaned information on existing protocols
- Inform Screening Laboratories through Scheme that Pilot Phase will be taking place later in the year
- Designed flexible Pre-pilot study including specifications for internal and external activities
- Identified suppliers of raw materials and sourced same
- Visited BCH to ensure practicalities of pre-pilot specimens disc-cutting
- Changes to software to allow production of 3 specimen Scheme design and to enable full colour Network Report

Finlay MacKenzie and Jane French, August 2009





Recovery data to help validate Targets

200X validity of target Recoveries

Phe										
SPEC	PO	DIST	RETURN_DATE	expected	ALTM	LTMCV	% expecte	diff	iff added	diff recov
200G		200X	29 Nov 2009	100	129.77	11.16	129.77	0.0	0	
200H		200X	29 Nov 2009	200	211.42	11.74	105.71	81.7	100	81.65
200J		200X	29 Nov 2009	300	297.92	13.74	99.31	168.2	200	84.08
200K		200X	29 Nov 2009	400	391.62	13.56	97.91	261.8	300	87.28
200L		200X	29 Nov 2009	500	479.10	12.59	95.82	349.3	400	87.33
200M		200X	29 Nov 2009	600	553.30	11.67	92.22	423.5	500	84.71
	_			•				-	-	
Т	1									

Tyr										
SPEC	PO	DIST	RETURN_DATE	expected	ALTM	LTMCV	% expecte	ed		diff recov
200G		200X	29 Nov 2009	600	546.32	13.17	91.05	426.9	500	85.37
200H		200X	29 Nov 2009	500	443.71	15.71	88.74	324.3	400	81.06
200J		200X	29 Nov 2009	400	370.61	13.14	92.65	251.1	300	83.71
200K		200X	29 Nov 2009	300	299.25	19.16	99.75	179.8	200	89.89
200L		200X	29 Nov 2009	200	212.34	17.86	106.17	92.9	100	92.88
200M		200X	29 Nov 2009	100	119.46	19.35	119.46	0.0	0	

C8									
SPEC	PO DIST	RETURN_DATE	expected	ALTM	LTMCV	% expecte	ed		diff recov
200G	200X	29 Nov 2009	0.4	0.41	11.50	103.25	0.0	0	
200H	200X	29 Nov 2009	0.8	0.69	10.72	86.63	0.3	0.4	70.00
200J	200X	29 Nov 2009	1.2	0.98	12.20	81.25	0.6	0.8	70.25
200K	200X	29 Nov 2009	1.6	1.41	10.92	88.31	1.0	1.2	83.33
200L	200X	29 Nov 2009	2	1.80	10.52	89.80	1.4	1.6	86.44
200M	200X	29 Nov 2009	3	2.45	11.68	81.50	2.0	2.6	78.15

0									
SPEC	PO	DIST	RETURN_DATE	expected	ALTM	LTMCV	% expecte	ed	diff recov
200G		200X	29 Nov 2009	0.2	0.34	27.71	169.50	0.0	
200H		200X	29 Nov 2009	0.4	0.50	28.08	124.50	0.2 0.2	79.50
200J		200X	29 Nov 2009	0.6	0.71	27.95	117.67	0.4 0.4	91.75
200K		200X	29 Nov 2009	0.8	0.91	24.22	113.38	0.6	94.67
200L		200X	29 Nov 2009	1	1.11	26.19	111.30	0.8	96.75
200M		200X	29 Nov 2009	1.6	1.64	26.54	102.69	1.3 1.4	93.14

73.09

ISH							
SPEC	PO	DIST	RETURN_DATE	expected	ALTM	LTMCV	
200G		200X	29 Nov 2009	20	19.96	11.42	0.0
200H		200X	29 Nov 2009	30	28.34	8.49	8.4
200J		200X	29 Nov 2009	40	35.66	11.23	15.7
200K		200X	29 Nov 2009	50	45.83	9.53	25.9
200L		200X	29 Nov 2009	60	56.15	11.23	36.2
200M		200X	29 Nov 2009	70	57.38	9.93	37.4

IRT							
SPEC	PO	DIST	RETURN_DATE	ed, but not	ALTM	LTMCV	
200G		200X	29 Nov 2009	60	52.17	12.82	
200H		200X	29 Nov 2009	60	45.31	13.41	
200J		200X	29 Nov 2009	60	46.85	10.17	
200K		200X	29 Nov 2009	60	35.01	9.35	
200L		200X	29 Nov 2009	120	84.64	6.60	

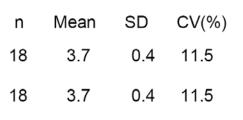
200X 29 Nov 2009

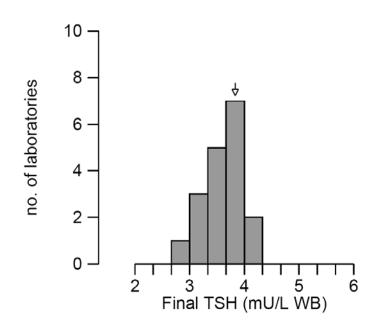
Н	
L	recov
	86.95
	75.51
	78.08
	58.36
	70.54
	60.91

NSB vs NSA - TSH



PE DELFIA

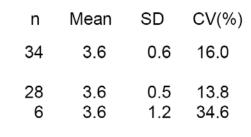


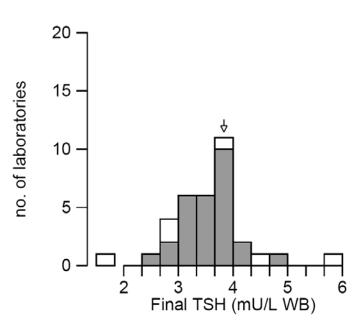


Specimen: 212B

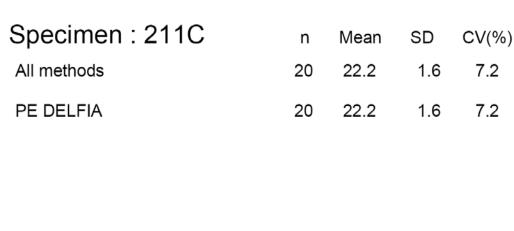
All methods

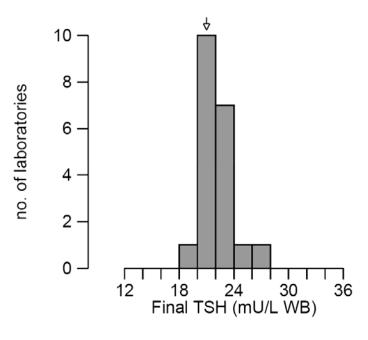
PE DELFIA Undefined





NSB vs NSA - TSH



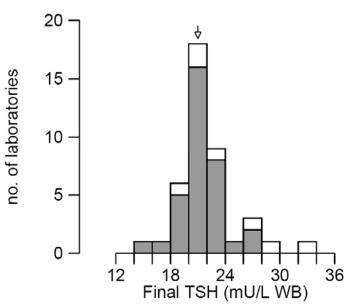


Specimen: 211C

All methods

PE DELFIA Undefined

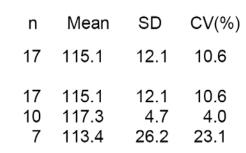
n	Mean	SD	CV(%
41	22.0	2.5	11.3
34 7	21.6 24.7	2.0 5.1	9.2 20.7

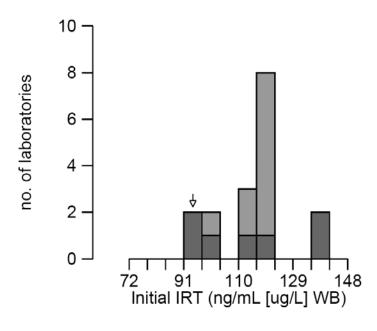


Specimen: 211C

All methods

PE DELFIA
Buddy Group A
Buddy Group B



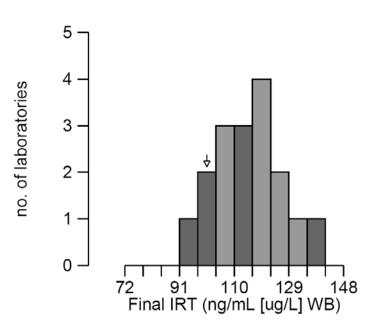


Specimen: 211C

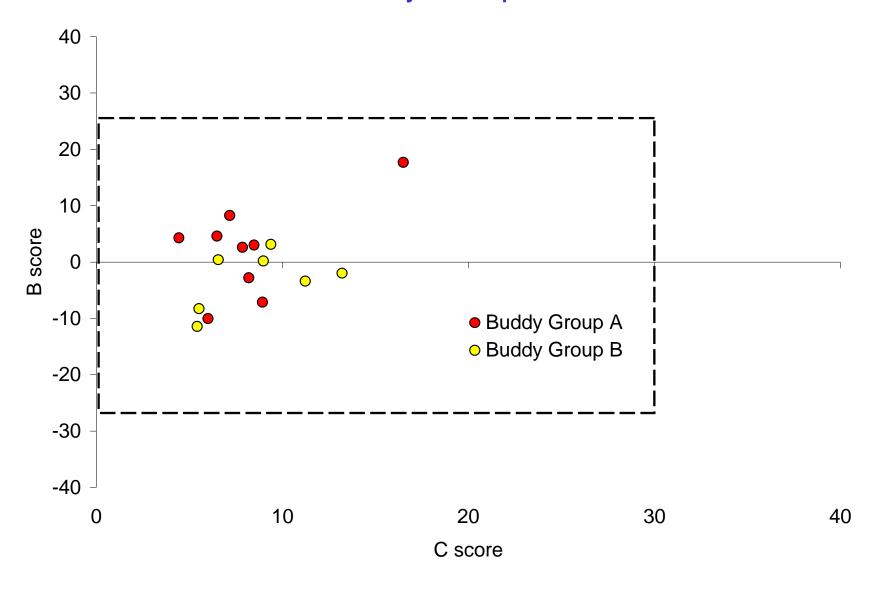
All methods

PE DELFIA
Buddy Group A
Buddy Group B

n	Mean	SD	CV(%)
17	115.7	11.4	9.9
17	115.7	11.4	9.9
10 7	118.6 109.7	8.9 12.1	7.5 11.0



IRT Buddy Group at 205

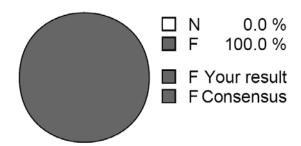






Initial IRT

Specimen: 211C

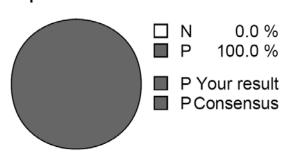


Your result	F
Total responses	17
N - No further action F - Further action	0 17

115 ng/mL

Final IRT

Specimen: 211C



Your result	Ρ
Total responses	17
N - Presumptive screen negative P - Presumptive screen positive	

116 ng/mL

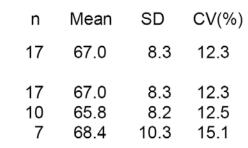


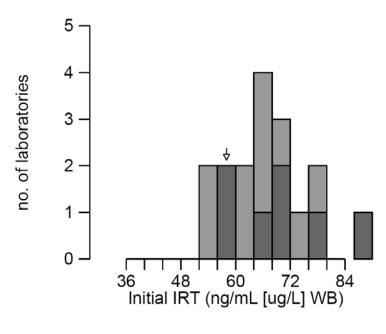


Specimen	:	21	0	١

All methods

PE DELFIA
Buddy Group A
Buddy Group B



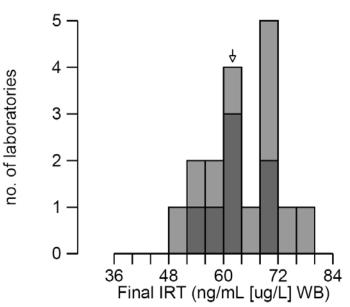


Specimen: 210A

All methods

PE DELFIA
Buddy Group A
Buddy Group B

n	Mean	SD	CV(%)
17	64.6	7.7	12.0
17	64.6	7.7	12.0
10	65.5	9.8	15.0
7	63.6	5.7	9.0

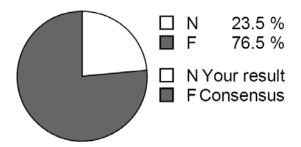


Initial IRT

Final IRT

Specimen: 210A

Specimen: 210A



	N P	52.9 % 47.1 %
		our result onsensus

Your result	N
Total responses	17
N - No further action	4
F - Further action	13

Total responses	17
N - Presumptive screen negative P - Presumptive screen positive	9

Your result

67 ng/mL

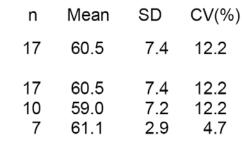
65 ng/mL

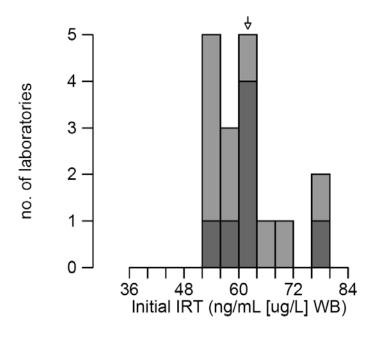




Ν





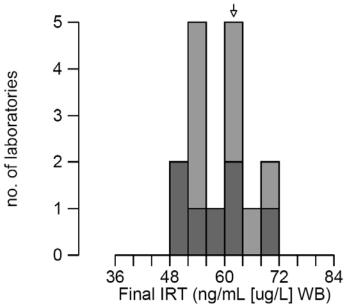


Specimen	:	21	0B

All methods

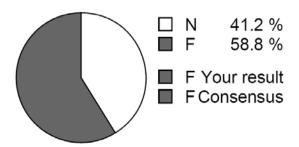
PE DELFIA
Buddy Group A
Buddy Group B

n	iviean	SD	CV(%
16	59.7	6.4	10.7
16 9	59.7 59.9	6.4 6.5	10.7 10.8
7	58.7	8.2	14.0



Initial IRT

Specimen: 210B

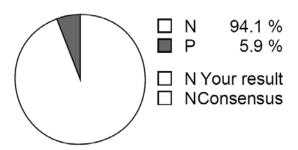


Your result	F
Total responses	17
N - No further action F - Further action	7 10

60 ng/mL

Final IRT

Specimen: 210B



Your result	١
Total responses	17
N - Presumptive screen negative P - Presumptive screen positive	16 1

60 ng/mL





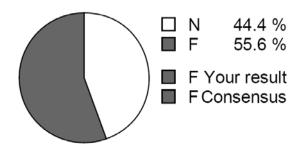
Initial Phe at 200 umol/L Cut-off

Specimen: 211A

All methods

n	Mean	SD	CV(%)
18	204	32	15.8

Specimen: 211A

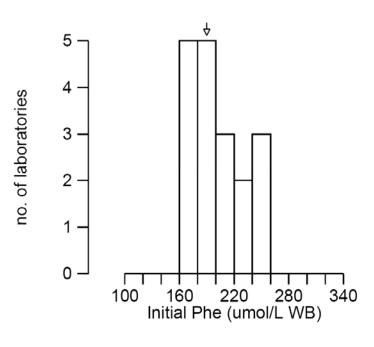


Your result	F
Total responses	18
N - No further action F - Further action	8 10

204 umol/L







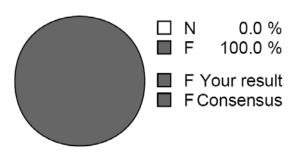
Initial C8 ~ everyone says F - Further action

Specimen: 211B

n Mean SD CV(%) 17 0.80 0.10 12.5

All methods

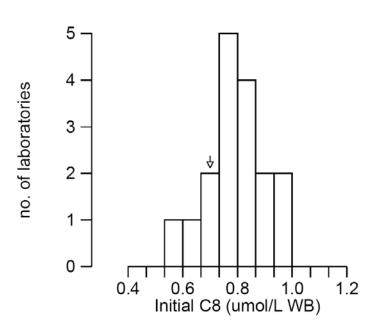
Specimen: 211B



Your result F

Total responses 17

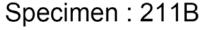
N - No further action 0
F - Further action 17



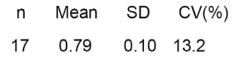


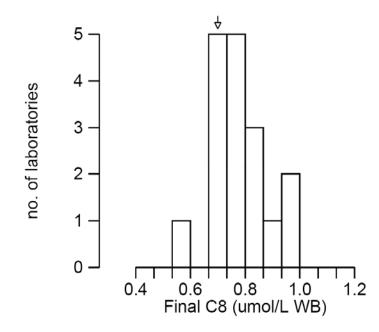


Individual C8 and C10 near cut-off ratio of 1.0



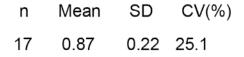
All methods

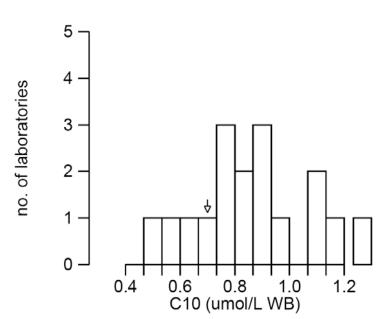




Specimen: 211B

All methods





C8/C10 ratios near cut-off of 1.0

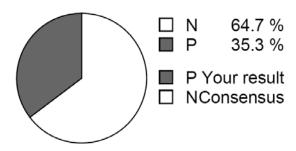
Specimen: 211B

n Mean SD CV(%)

All methods

17 0.93 0.19 20.7

Specimen: 211B

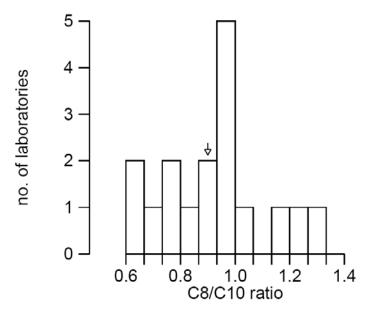


Your result F

Total responses 17

N - Presumptive screen negative 11

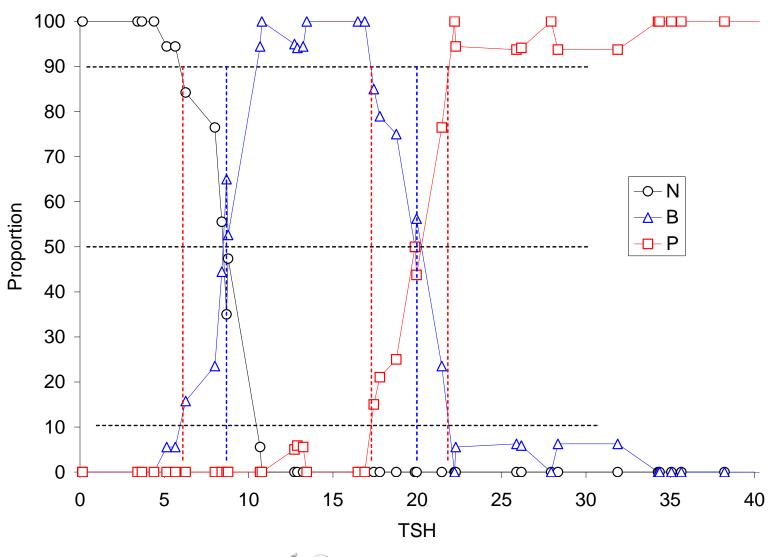
P - Presumptive screen positive 6







Example Proportions and Empirical Cut-offs ~ TSH/CHT





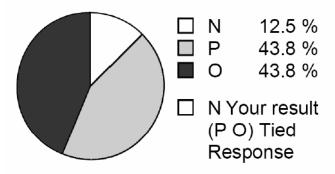
I have chosen to highlight a specimen which was enriched with 240 umol/L Phenylalanine and 240 umol/L Tyrosine. Given the difficulty of measuring low levels, we cannot be sure as to what the unspiked base value was, but the ALTMs of 37 and 35 umol/L are probably not too far from the truth. The recovery of added Phenylalanine was around 95%, while closer to 90% for Tyrosine. Not quantitative, but certainly acceptable for a screening assay. Even if all labs were rather good at the analysis, we all know that if I were to dispatch a specimen containing exactly 240 umol/L Phenylalanine I would have half the labs getting above and half the labs getting below. No one is disputing this. The issue for an EQA Organiser is to try to quantify this effect in some way. For example, would it be acceptable nationally if 80% of labs got values above 200 umol/L on such a sample? Would it have to be 90%? I am trying to collect data to try to help make the judgement between practical and theoretical considerations of both analysis and interpretations. I am trying to provide data to assist in the debate, not trying to stifle debate.





British Isles subset

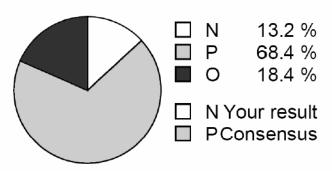
Specimen: 208B



Your result	Ν
Total responses	16
N - Presumptive screen negative O - Screen positive - other P - Presumptive screen positive	2 7 7

Full Scheme data

Specimen: 208B



Your result	Ν
Total responses	38
N - Presumptive screen negative O - Screen positive - other P - Presumptive screen positive	7





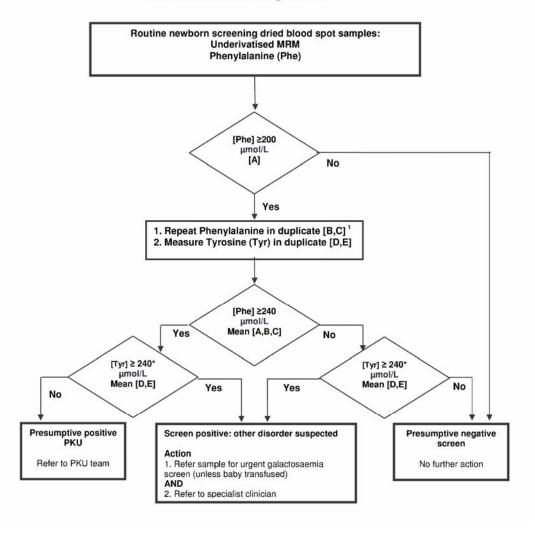
Results for 208B, laboratories' data ranked by increasing Phenylalanine concentration.

Dhamada	Phe	Tyr	DIGIT	Approriate response for	Right	Approriate
Phe rank	umol/L WB	umol/L WB	PKU I	results?	answer?	and Right?
1	195	182	N	Yes	No	No
2	232	230	N	Yes	No	No
3	242	243	0	Yes	Yes	Yes
4	247	234	Р	Yes	No	No
5	248		0	No	Yes	No
6	254	230	0	No	Yes	No
7	255	283	Р	No	No	No
8	256	231	0	No	Yes	No
9	264	214	Р	Yes	No	No
10	268	226	Р	Yes	No	No
11	270	239	Р	Yes	No	No
12	272		Р	Yes	No	No
13	274	283	Р	No	No	No
14	277	285	no intepretation			
15	280	279	0	Yes	Yes	Yes
16	293	232	no intepretation			
17	320	258	0	Yes	Yes	Yes
18	328	326	0	Yes	Yes	Yes





PKU Newborn Screening Protocol







Multi-Analyte Decision Trees and Interpretations

Pa	thways and	de	cision trees									
PK	U Tree											
Phe	First Phe [A]	S		greater than or equal to	200							Presumptive SN
					200	Y						go on to measure Phe and Tyr
Phe	Repeat [B] and [C]	D	mean of [A]+[B]+[C]	greater than or equal to	240	N	and	Tyr	greater than or equal to	240	N	Presumptive SN
					240	Υ			greater than or equal to	240	N	Presumptive Positive PKU
				greater than or equal to	240	N	and	Tyr	greater than or equal to	240	Υ	Screen positive: other disorder
					240	Υ			greater than or equal to	240	Υ	Screen positive: other disorder
Sum	mary											
	numerical first Phe	ΓΛΊ		stats		ol	otions					
	Interpretation of [gte 200 Y N			2					
	mean of Phe [A]+[E	3]+		stats								
		ne	an of Phe [A]+[B]+[C]				2					
	numerical Tyr			stats								
	Interpretation of 1			gte 240 Y N			2					
	Final Interpretation	on		PP PKU			3					
				or SP other dis	sorde	r or I	SN					
Ever	though there are in	npli	cit responses, we MUS	T have EXPLIC	T inte	rpreta	ations					





Multi-Analyte Decision Trees and Interpretations

Pa	thways and	de	cision trees								
MC	CADD Tree										
	1 1100										
				greater than or							
C8	FirstC8 [A]	s		equal to	0.40	N					Presumptive SN
				- 1	0.40	Υ					go on to measure C8 and C10
C8	Repeat [B] and [C]	D	mean of [A]+[B]+[C]								
C10		?									
				Calculate C8 to C10 ratio							
				greater than or					_		
C8			mean of [A]+[B]+[C]	0	0.50	N					Presumptive SN
			mount of [/t] [D] [to]	oquai to	0.00			C8 to C10 ratio			Trodumpulo eri
								greater than or			
					0.50	Υ		egual to	1.00	N	Presumptive SN
						-		C8 to C10 ratio			
								greater than or			
					0.50	Υ		equal to	1.00	Υ	Presumptive Screen Positive
Sum	nmary						4:				
		A 1				ol	otions				
	numerical first C8 [Interpretation of			gte 0.40 Y N			2		_		
	mean of [A]+[B]+[0			stats			2				
	Interpretation of		·[B]+[C]	gte 0.50 Y N			2				
	numerical C10	.~;		stats			_				
	C8/C10 ratio			stats							
	Final Interpretation	on					4				
				Screen Negati	ve by	virtu	e of initi	al C8			
				Screen Negative by virtue of mean C8							
				Screen Positive by virtue of mean C8 and C8:C10							
				Screen Negati	ve by	virtu	e of me	an C8 and C8:C10	ratio		
	n though there are in										





Birmingham Quality's Newborn Screening Live!

The Scheme will be 3-Specimen, Monthly for:-

1 TSH

2 CHT interpretation

3 IRT

4 CF interpretation

5 Initial Phe

6 Initial Phe interpretation

7 Final Phe

8 Tyr

9 PKU interpretation

10 Initial C8

11 Initial C8 interpretation

12 Final C8

13 C10

14 C8/C10 ratio

15 MCADD interpretation

9 numeric analytes

and

6 interpretations*

*2 analyte bifurcation interpretations and

*4 Disease state interpretations

Even this has now been superseded





Birmingham Quality's Newborn Screening Current Live!

The Scheme will be 3-Specimen, Monthly for:-

- 1 Initial TSH
- 2 Initial TSH interpretation
- 3 Final TSH
- 4 CHT interpretation
- 5 Initial IRT
- 6 Initial IRT interpretation
- 7 Final IRT
- 8 CF interpretation
- 9 Initial Phe
- 10 Initial Phe interpretation
- 11 Final Phe
- 12 Tyr
- 13 PKU interpretation
- 14 Initial C8
- 15 Initial C8 interpretation
- 16 Final C8
- 17 C10
- 18 C8/C10 ratio
- 19 MCADD interpretation

11 numeric analytes and

8 interpretations*

*4 analyte bifurcation interpretations and

*4 Disease state interpretations





Fresh vs Frozen

- ❖ At Distribution 211, we used cards that were 1st prepared for Distribution 205.
- They had been stored at -40°C since April 2010 and were dispatched again at October 2010.
- See the following slides for a comparison of 'Fresh versus Frozen.
- We can see that freezing cards at -40°C does not significantly affect the results.



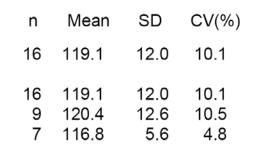


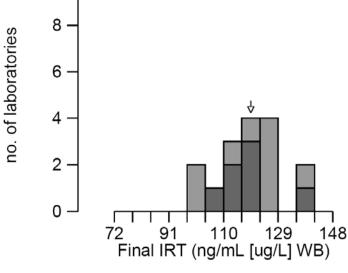
Fresh vs Frozen – Final IRT

Specimen: 205C

All methods

PE DELFIA Buddy Group A **Buddy Group B**





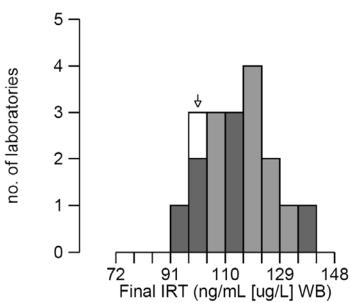
10 -

Specimen: 211C

All methods

PE DELFIA Buddy Group A Buddy Group B

n	Mean	SD	CV(%)
18	114.8	11.9	10.4
17 10	115.7 118.6	11.4 8.9	9.9 7.5
7	109.7	12.1	11.0

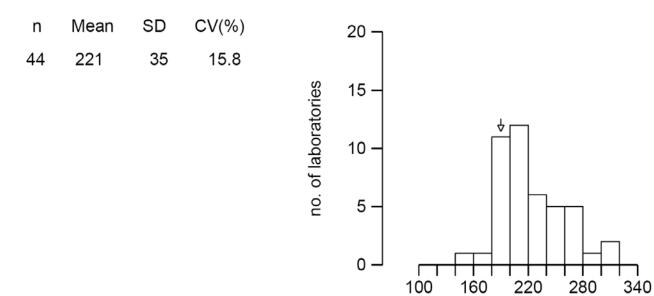


30

Fresh vs Frozen – Final Phe

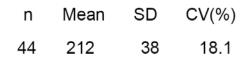
Specimen: 205A

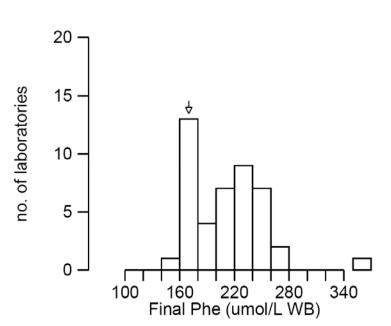
All methods



Specimen: 211A

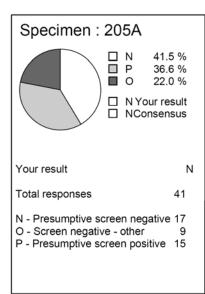
All methods

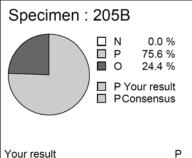




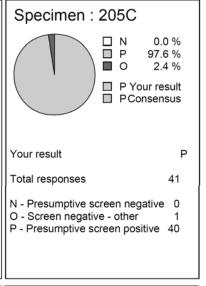
Final Phe (umol/L WB)

Fresh vs Frozen – PKU Interpretation



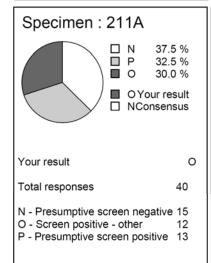


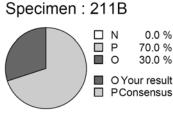
Total responses



Specimen: 211C

□ P

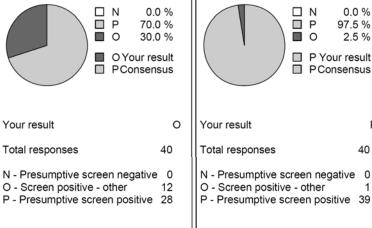




N - Presumptive screen negative 0

P - Presumptive screen positive 31

O - Screen negative - other





Your result

Total responses

O - Screen positive - other



41

10

0.0 %

97.5 %

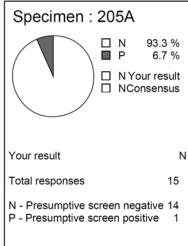
☐ P Your result

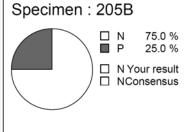
□ PConsensus

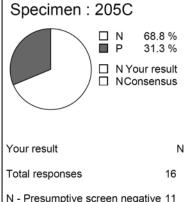
2.5 %

40

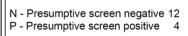
Fresh vs Frozen – MCADD Interpretation







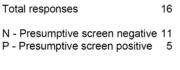
P - Presumptive screen positive	1	

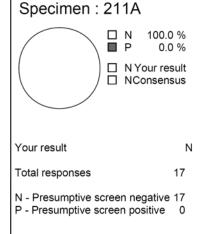


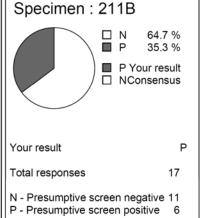
16

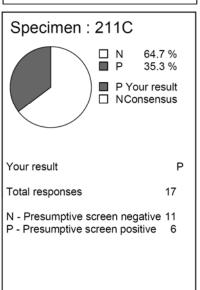
Your result

Total responses



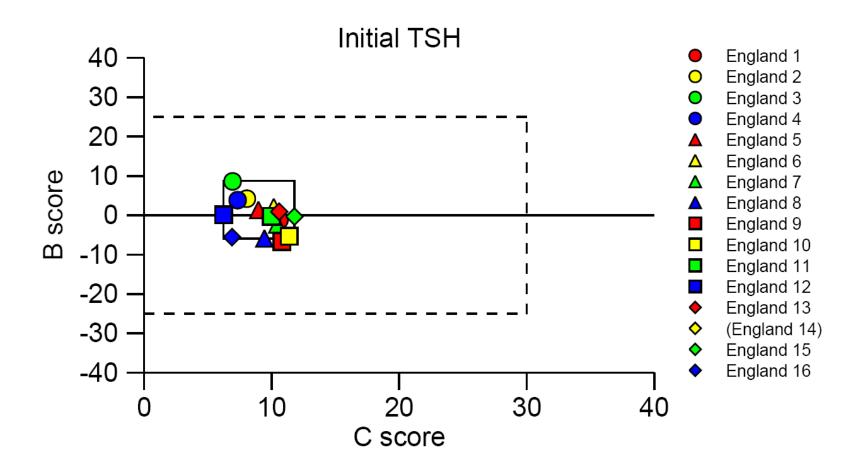






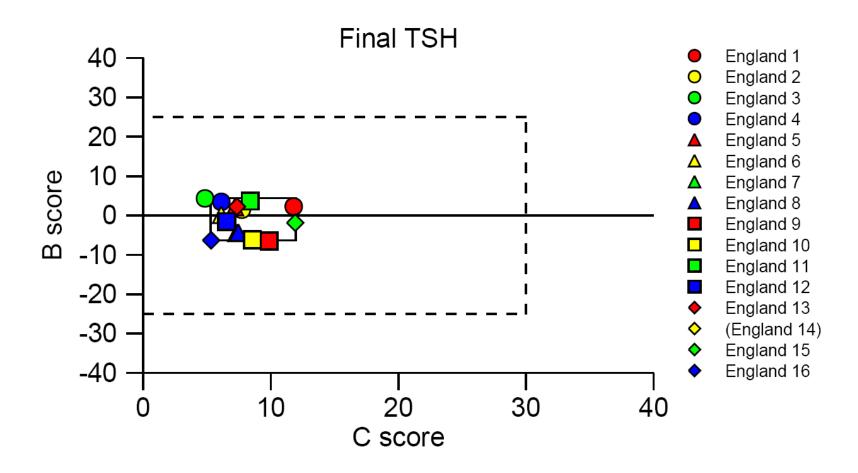






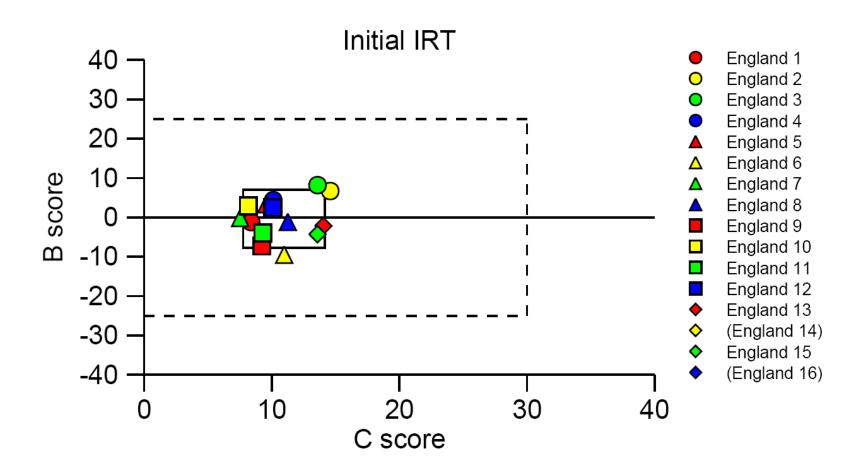






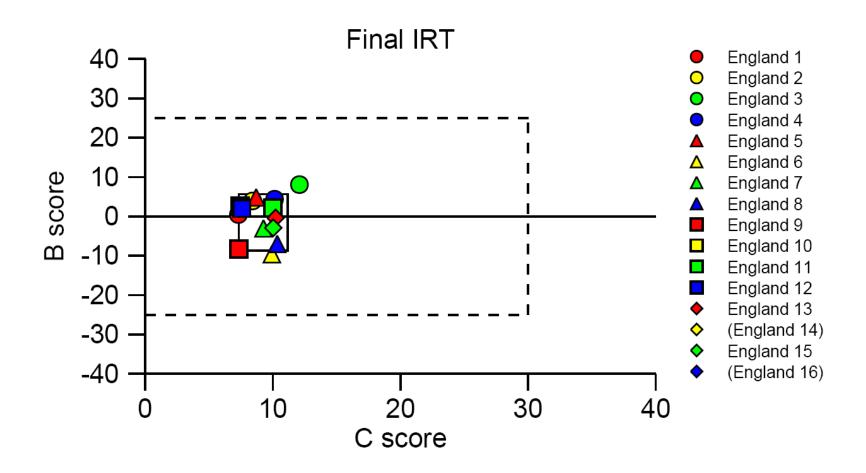






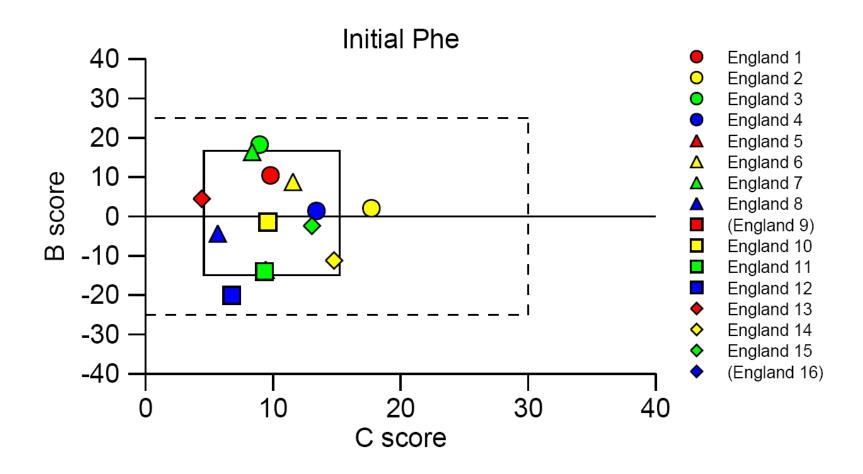






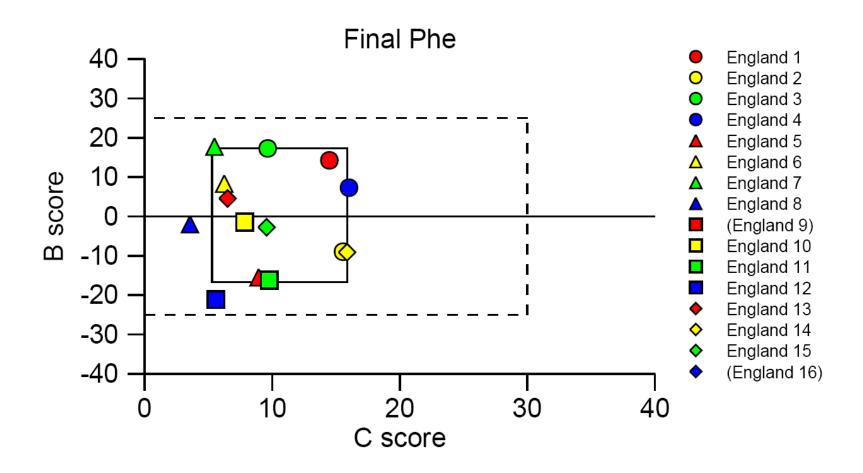






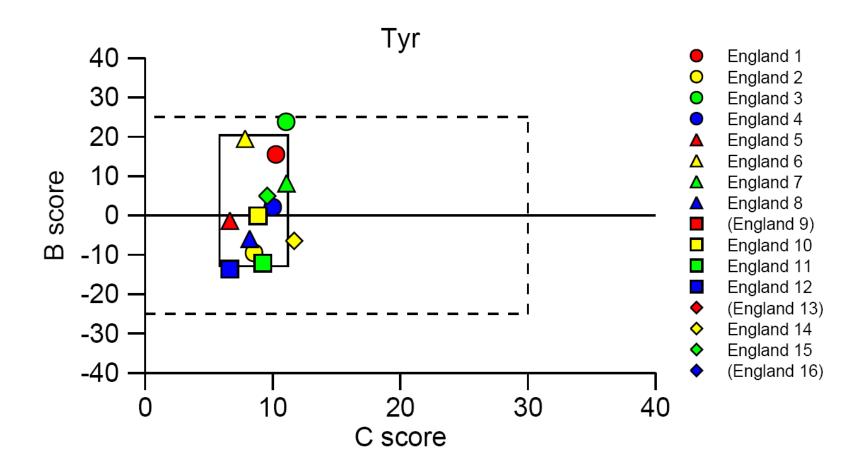








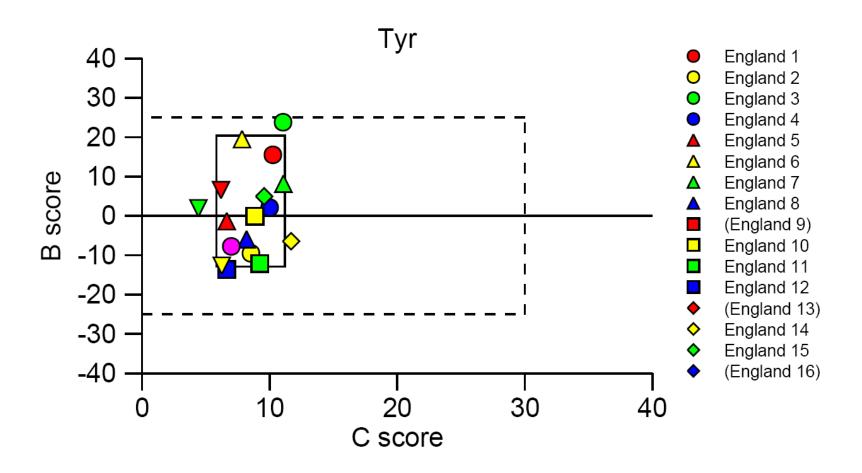






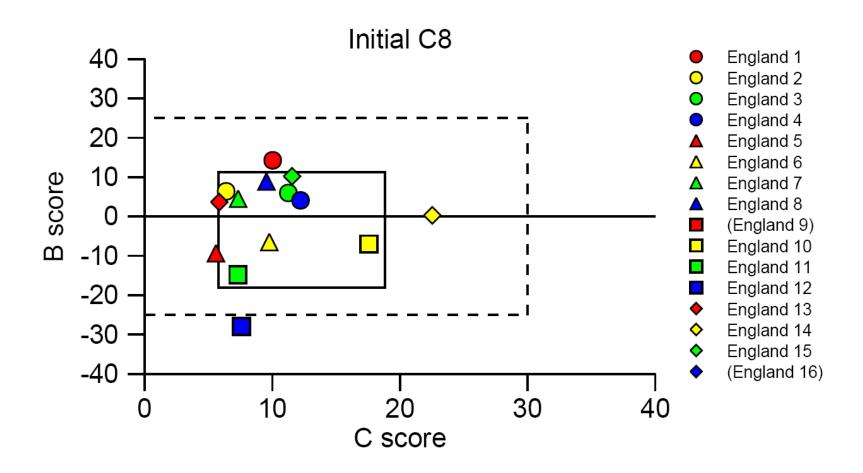


Penalty Box Plot ~ British Isles / all British Labs



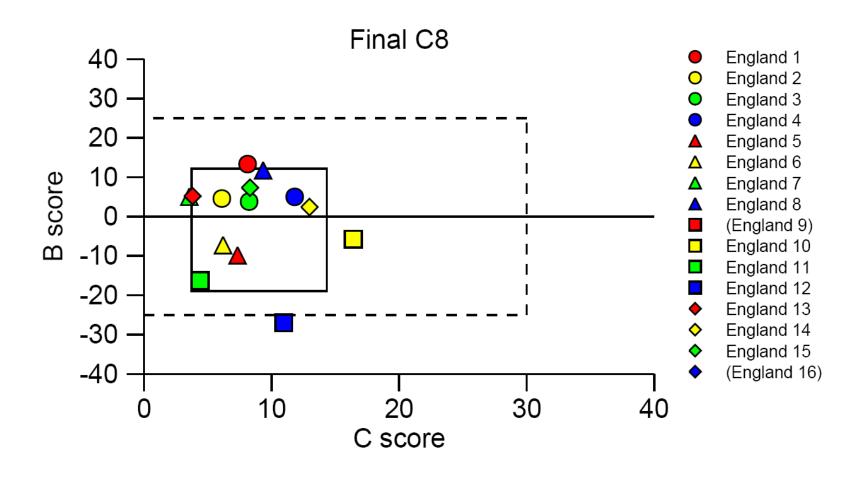






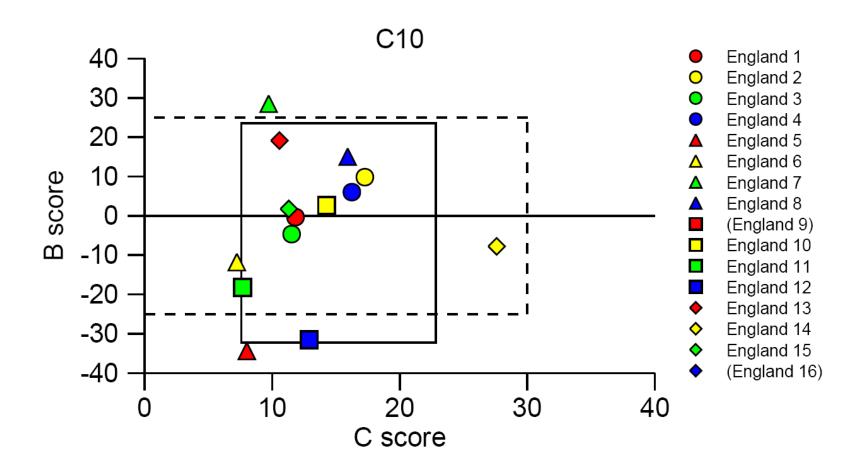






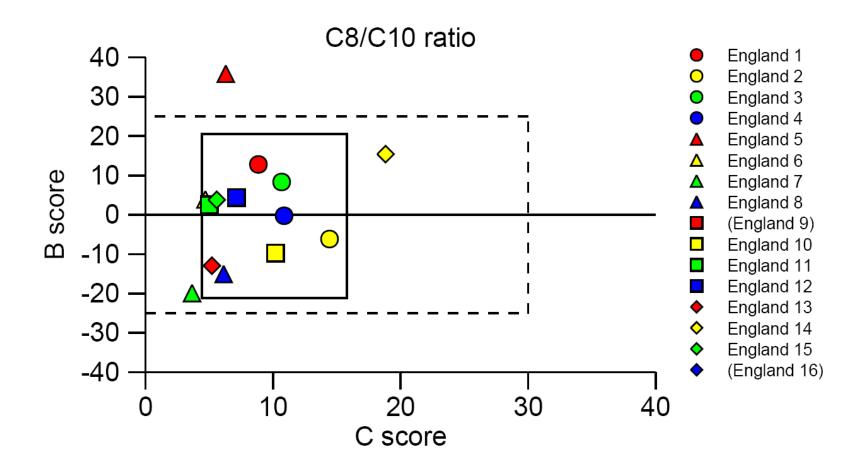






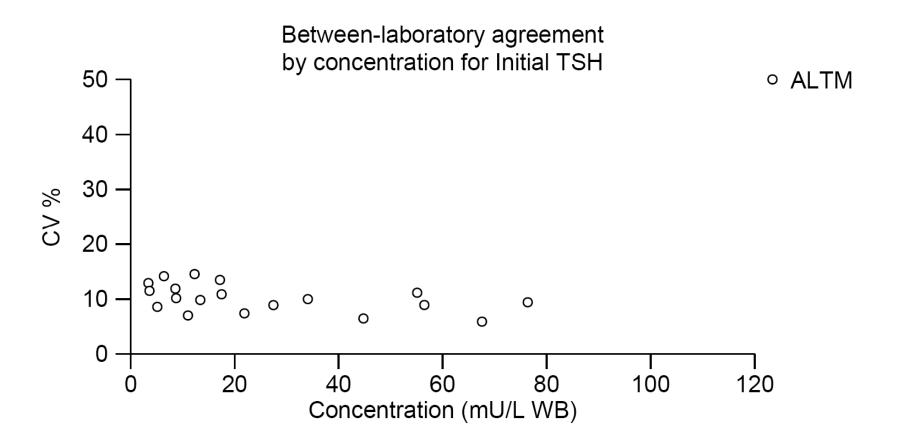






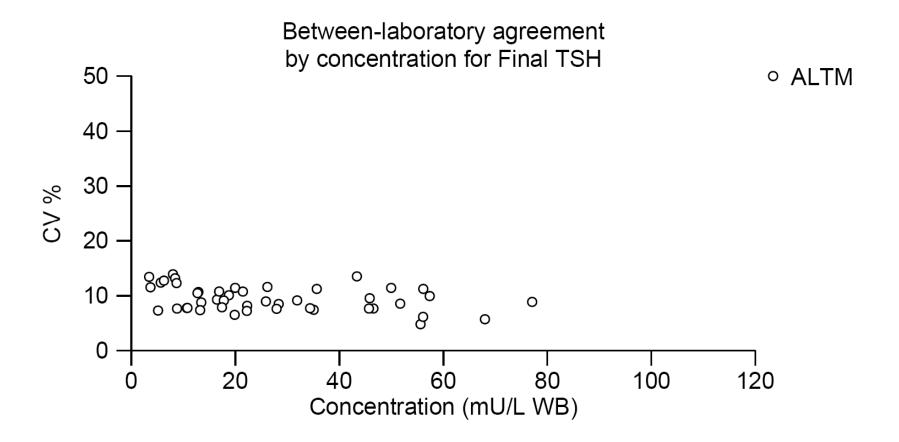






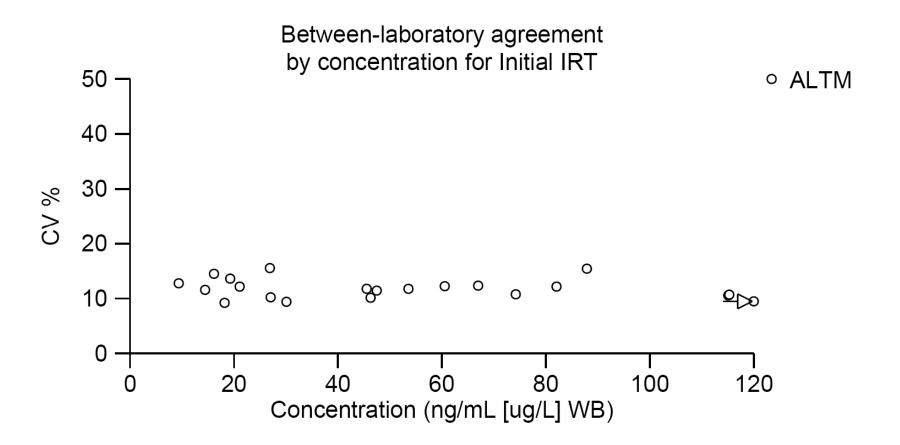






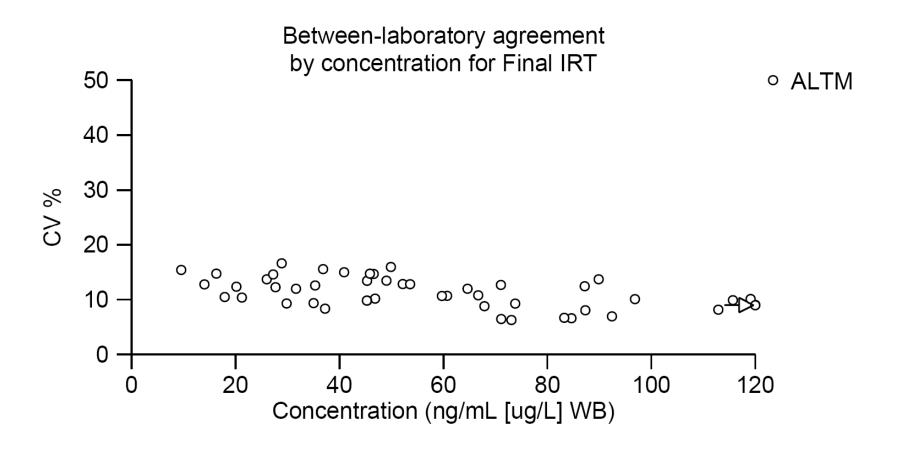






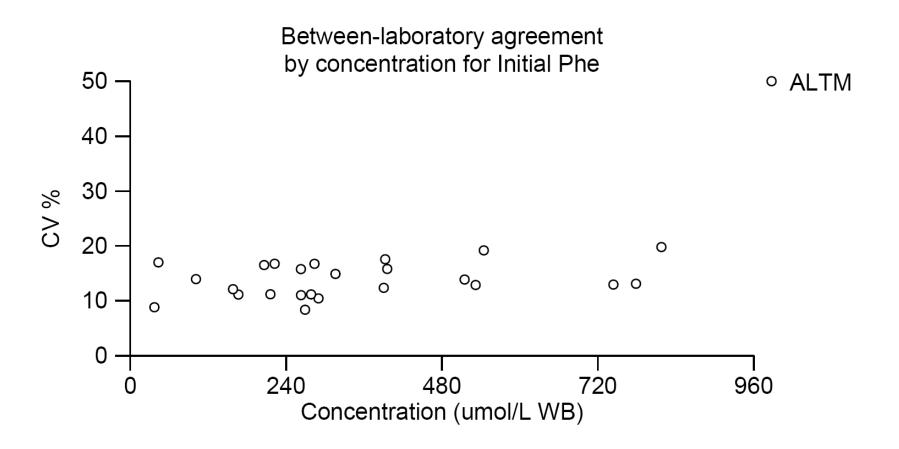






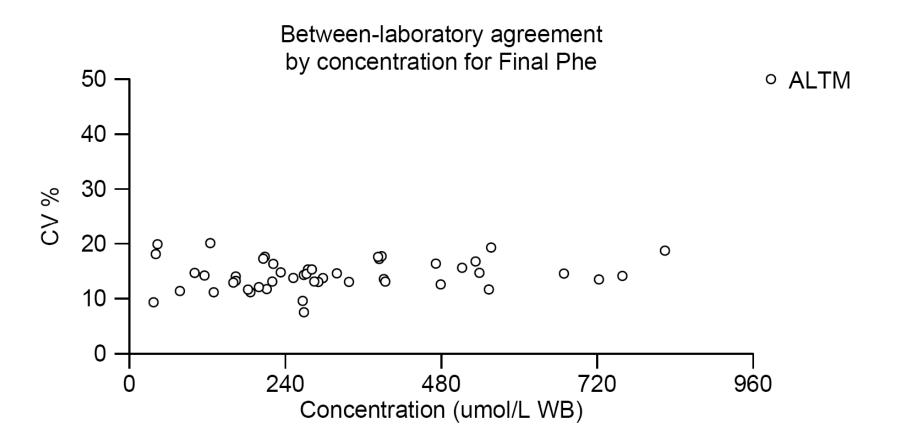






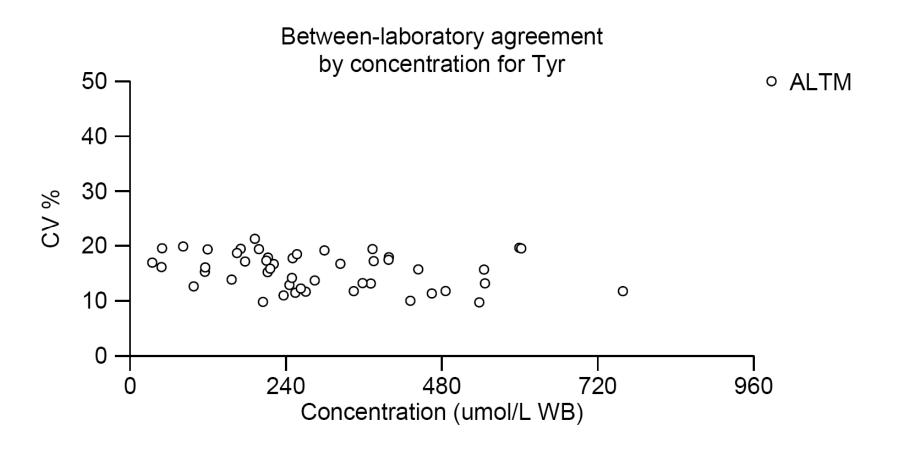






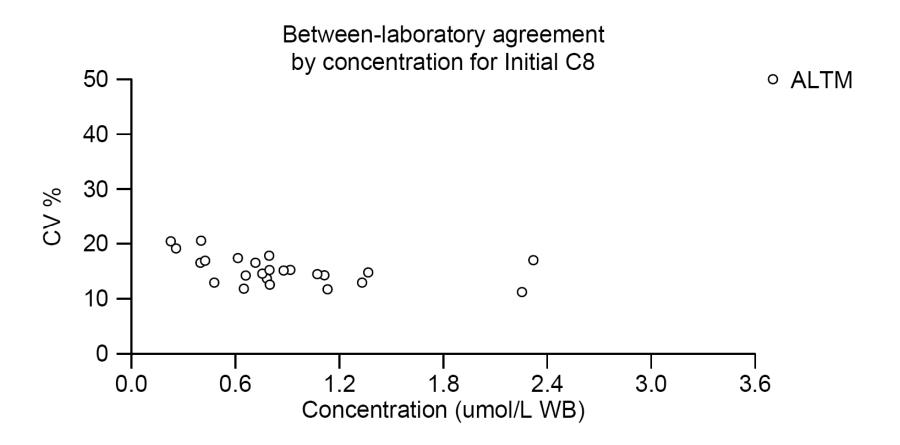






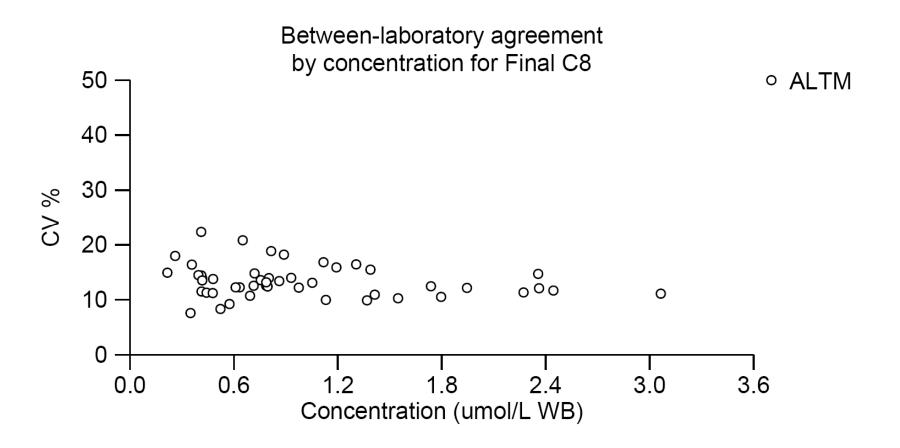






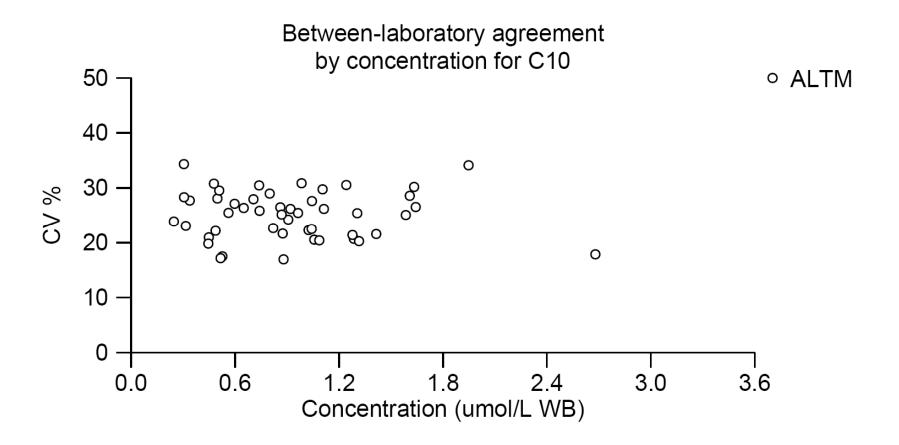






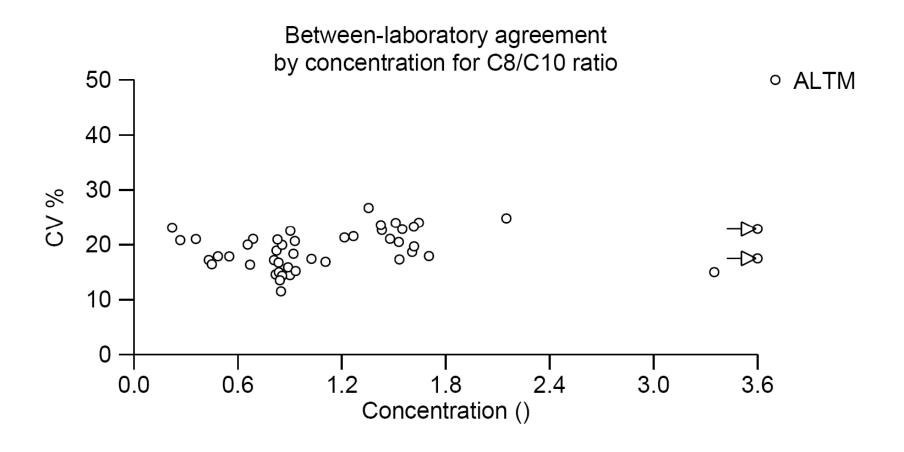
















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