The Irish Reference Interval Harmonisation Project

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Background

It is well recognised that having different reference intervals for the same analyte measured in different laboratories is a source of confusion and annoyance for users of laboratory services and could constitute a risk for misdiagnosis. For some analytes there are valid technical reasons for different ranges but for others that does not apply.

International efforts to achieve common reference intervals (RIs) have not been particularly successful, but in recent years a project in the UK, Pathology Harmony (PH), has adopted a pragmatic approach. It started with ten standard clinical chemistry analytes and, with subsequent UK Dept. of Health endorsement, the proposed common RIs are being widely adopted across the UK.

A working group, representing ACBI, ACSLM, IEQAS, and RCPI (Faculty of Pathology), investigated the possibility of producing similar common RIs for the Republic of Ireland for the ten analytes initially covered by PH. A survey was used to collect data on methods, RIs, and source of RIs. With very active follow-up of non-responders, responses were achieved for a total of 50 labs, including all major hospitals and private labs.

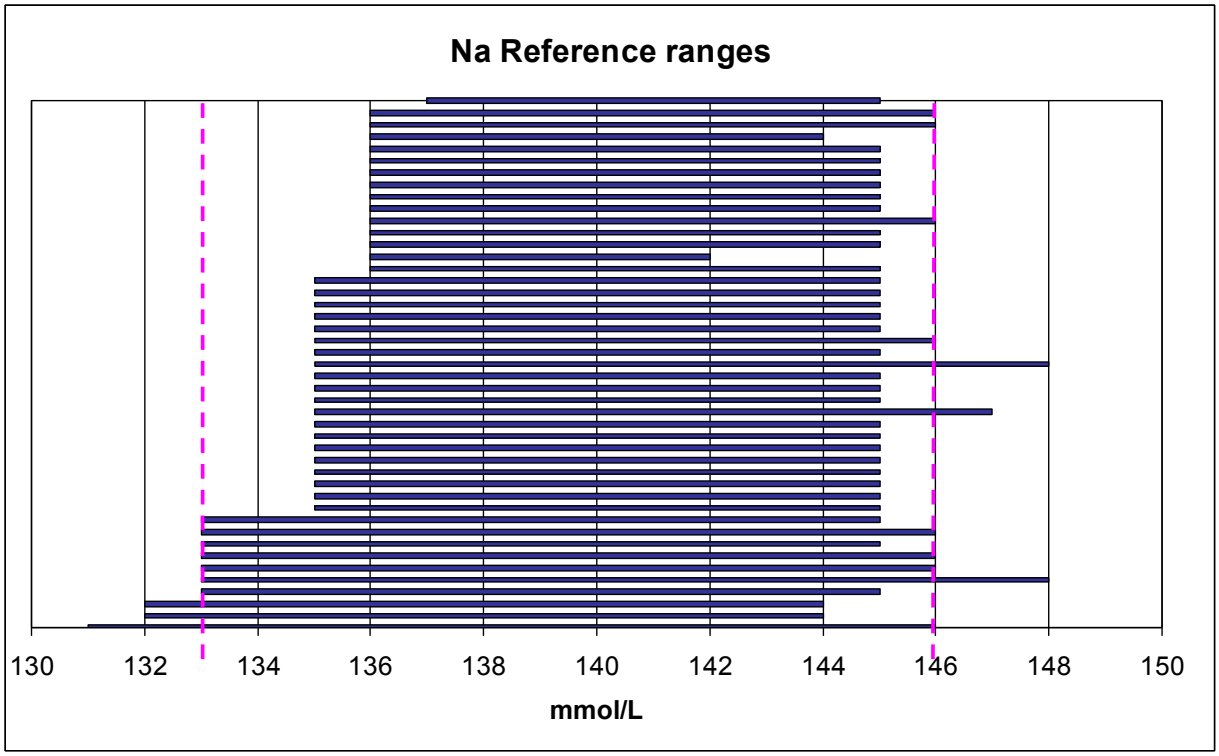
Review of RIs

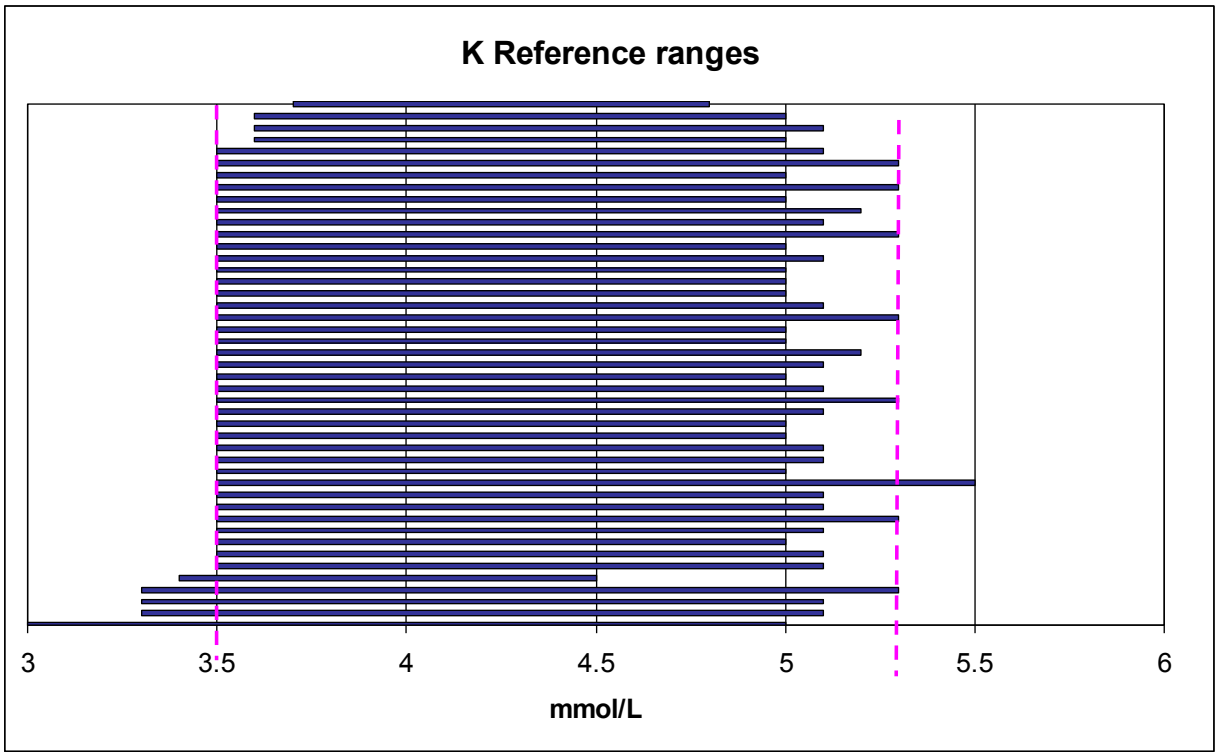
RIs in use were reviewed and compared to harmonised RIs in use in the UK and New Zealand / Australia (NZ/Aus). RIs were agreed and subjected to verification (below). These intervals are the same as those of PH UK except for Sodium where the lower limit of 133 was considered inappropriately low. The NZ / Aus RI of 135-145 was chosen.

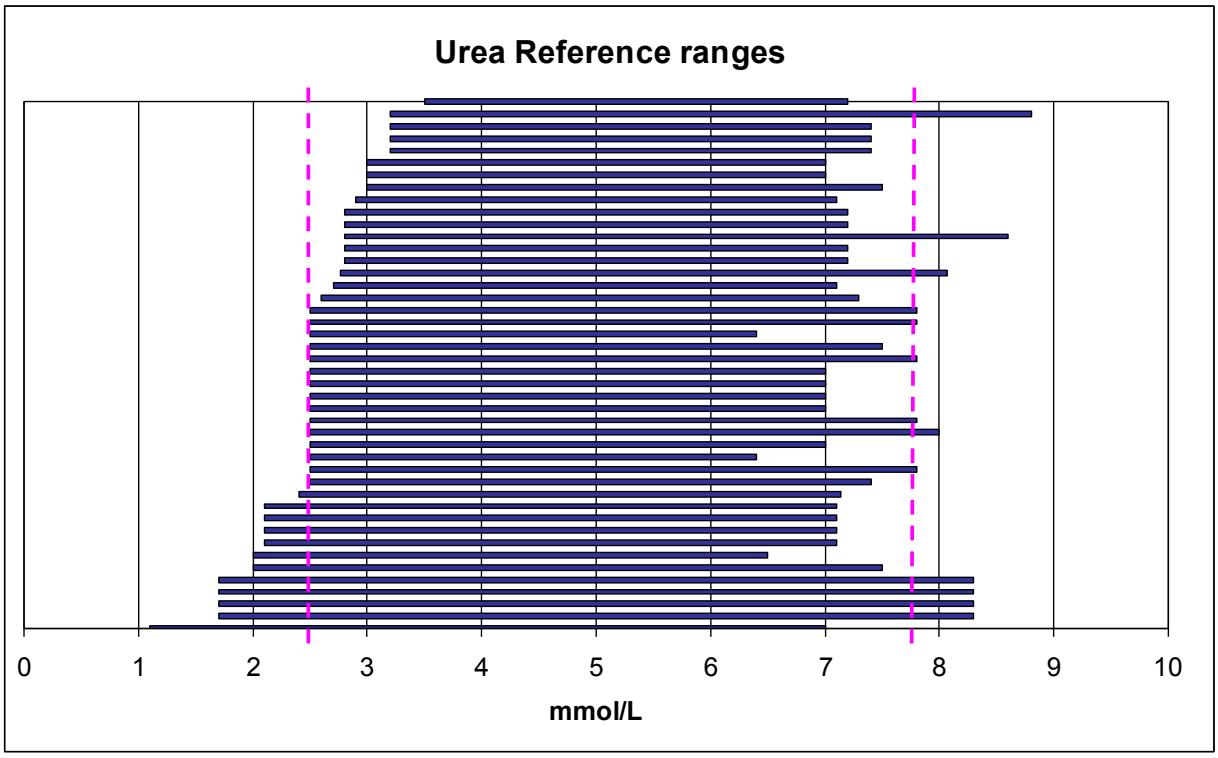
Overview of Survey Results

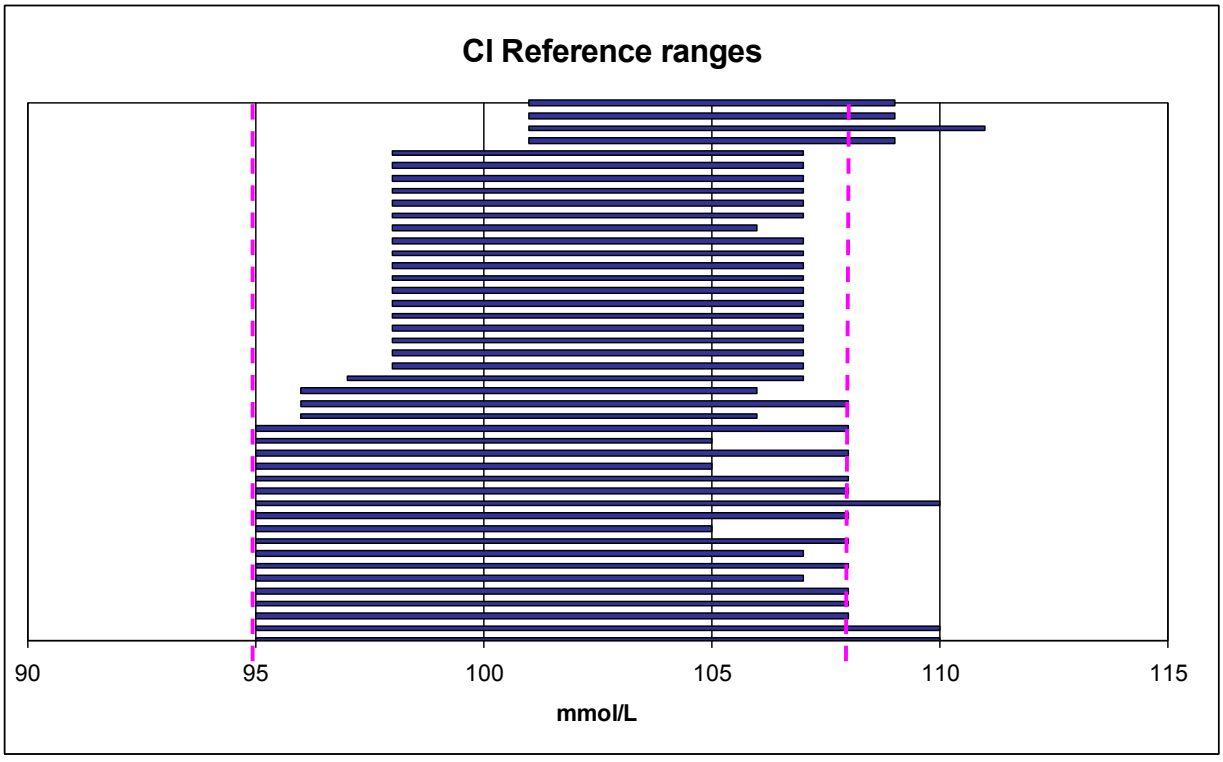
Figure 1 shows the different range of reference intervals reported from the various laboratories (not all laboratories provided a service for all analytes). The PH range is marked on each graph.

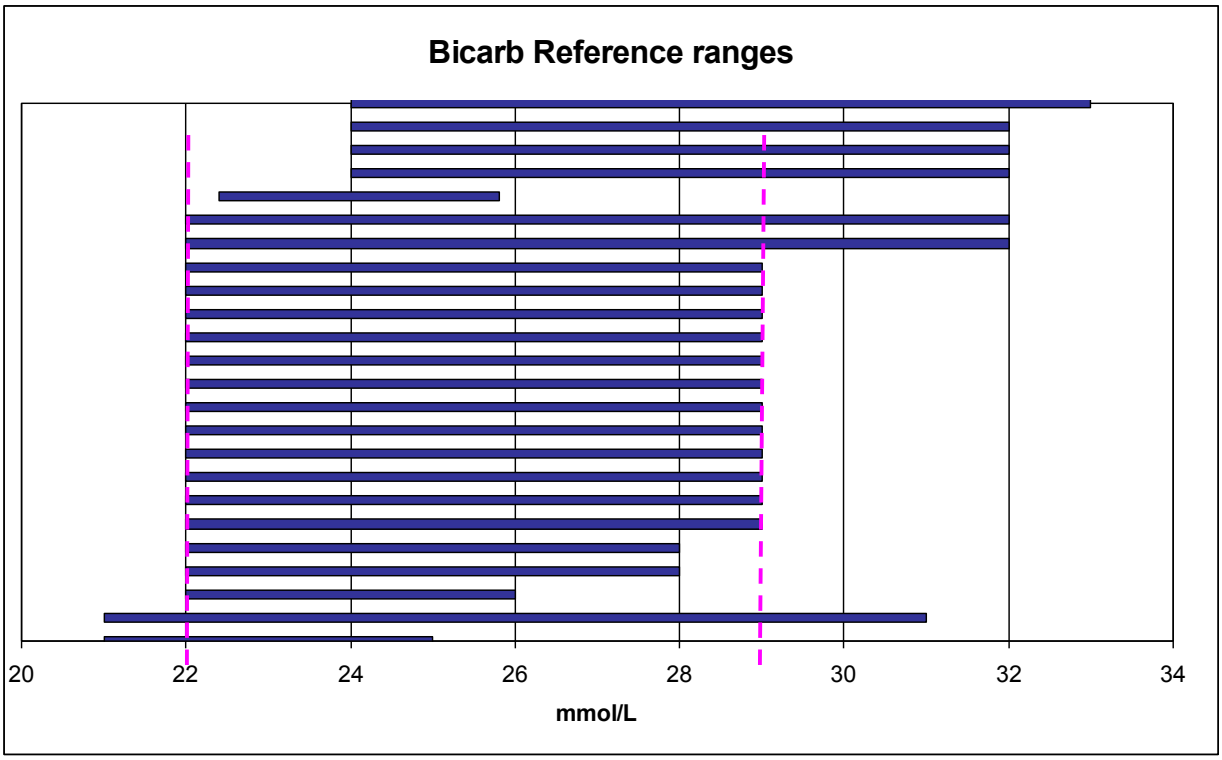
Figure 1: Spread of reference intervals for 10 common clinical chemistry analytes

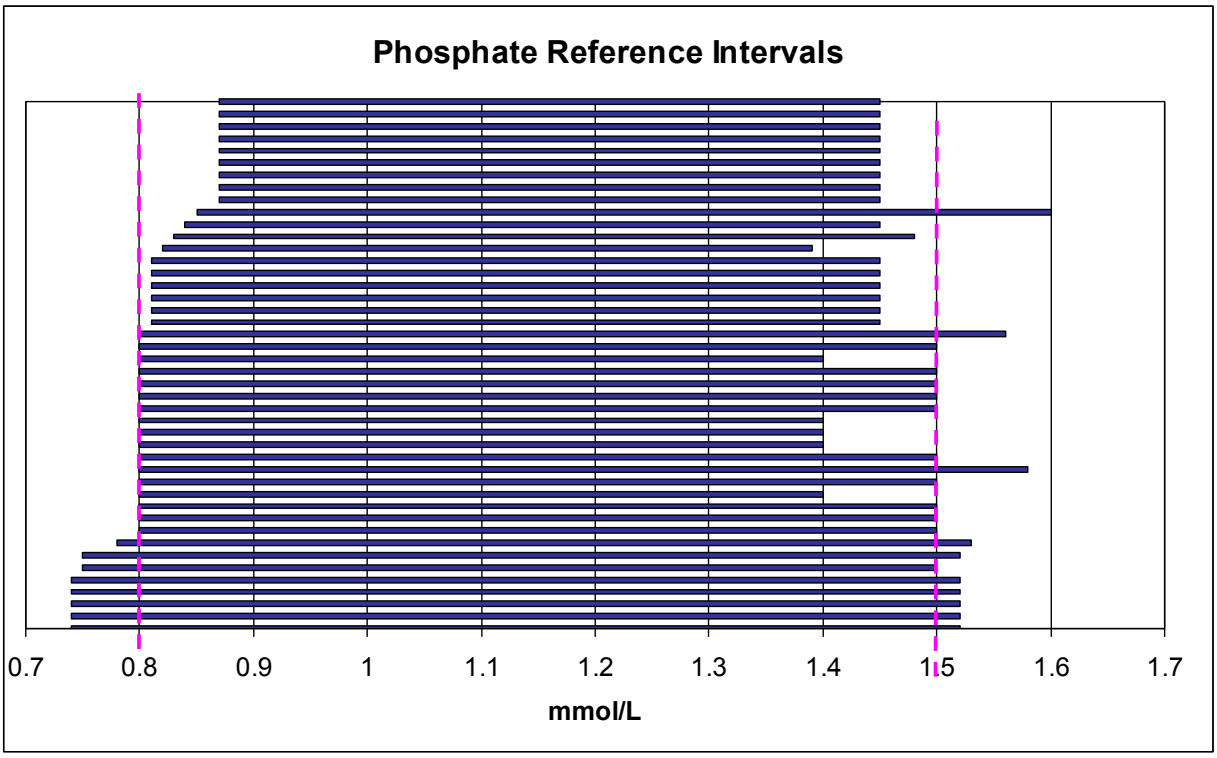


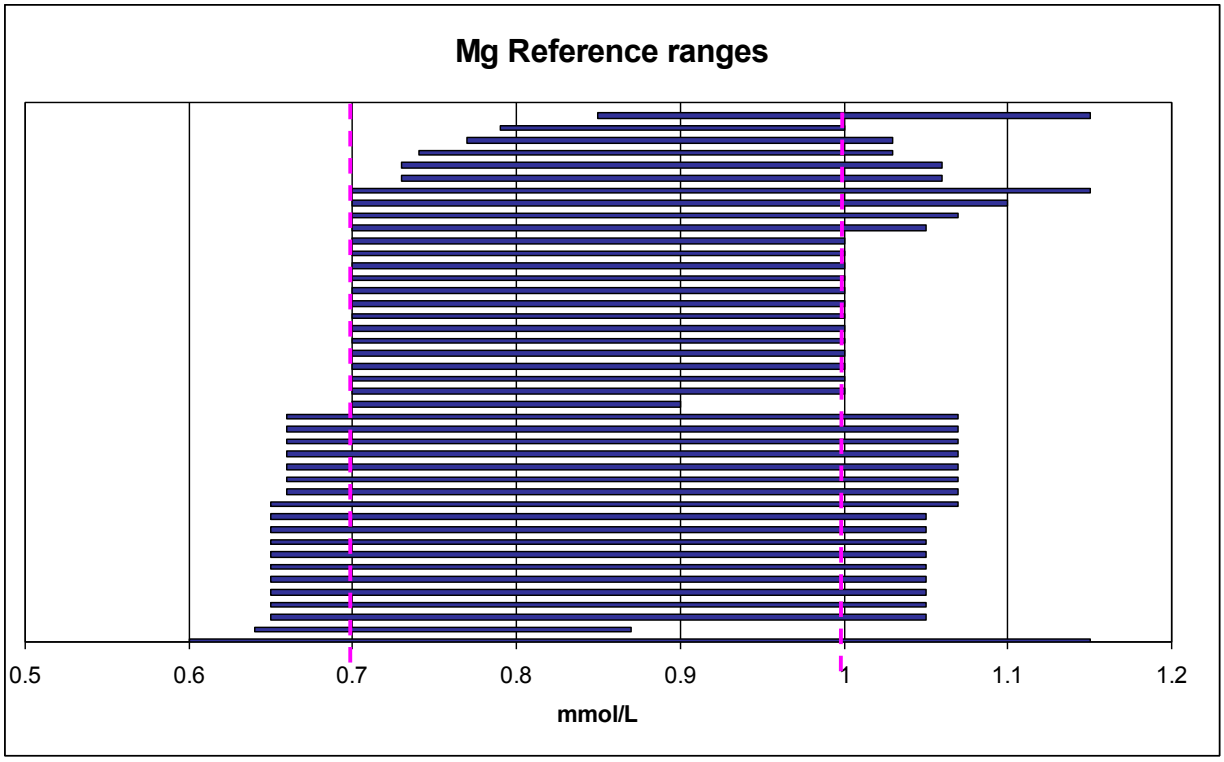


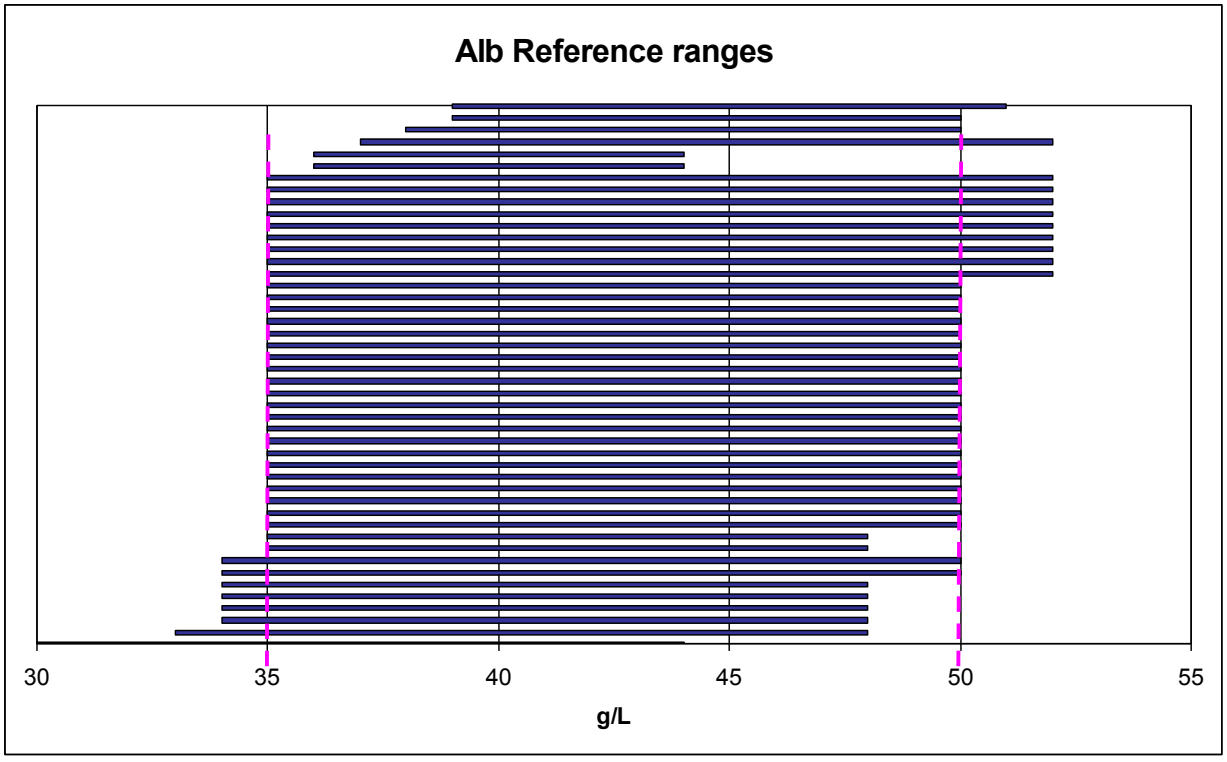

Urea Reference ranges
0
1
2
3
4
5
6
7
8
9
10
mmol/L

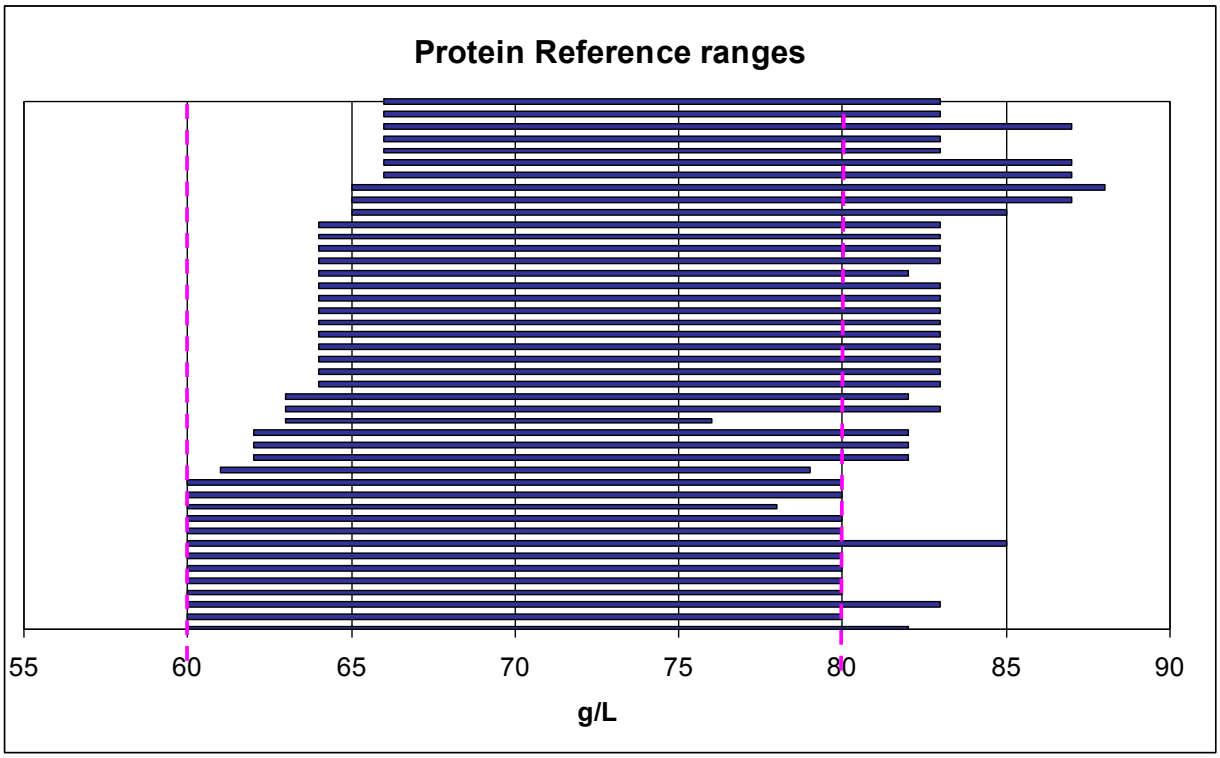

Cl Reference ranges
90
95
100
105
110
115
mmol/L

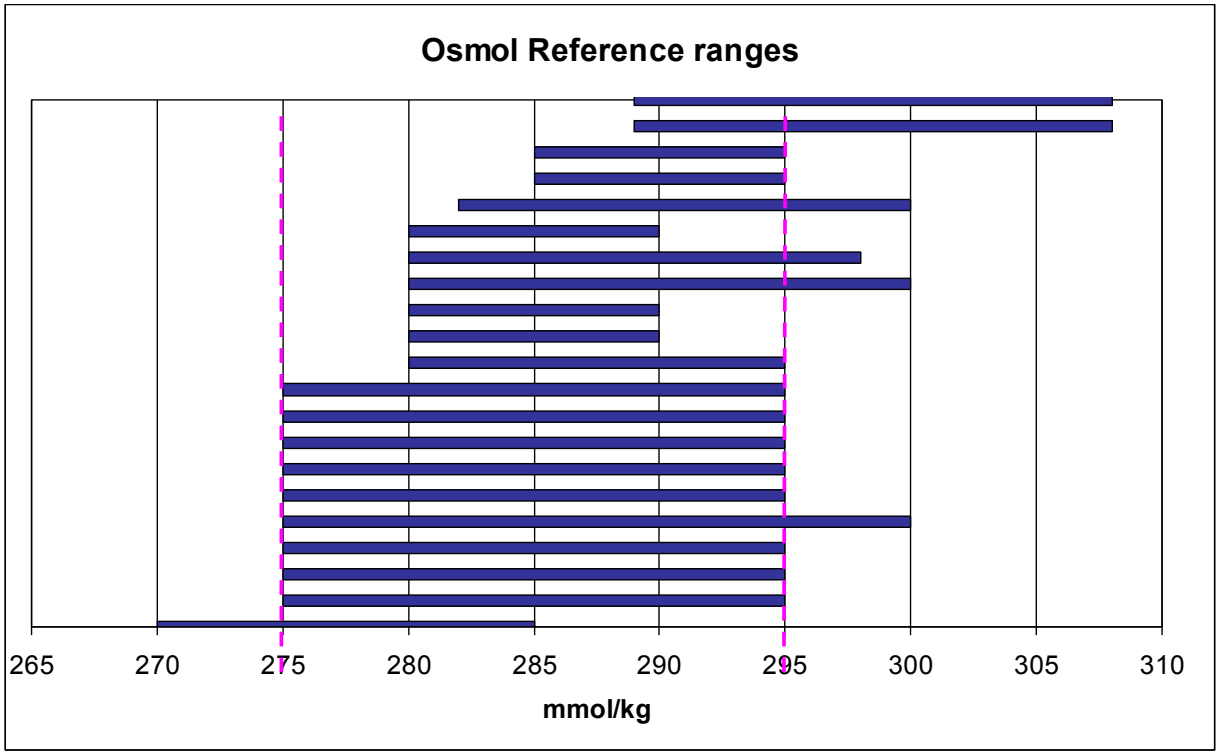

Bicarb Reference ranges
20
22
24
26
28
30
32
34
mmol/L


Phosphate Reference Intervals
0.7
0.8
0.9
1
1.1
1.2
1.3
1.4
1.5
1.6
1.7
mmol/L


Mg Reference ranges
0.5
0.6
0.7
0.8
0.9
1
1.1
1.2
mmol/L


Alb Reference ranges
30
35
40
45
50
55
g/L


Protein Reference ranges
55
60
65
70
75
80
85
90
g/L


Osmol Reference ranges
265
270
275
280
285
290
295
300
305
310
mmol/kg

Key findings

A number of key findings emerged from review of this data.

- A wide variety of RIs are in use for some of the analytes, without any clear reason why.
- For most analytes there is no single range that would be identical to the current reference intervals in use in a majority of hospitals.
- Many laboratories have different RIs despite using the same method on the same analyser and stating they have adopted the manufacturer's recommended reference range. Table 1 shows an example of this in respect of urea (an analyte with no issues in relation to gender or plasma versus serum).
- Only some laboratories appear to have taken into consideration known differences between serum and plasma for Potassium and Total Protein, and between BCG and BCP methods for albumin.
- A number of laboratories are already using PH ranges for particular analytes.
- Only three laboratories had derived their own reference intervals; these RIs covered a number of the analytes (but not all).
- Some smaller hospitals grouped with larger hospitals had achieved a degree of common reference intervals through agreement following purchase of similar analysers.

Table 1: Variation in Urea Reference Intervals and their sources in Irish Clinical Laboratories (data collected 2012)

	Total [1]	Kit [1]	Other [1]
Abbott Architect	11 (9)	8 (6)	3 (3)
Beckman AU	9 (3)	3 (1)	6 (2)
Beckman Synchron	8 (5)	4 (3)	4 (3)
Roche Modular	11 (7)	8 (6)	3 (3)
Other	5 (5)	4 (4)	1 (1)
Total	44 (25)	27 (18)	17 (10)

[[1]Total number of laboratories (number different ranges)]

Verification

To support laboratories in adopting the proposed ranges the group undertook to perform verification studies according to CLSI / IFCC criteria. An RI is deemed valid for transfer if two or less samples from twenty healthy individuals fall outside the proposed interval.

Of the 20 samples distributed to each laboratory just ≤ 1 result outside the proposed RI was obtained for serum and plasma for Na, K, Urea, Cl, PO4, Mg, BCG Albumin, and Total Protein. For BCP Albumin 2/4 laboratories reported 2 results (33-34 g/L) outside RI.

For Bicarbonate only one result outside the RI was obtained at the primary laboratory and at one laboratory nearby. Laboratories further away (>1hour transport time) reported 4 to 9 results outside range.
For Osmolality only one laboratory (1 result outside RI) complied with CLSI requirement for verification. Five other laboratories which measured Osmolality reported 3 to 5 outliers. A second set of 20 samples at one laboratory gave a similar result. Additionally the mean Osmolality for 127 measurements from the 6 labs was 292 mmol/kg (SD=5), not consistent with an RI of 275-295 mmol/kg.

Expected differences were verified for serum versus plasma (K, PO4, Total Protein) and BCG versus BCP Albumin.

Survey Results (Analytes) and Recommendations

Recommendations are summarised in Table 3, a table which also includes UK and New Zealand current practice as well as proposed Australasian recommendations for agreed RIs.

Table 2: Survey results and recommendations for 10 analytes

Analyte	Recommendation
Sodium:	The group recommends not adopting the PH range, as it was felt that the lower limit (LL) of 133 was too low. A range of 135-145 is proposed as being more in keeping with our survey findings, with clinical limit and target values in European and US guidelines[1-3], and ranges agreed for New Zealand (NZ).
Potassium:	The group recommends 3.5-5.3, as per PH, but for serum only. LL should apply to plasma, but more work is needed before a recommendation can be made on this.
Urea:	The PH range offers a reasonable compromise if an agreed range is to be introduced. The LL of 2.5 is also an average for our Irish labs. The upper limit (UL) of 7.8 is higher than the average from our survey but less than the UL derived in-house by three labs and is in agreement with NZ ranges.
Chloride:	Adopt PH range.
Bicarbonate / Total CO_2:	Adopt the PH interval. Majority of labs already use this RI.
Phosphate:	Adopt PH. The PH interval is close to the RIs currently used in RoI.
Magnesium:	Either 0.65 or 0.70 would agree with equal proportions of RIs in our survey but the group felt that the 0.70 was a better guide clinically. At the higher level the differences in UL of RI were not felt to be important and therefore we recommend the PH range of 0.7-1.0.
Albumin:	Of 45 labs who reported their RIs to us 31 used BCG and 14 BCP. No account seemed to be taken, by most labs and manufacturers, of differences in these methods. We recommend 35-50 for labs using BCG. More work is needed before making a recommendation on BCP.
Total Protein:	There is an equal weight of evidence behind the PH interval of 60-80 and a range of 63-83. The group is recommending the PH interval due to advantage of agreeing with UK practice.
Osmolality:	We recommended the PH interval as being in use by around half of labs reporting osmolality and being clinically valid. We have concerns about some of the higher ULs in use. However, the verification process did not support this range.

Discussion

Lack of sample stability is likely to have affected bicarbonate in the study. The verification studies have shown that the other proposed RIs are valid except for Osmolality. Based on our study findings, we do not support a harmonised RI for Osmolality.

Review of the impact on proposed RIs of plasma versus serum and BCP versus BCG is nearing completion.

Adopting the proposed Bicarbonate interval, which is the same as the PH interval, seems the most appropriate choice and remains our recommendation.

Conclusion

This study confirms significant variation in RIs quoted by Irish Clinical Chemistry laboratories. Proposed harmonised RIs have been tested for serum and plasma in 8 laboratories using 7 analyser platforms covering the major analysers in current use. From this study we propose national adoption of harmonised RIs for 9 of 10 analytes studied and we encourage all clinical laboratories to adopt these intervals.

We recommend that Irish laboratories adopt these common ranges and that the process be coordinated centrally.

Table 3: Proposed Reference Intervals for Republic of Ireland and Comparable International RIs

Analyte	Units	IRIH Proposal (Ireland)	Pathology Harmony (UK)	SIQAG (NZ)	ARQAG (NZ)	AACB proposal (Aus+NZ)
Sodium	mmol/L	135 - 145	133 - 146	135 - 145	135 – 145	135 - 145
Potassium	mmol/L	3.5 - 5.3 (serum)	3.5 - 5.3	3.5 - 5.2 (serum & plasma)	3.5 - 5.2	3.5 - 5.2
Urea	mmol/L	2.5 - 7.8	2.5 - 7.8	3.2 - 7.7	3.2 - 7.7	
Chloride	mmol/L	95 - 108	95 - 108	95 - 110	95 – 110	95 - 110
Bicarbonate	mmol/L	22 – 29	22 - 29		22 – 31	22 - 32
Phosphate	mmol/L	0.8 - 1.5	0.8 - 1.5	0.8 - 1.5	0.7 - 1.5	0.75 - 1.50
Magnesium	mmol/L	0.7 - 1.0	0.7 - 1.0	0.8 - 1.5	0.7 - 1.0	0.7 - 1.1
Albumin	g/L	35 - 50 (BCG)	35 - 50	35 - 50 (BCG)	38 – 52	
Total Protein	g/L	60 - 80 (serum)	60 - 80	64 - 83	66 – 84	60 - 80
Osmolality	*mmol/kg*	*275 – 295 Rejected*	*275 - 295*			

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