

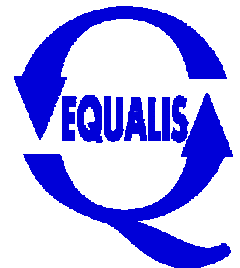
NORIP - Haematology

Preliminary results from
the Nordic Reference Interval Project

2003-06-26

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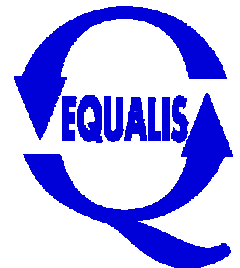
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NORIP - Haematology

60 Nordic laboratories

Denmark: 8

Finland: 26

Iceland: 1

Norway: 1

Sweden: 24

Ca 1 800 reference persons

Ca 20 700 results

Finland

Sample collection day

Local measurement

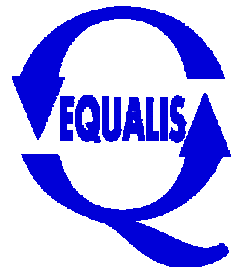
Day 2

Local and central
measurement

Other countries

**Sample
collection day:**

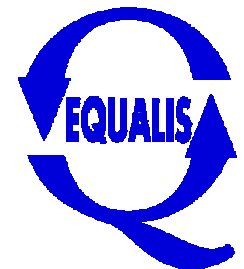
Local measurement



NORIP - Preliminary Haematology results

Country	Number of results
Denmark	230
Finland	854
Iceland	78
Norway	31
Sweden	677

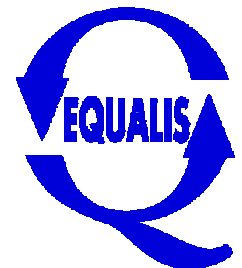
Most influence on the common results from Finland and Sweden.



Inclusion criteria for reference persons

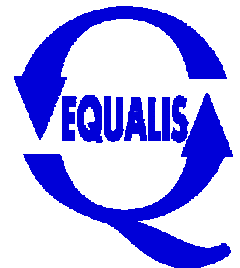
The reference individual should

- **be feeling subjectively well**
- **have reached the age of 18**
- **not be pregnant or breast-feeding**
- **not have been an in-patient in a hospital nor have been subjectively dangerously ill during the last month**
- **not have consumed more than 2 measures of alcohol (24 g) in the last 24 hours**
- **not have given blood as a donor in the last five months**
- **not have taken prescribed drugs other than the P-pill or estrogens during the last two weeks**
- **not have smoked in the last hour prior to blood sampling**

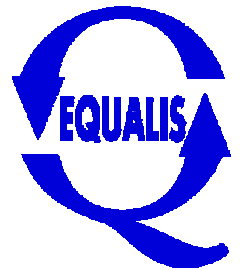


Data handling

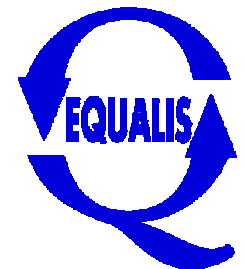
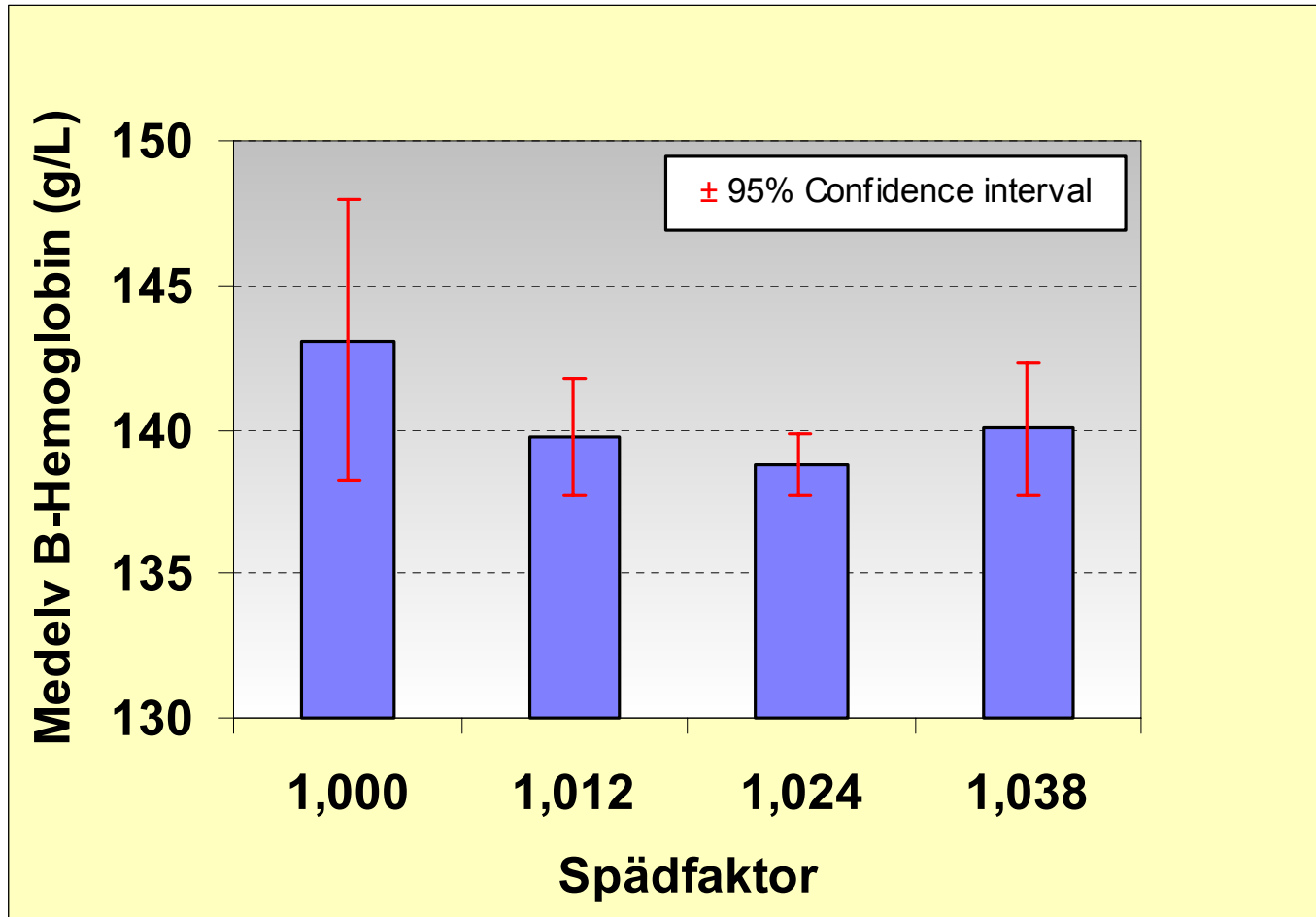
- 1. Collecting all results and reference person data into one common database.**
- 2. Correcting results for sample dilution.**
- 3. Excluding outliers.**
- 4. Test for partitioning.**
- 5. Nonparametric calculation of reference intervals – robust, not influenced by small numbers of outliers.**
- 6. Checking dependence on country, instrument etc.**



Correcting results for sample dilution.

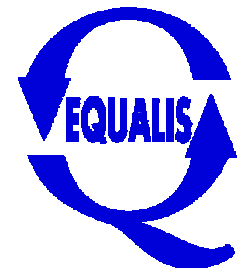


Influence of the type EDTA-tube on the mean B-Hb ?



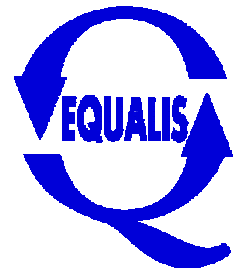
NORIP - Preliminary Haematology results

For which components are the results corrected with the dilution factor?	
Component	Dilution Factor used
(3-part) B-Granulocyter	Yes
(3-part) B-Lymfocyter	Yes
(3-part) B-Monocyter/MID	Yes
(5-part) B-Basofila granulocyter	Yes
(5-part) B-Eosinofila granulocyter	Yes
(5-part) B-LUC	Yes
(5-part) B-Lymfocyter	Yes
(5-part) B-Monocyter	Yes
(5-part) B-Neutrofila granulocyter	Yes
B-MPV	No
B-PDW	No
B-RDW	No
B-RDW fl	No
B-Retikulocyter	Yes
B-HDW	?
B-Leukocyter	Yes
B-Erythrocyter	Yes
B-Hemoglobin	Yes
B-Hematocrit	Yes
B-MCV	No
B-MCH	No
B-MCHC	No
B-Trombocyter	Yes



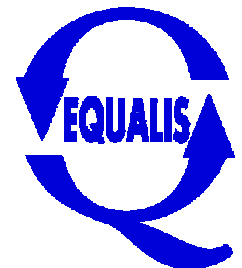
Exclusion rules for NORIP Haematology:

- **Single results have been excluded if they deviated more than +/- 5 SD from component mean. Exclusion according to this rule has been repeated until no result was excluded (twice needed).**
- **No results has been excluded for other reasons.**



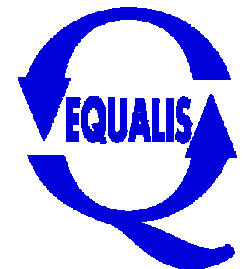
Results deviating >5 SD, first round

Component	A_ID	Lno	COUNTRY	Result	Deviation	SEX
(5-part) B-Basofila granulocyter	81943	4051	DENMARK	0,2048	5,166868	F
(5-part) B-Eosinofila granulocyter	82070	4051	DENMARK	13,312	27,32669	M
(5-part) B-LUC	80265	4021	DENMARK	8,192	6,242436	F
(5-part) B-Lymfocyter	68516	2437	SWEDEN	7,9948	5,311234	M
(5-part) B-Lymfocyter	79720	4019	DENMARK	23,4	19,06769	F
(5-part) B-Lymfocyter	75710	2468	SWEDEN	10,8544	7,864785	M
(5-part) B-Lymfocyter	76480	2478	SWEDEN	13,494	10,22188	F
(5-part) B-Monocyter	68341	2437	SWEDEN	1,4168	6,276406	M
(5-part) B-Neutrofila granulocyter	73094	2516	SWEDEN	9,846759	5,731105	F
(5-part) B-Neutrofila granulocyter	75096	2531	SWEDEN	9,6	5,517512	F
B-Hematocrit	120120	816	FINLAND	408	39,45325	F
B-Hemoglobin	78717	4081	DENMARK	71	-5,92328	F
B-Leukocyter	75716	2468	SWEDEN	15,9744	6,596135	M
B-Leukocyter	76486	2478	SWEDEN	16,1928	6,736474	F
B-Leukocyter	79726	4019	DENMARK	27,7	14,13079	F
B-Leukocyter	111845	406	FINLAND	16,728	7,080383	M
B-MCH	74925	2531	SWEDEN	22	-5,17498	M
B-MCH	78719	4081	DENMARK	15,5	-9,20839	F
B-MCHC	78720	4081	DENMARK	269	-6,63061	F
B-MCHC	74772	2531	SWEDEN	240	-9,46706	M
B-MCV	78721	4081	DENMARK	57,6	-7,88127	F
B-RDW	78724	4081	DENMARK	19,5	6,098778	F
B-RDW	81097	4029	DENMARK	19,7	6,288513	F
B-Retikulocyter	63911	2548	SWEDEN	302,7968	8,731866	M
B-Trombocyter	66792	2541	SWEDEN	580,608	5,980262	M

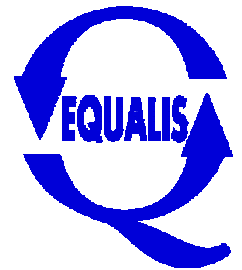


Results deviating >5 SD, second round

Component	Lno	PNO	Cno	COUNTRY	Result	SEX	SD	SDII
(5-part) B-Eosinofila granulocyter	2525	12812	0	SWEDEN	0,74736	F	1,144913	5,093687
(5-part) B-Neutrofila granulocyter	2800	3423	0	ICELAND	8,855	F	4,872642	5,089655
(5-part) B-LUC	2800	4301	0	ICELAND	6,3	F	4,675705	5,065325



Test for partitioning



Percentage (p) of subpopulation results outside the common reference limits determines if separate reference intervals for the subpopulations are recommended:

- **If the big p $<3,2$ % and the small p $\geq 1,8$ % \Rightarrow
Common reference interval is recommended = No partitioning.**
- **If the small p $\geq 0,9$ % but $<1,8$ % or
the big p $\geq 3,2$ % but $<4,1$ % \Rightarrow
Separate reference interval is possibly justified = No partitioning
is proposed in NORIP Haematology.**
- **If the small p $<0,9$ % or the big $\geq 4,1$ % \Rightarrow
Separate reference interval is recommended = Partitioning.**



Clin Chem (2002) 48:2, 338-352

Clinical Chemistry 48:2
000-000 (2002)

Laboratory
Management

Objective Criteria for Partitioning Gaussian-distributed Reference Values into Subgroups

Ari Lahti,^{1*} Pasi Heikkilä-Petäjänen,^{1,2} James C. Boyd,³ Callum G. Peaker,⁴ and Niilo Järvelinmäki⁵

Background: The aim of this study was to develop new and useful criteria for partitioning reference values into subgroups applicable to Gaussian distributions and to distributions that can be transformed to Gaussian distributions.

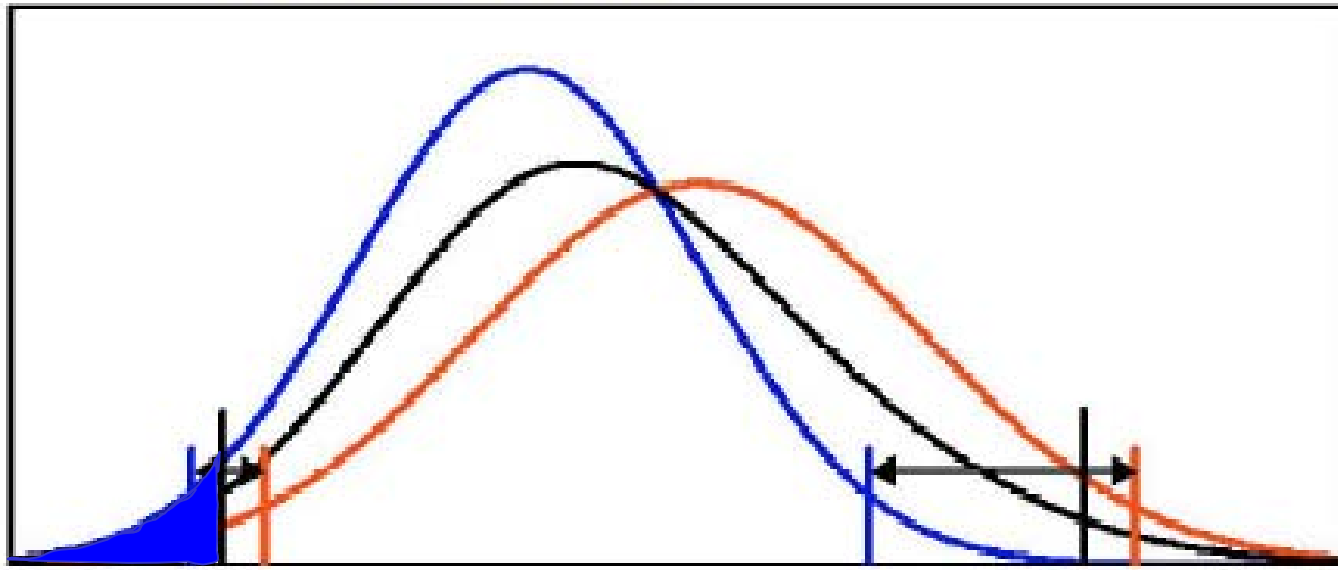
Methods: The proposed criteria relate to percentages of the sample means over or under certain limits of the standard distribution. Critical values suggested as partitioning criteria for these percentages were derived from analytical bias quality specifications for using common reference intervals throughout a geographic area. An alternative partitioning criteria to the actual percentages, these were formulated mathematically as critical distances between the reference limits of the

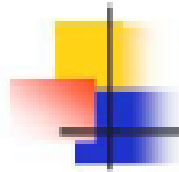
between these two values should be classified as marginal, implying that statistical considerations are required to make the final decision on partitioning. The correlation between the actual percentages and the critical distances was mathematically perfect in the new model, whereas this correlation is rather approximate in the Harris-Boggs model because focus on the distance between means in this model creates high percentage limit to achieve. The application examples suggested that the new model is more rational than the Harris-Boggs model. **Conclusions:** New percentage and distance criteria to be used for partitioning Gaussian-distributed data, have been developed. The distance criteria applied separately to both reference limit pairs of the subgroup



New Model: Principle

Proportion (or distance criteria)





New Model: Summary

- Each end of the distributions is treated separately
- The proportion vs. distance curves are determined by using mathematical calculations

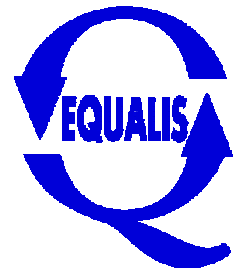
Correlation between distance and proportion criteria for partitioning is good



Summary

- **The new model for distance criteria is**
 - **more accurate than the Harris-Boyd model**
 - **easily adjustable to any new values for the critical proportions**
- **Use of distance criteria should be restricted to gaussian distributions**
- **Proportion criteria are applicable to both gaussian and nongaussian distributions**

Nonparametric calculation of reference intervals



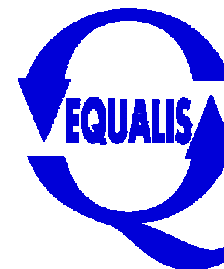
NORIP - Preliminary Haematology results

**Non-
parametric
determination
of reference
limits.**

**Example 1:
B-Hb, women,
lower limit**

**Limit value at:
2,5 % of
totally 960
results
= 24,0**

Order no	Analyte	Result	AGE	SEX
1	B-Hemoglobin	93,0	23	F
2	B-Hemoglobin	102,0	36	F
3	B-Hemoglobin	106,1	53	F
4	B-Hemoglobin	111,2	19	F
5	B-Hemoglobin	113,2	51	F
6	B-Hemoglobin	113,2	51	F
7	B-Hemoglobin	113,3	44	F
8	B-Hemoglobin	114,3	43	F
9	B-Hemoglobin	114,3	28	F
10	B-Hemoglobin	115,3	70	F
11	B-Hemoglobin	115,4	18	F
12	B-Hemoglobin	115,7	44	F
13	B-Hemoglobin	115,7	23	F
14	B-Hemoglobin	115,7	23	F
15	B-Hemoglobin	115,9	50	F
16	B-Hemoglobin	116,0	41	F
17	B-Hemoglobin	116,3	78	F
18	B-Hemoglobin	116,3	46	F
19	B-Hemoglobin	116,3	73	F
20	B-Hemoglobin	116,8	25	F
21	B-Hemoglobin	117,3	62	F
22	B-Hemoglobin	117,3	80	F
23	B-Hemoglobin	117,4	77	F
24	B-Hemoglobin	117,4	24	F
25	B-Hemoglobin	117,8	22	F
26	B-Hemoglobin	117,8	27	F
27	B-Hemoglobin	118,0	79	F
28	B-Hemoglobin	118,3	45	F
29	B-Hemoglobin	118,3	36	F
30	B-Hemoglobin	118,3	21	F

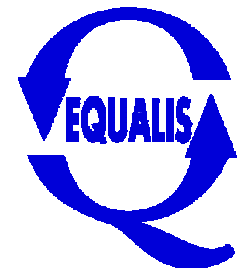


**Non-parametric
determination
of reference limits.**

**Example 2:
B-Hb, women, high limit**

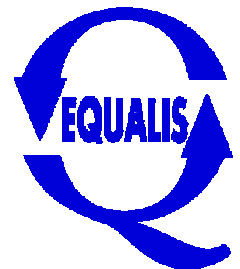
**Limit value at:
2,5 % of 960 results
= 24,0 results**

Order no	Analyte	Result
30	B-Hemoglobin	152,0
29	B-Hemoglobin	152,0
28	B-Hemoglobin	152,0
27	B-Hemoglobin	152,6
26	B-Hemoglobin	152,8
25	B-Hemoglobin	153,0
24	B-Hemoglobin	153,0
23	B-Hemoglobin	153,0
22	B-Hemoglobin	153,0
21	B-Hemoglobin	153,6
20	B-Hemoglobin	154,8
19	B-Hemoglobin	155,0
18	B-Hemoglobin	155,0
17	B-Hemoglobin	155,6
16	B-Hemoglobin	155,7
15	B-Hemoglobin	155,7
14	B-Hemoglobin	155,7
13	B-Hemoglobin	156,1
12	B-Hemoglobin	157,1
11	B-Hemoglobin	158,1
10	B-Hemoglobin	159,1
9	B-Hemoglobin	159,1
8	B-Hemoglobin	159,1
7	B-Hemoglobin	159,7
6	B-Hemoglobin	159,9
5	B-Hemoglobin	160,8
4	B-Hemoglobin	161,2
3	B-Hemoglobin	164,2
2	B-Hemoglobin	165,2
1	B-Hemoglobin	166,0



Bias

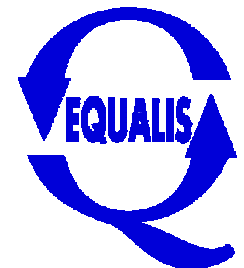
**between haematology instruments,
when comparing all instrument groups
with more than 100 results?**



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Code	Instrument models in the group	Short name
-1	Unknown	
11	Coulter M2, M4, CBC 5, M530	
12	Coulter S 880	
13	Coulter SPlus II-VI, STKR, STKS, MaxM, Onyx, GenS	Coulter big
14	Coulter T540, T660, T850, TC10, Js, MD8, MD18, MDII 18, AcT	
20	Cell-Dyn 300, 400, 500, 610, 700, 800, 900, 1000	
21	Cell-Dyn 1300, 1400, 1500, 1600, 1700, 2000	
22	Cell-Dyn CS 3000, 3500	Cell-Dyn 3500
23	Cell-Dyn 3200	
24	Cell-Dyn 4000	Cell-Dyn 4000
27	ABX Pentra	
30	Sysmex CC130, 150, 170, 180, 780	
31	Sysmex F 300, 500, 520, 800, 820	
32	Sysmex K 800, K-1000, K-4500, M-2000, KX-21	Sysmex small
33	Sysmex NE 1500, NE 8000, SE 9000, SF 3000, XE 2100	Sysmex big
40	Bayer H-1, H-1 Junior, H-2, H-3	Bayer H
41	Bayer Advia	Bayer Advia
50	Cobas Micros, Minos ST, STE, STX	
51	Cobas Argos, Helios, Vega	
60	Medonic Ca 460, 480, 580A, 610	
65	Celltac MEK 6108K, 8118K	
68	Serono	
70	QBC II Plus	
80	Swelab	
85	Contraves Digicell	
88	Laborscale	
90	Uleselig	

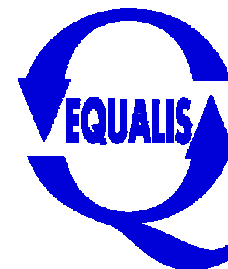
**Instrument
groups
used**



NORIP - Preliminary Haematology results

Instrument bias compared to the reference interval

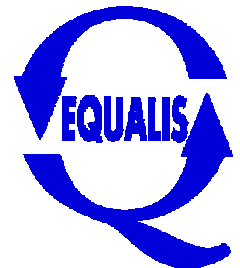
	Gender subgroup	NORIP calculated reference limits			Instrument mean			(Max – Min) in % of ref. interval
		Low	High	Range	Min	Max	Range	
B–Haemoglobin (g/L)	Women	117	153	36	142,7	143,4	0,7	2
	Men	134	170	36	142,7	143,4	0,7	2
B–Erc, volume fraction	Women	0,348	0,459	0,111	0,419	0,426	0,007	6
	Men	0,395	0,5	0,105	0,419	0,426	0,007	7
B–Erythrocytes ($10^{12}/L$)	Women	3,94	5,16	1,22	4,64	4,78	0,14	11
	Men	4,25	5,71	1,46	4,64	4,78	0,14	10



NORIP - Preliminary Haematology results

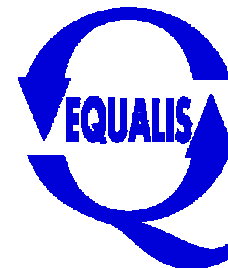
Instrument bias compared to the reference interval

	Gender subgroup	NORIP calculated reference limits			Instrument mean			(Max – Min) in % of ref. interval
		Low	High	Range	Min	Max	Range	
Erc-MCV (fL)		82	98	16	88,7	91,2	2,5	16
Erc-MCH (pg)		27,1	33,3	6,2	30	30,8	0,8	13
Erc-MCHC (g/L)		317	357	40	334	341	7	18



Instrument bias compared to the reference interval

	Gender subgroup	NORIP calculated reference limits			Instrument mean			(Max – Min) in % of ref. interval
		Low	High	Range	Min	Max	Range	
B–Leukocytes (10 ⁹ /L)		3,47	8,81	5,34	5,4	5,9	0,5	9
B–Thrombocytes (10 ⁹ /L)	Women	165	387	222	237	261	24	11
	Men	145	348	203	237	261	24	12
	All	153	367	214	237	261	24	11

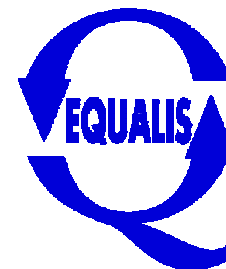


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NORIP reference intervals corrected for liquid anticoagulant

Finnish reference intervals corrected for liquid anticoagulant (2 %)

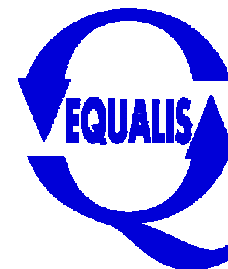
	Women	Men	Women and men
B-Hb (g/L)	117 - 153	134 - 170	
	117 - 155	134 - 167	
B-Erc, volume fraction	0,35 - 0,46	0,40 - 0,50	
	0,35 - 0,46	0,39 - 0,50	
B-Erythrocytes ($10^{12}/L$)	3,9 - 5,2	4,2 - 5,7	
	3,90 - 5,20	4,25 - 5,70	
Erc-MCV (fL)			82 - 98
			82 - 98
Erc-MCH (pg)			27 - 33
			27 - 33
Erc-MCHC (g/L)			317 - 357
			-
B-Leukocytes ($10^9/L$)			3,5 - 8,8
			3,4 - 8,2
B-Thrombocytes ($10^9/L$)	165 - 390	145 - 350	145 - 390
	165 - 365	140 - 355	150 - 360



NORIP - Preliminary Haematology results

Preliminary haematology reference intervals

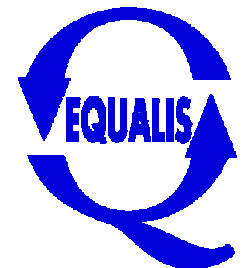
Analyte	Gender subgroup	NORIP calculated	NORIP suggested
B-Haemoglobin (mmol/L)*	Women	7,09 – 9,27	7,1 – 9,3
	Men	8,12 – 10,30	8,1 – 10,3
B-Haemoglobin (g/L)	Women	117 – 153	117 – 153
	Men	134 – 170	134 – 170
B-Erc, volume fraction	Women	0,348 – 0,459	0,35 – 0,46
	Men	0,395 – 0,500	0,40 – 0,50
B-Erythrocytes ($10^{12}/L$)	Women	3,94 – 5,16	3,9 – 5,2
	Men	4,25 – 5,71	4,2 – 5,7



NORIP - Preliminary Haematology results

Preliminary haematology reference intervals

Analyte	Gender subgroup	NORIP calculated	NORIP suggested
Erc-MCV (fL)		82,0 – 98,0	82 – 98
Erc-MCH (fmol)*		1,64 – 2,02	1,6 – 2,0
Erc-MCH (pg)		27,1 – 33,3	27 – 33
Erc-MCHC (mmol/L)*		19,2 – 21,6	19,2 – 21,6
Erc-MCHC (g/L)		317 – 357	317 – 357

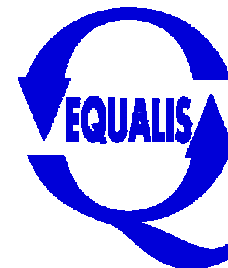


Preliminary haematology reference intervals

Analyte	Gender subgroup	NORIP calculated	NORIP suggested
B–Leukocytes ($10^9/L$)		3,47 – 8,81	3,5 – 8,8
B–Thrombocytes ($10^9/L$) [#]	Women	165 – 387	–
	Men	145 – 348	–
	All	153 – 367	145 – 390

* Unit recommended by IFCC/IUPAC.

For B–Thrombocytes the partitioning rules suggest separate low reference limits for women and men but the working group tends to propose a common reference interval for both genders.



Suggestions

- ◆ All laboratories in the Nordic countries should be recommended by NFKK and the national societies to implement NORIP reference intervals
 - Reasonable time table - during 2003?
- ◆ Information material from NFKK and the national societies concerning information about NORIP to be presented for
 - Laboratories and clinicians
 - Patients and other end users
 - Professional journals
 - Professional meetings

Thanks !

These presentations are made
with good support from

Gunnar Nordin, Pål Rustad,
Ari Lahti, Helge Erik Solberg and the working
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