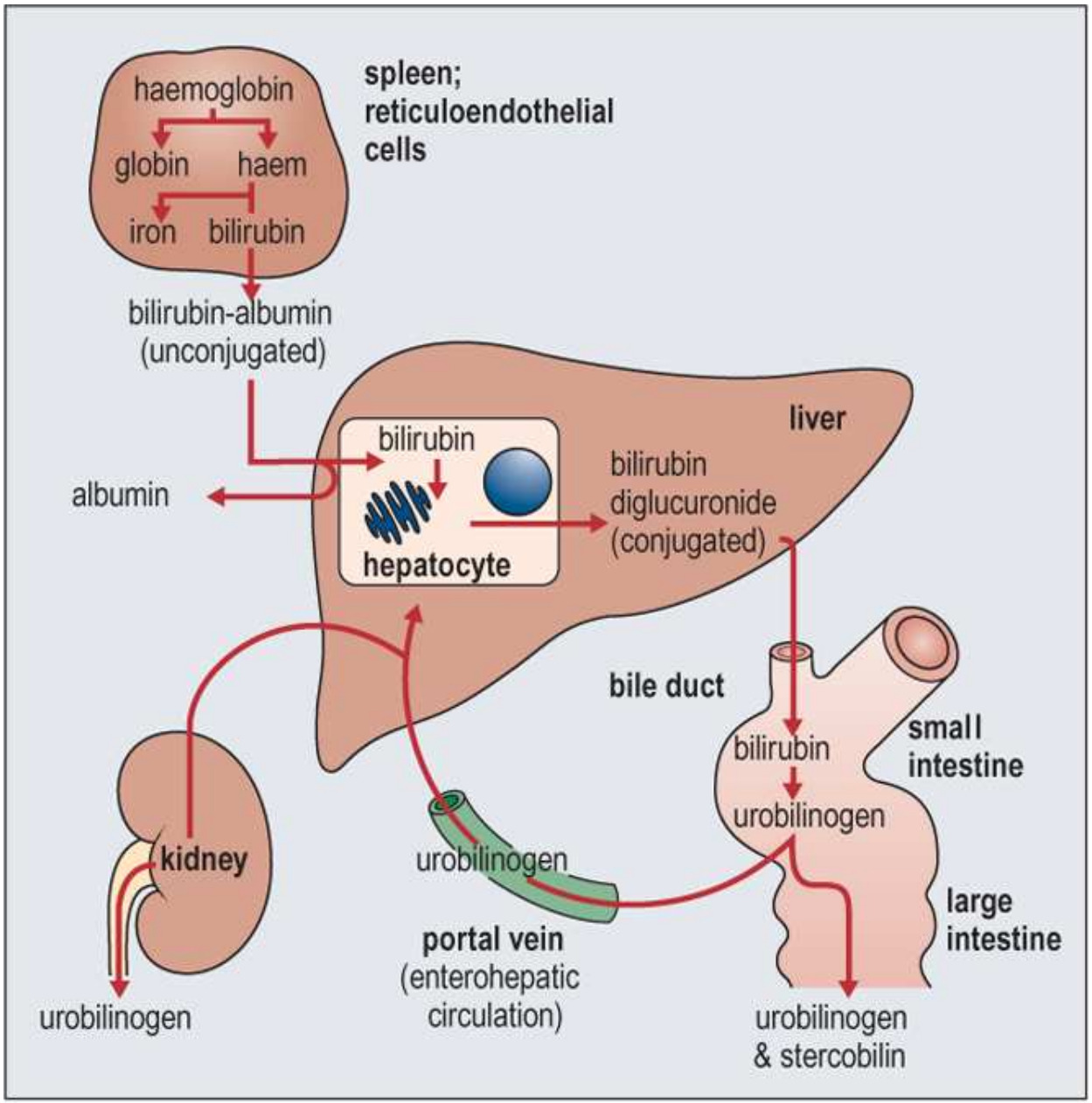
Bilirubine: een veelkoppig monster ?

SKML Sectie Algemene Chemie

Gebruikersdag 3 juni 2010

prof dr ir Huib L. Vader

máxima
medisch centrum



Bilirubin fractionation by HPLC

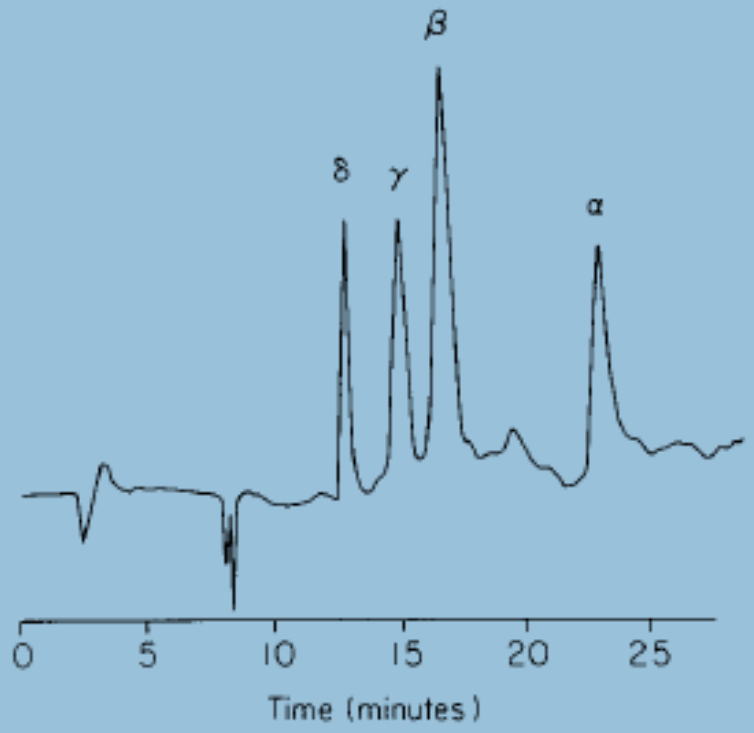
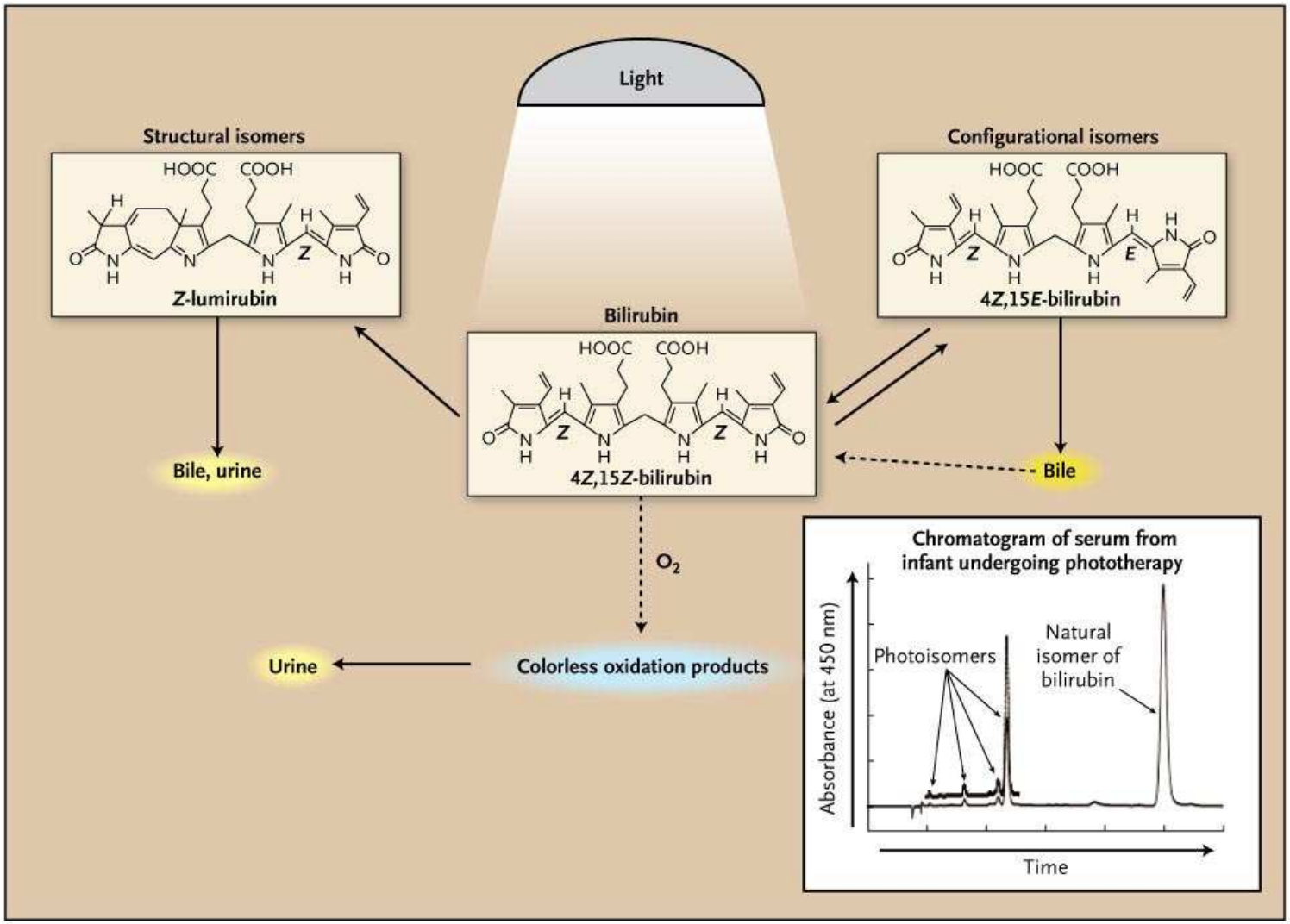


FIG. 1. Separation of bilirubin fractions in the serum of an infant with obstructive jaundice (neonatal giant-cell hepatitis), by reverse-phase high-performance liquid chromatography (absorbance at 450 nm). Bilirubin components are: unconjugated (α), monoconjugated (β), diconjugated (γ), and albumin-bound (δ) bilirubin.

Delta bilirubine

- In de circulatie gevormd uit geconjugeerd bilirubine en albumine
- Langzame, niet-enzymatische vervanging van glucuronzuur door albumine (als GHb)
- Pas aantoonbaar na een langdurige periode van geconjugeerde hyperbilirubinemie
- Verdwijnt langzaam uit de circulatie. $T_{1/2}$ als albumine 2-3 weken



Maisels M, McDonagh A. N Engl J Med 2008;358:920-928

The NEW ENGLAND JOURNAL of MEDICINE

Clin Chem Lab Med 2005;43(5):531–535 © 2005 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2005.092

Do we measure bilirubin correctly anno 2005?

Joke J. Apperloo*, Fedde van der Graaf, Volkher Scharnhorst and Huib L. Vader

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Abstract

We observed 30% discrepancy between liquid chemistry and dry chemistry analysers for the determination of total bilirubin in human adult serum samples, which were consistent with a 20% overestimation and 10% underestimation relative to a Jendrassik-Grof reference method, respectively. In contrast, standard reference material SRM916, which was recently recommended as being the most suita-

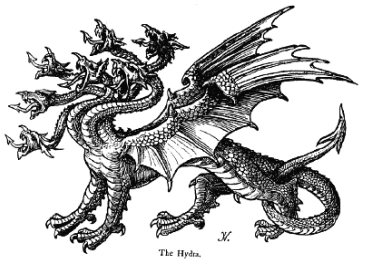
Materials and methods

During several weeks, 20 adult patient samples were selected on the basis of their total bilirubin concentrations to obtain a range more or less evenly distributed from 0 to 400 μmol/L; samples were anonymised, aliquoted into three portions, and frozen directly. The frozen samples (light-protected) were sent to three laboratories. Measurements on different analysers happened at approximately the same time and directly after thawing to minimise interfering effects due to UV degradation. The bilirubin assays for all chemistry analysers (Vitros 250/950, Ortho Diagnostics, Beerse, Belgium; Hitachi 917, Roche, Almere, The Netherlands; Modular, Roche; and Mega, Merck, Darmstadt, Germany) are based on the diazo reaction. The quality of the analysers was assured using calibrations and controls.

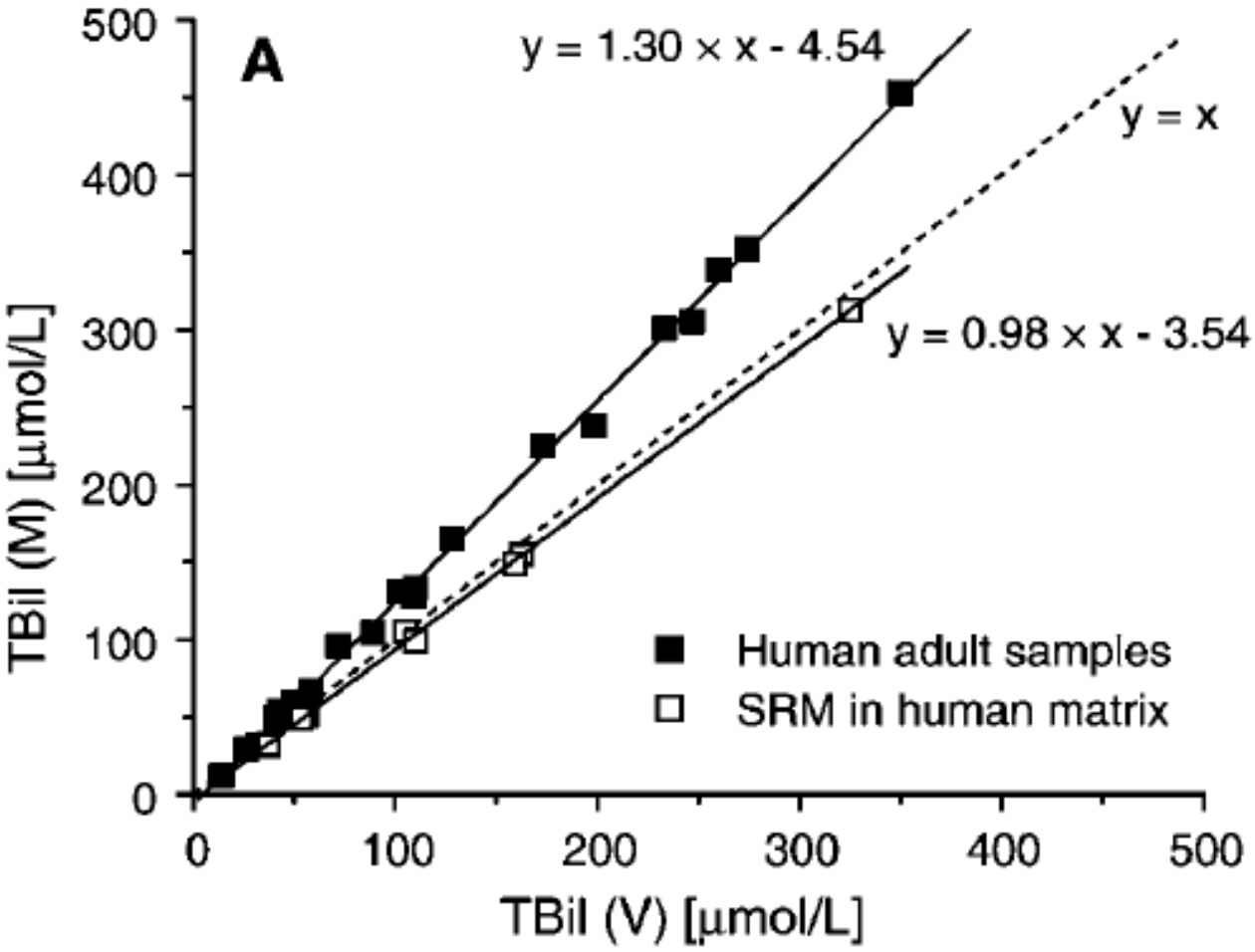
As the reference method, the manual Doumas modified Jendrassik-Grof method was used, according to the description in reference (5). Standard reference materials provided

Do we measure bilirubin correctly anno 2005?

- Observaties in hoge concentratiegebied (300-400 μmol/l)
- 30% verschil tussen vloeistof chemie (Merck Mega en Roche Modular) en droge chemie (Vitros)
  - Mega en Modular 20% verhoogd t.o.v. ref. methode
  - Vitros 10% verlaagd t.o.v. referentiemethode
- SRM916 wordt in beide systemen zeer goed terug gevonden
- Discrepanties lijken te worden veroorzaakt door de aanwezigheid van geconjugeerd of δ-bilirubine



Relatie Vitros 250 ⇔ Modular in monsters volwassenen



Bilirubin Fractions by Method

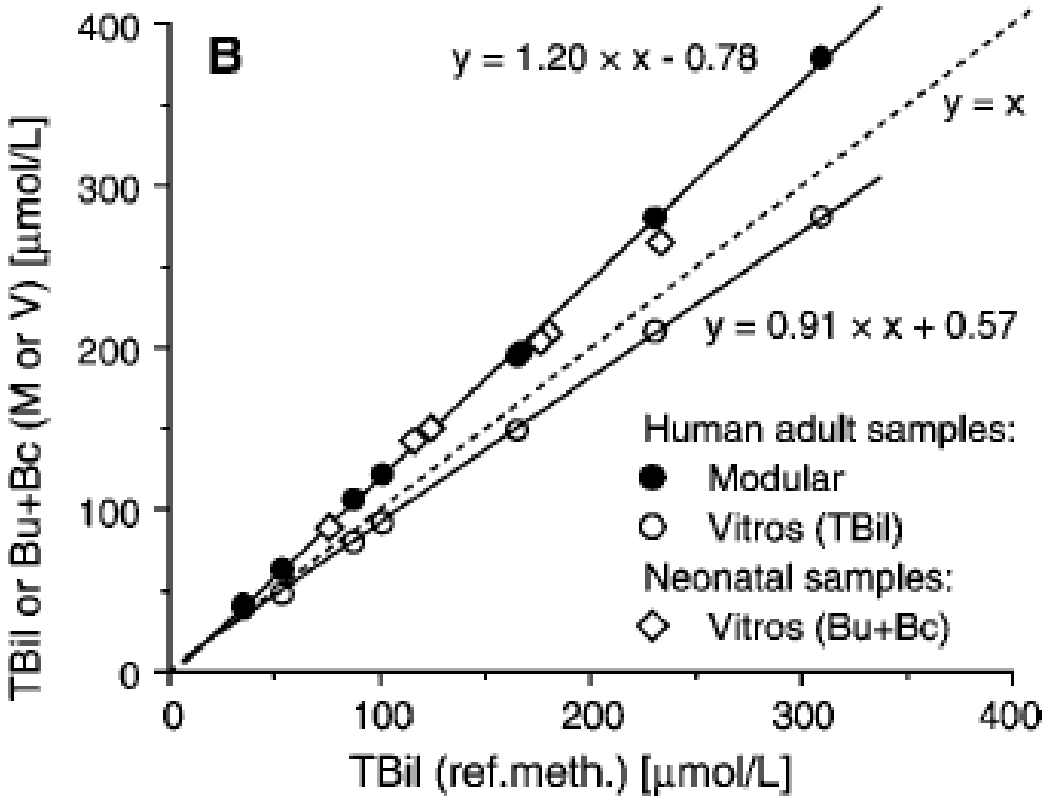
HPLC Peak	α	β	γ	δ
Bilirubin Species	Unconjugated	Singly Conjugated	Doubly Conjugated	Conjugated to Albumin
Traditional Methods	Total			
	Indirect (Total – Direct)	?	Direct	
Vitros Methods	Total			
	Unconjugated (Bu)	**Conjugated** (Bc)		
	Neonatal *(Bu+Bc)*			***Delta*** *(Total – [Bu+Bc])*
		Direct *(Total – Bu)*		

Table 2 Bilirubin fractions present in the human adult serum samples.

Bilirubin concentration, μmol/L							
Vitros 250					Modular		
TBil	Bu	Bc	'δ-bili'[a]	Bd[b]	TBil	Bd	Bu[c]
14	9 (64%)	1 (7%)	4 (29%)	5 (36%)	11.8	–	–
26	13 (50%)	3 (12%)	10 (38%)	13 (50%)	29.3	18.7 (64%)	10.6 (36%)
32	5 (16%)	22 (69%)	5 (16%)	27 (84%)	31.3	29.4 (94%)	1.9 (6%)
41	22 (54%)	4 (10%)	15 (37%)	19 (46%)	49.2	22.7 (46%)	26.5 (54%)
43	26 (60%)	4 (9%)	13 (30%)	17 (40%)	53.7	31.6 (59%)	22.1 (41%)
50	13 (26%)	19 (38%)	18 (36%)	37 (74%)	59.3	38.2 (64%)	21.1 (36%)
58	12 (21%)	39 (67%)	7 (12%)	46 (79%)	66.8	60.2 (90%)	6.6 (10%)
72	23 (32%)	19 (26%)	30 (42%)	49 (68%)	95.7	67.2 (70%)	28.5 (30%)
89	23 (26%)	44 (49%)	22 (25%)	66 (74%)	104.1	–	–
102	31 (30%)	42 (41%)	29 (28%)	71 (70%)	130.6	102.5 (78%)	28.1 (22%)
109	14 (13%)	74 (68%)	21 (19%)	95 (87%)	128.5	117.8 (92%)	10.7 (8%)
110	48 (44%)	43 (39%)	19 (17%)	62 (56%)	133.5	97.5 (73%)	3.6 (27%)
128	14 (11%)	90 (70%)	24 (19%)	114 (89%)	165.1	143.5 (87%)	21.6 (13%)
173	32 (18%)	97 (56%)	44 (25%)	141 (82%)	224.8	198.8 (88%)	26.0 (12%)
198	71 (36%)	95 (48%)	32 (16%)	127 (64%)	237.8	197.4 (72%)	40.4 (28%)
233	38 (16%)	137 (59%)	58 (25%)	195 (84%)	301	–	–
247	34 (14%)	149 (60%)	64 (26%)	213 (86%)	305.5	265.1 (87%)	40.4 (13%)
260	42 (16%)	158 (61%)	60 (23%)	218 (84%)	338.7	295.9 (87%)	42.8 (13%)
274	102 (37%)	117 (43%)	55 (20%)	172 (63%)	352.1	274.5 (78%)	77.6 (22%)
350	56 (16%)	228 (65%)	66 (19%)	294 (84%)	453.2	404.5 (89%)	48.7 (11%)

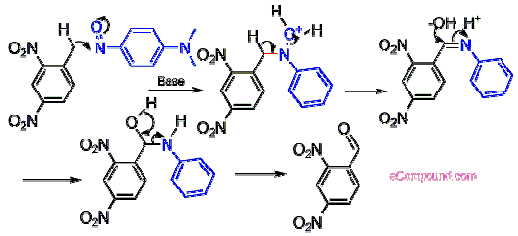
Percentages are relative to TBil. TBil, total bilirubin; Bu, unconjugated bilirubin; Bc, conjugated bilirubin; δ-bili, bilirubin covalently attached to albumin; Bd, directly reacting bilirubin (=conjugated+δ-bilirubin); V, Vitros 250; M, Modular. [a] Calculated as δ-bili (V)=TBil (V)−Bu (V)−Bc (V). [b] Calculated as Bd (V)=Bc (V)+δ-bili (V)=TBil (V)−Bu (V). [c] Calculated as Bu (M)=TBil (M)−Bd (M).

Correlatie tussen Modular/Vitros en referentiemethode



Referentie-techniek (totaal bilirubine

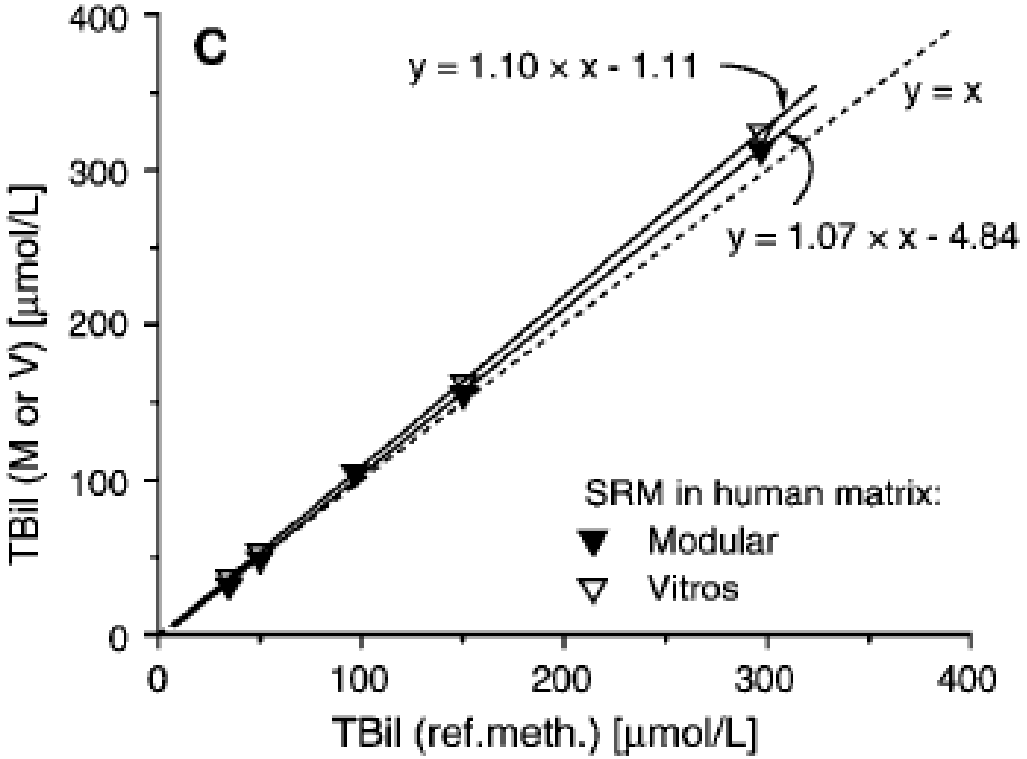
cf. Jendrassik en Gróf



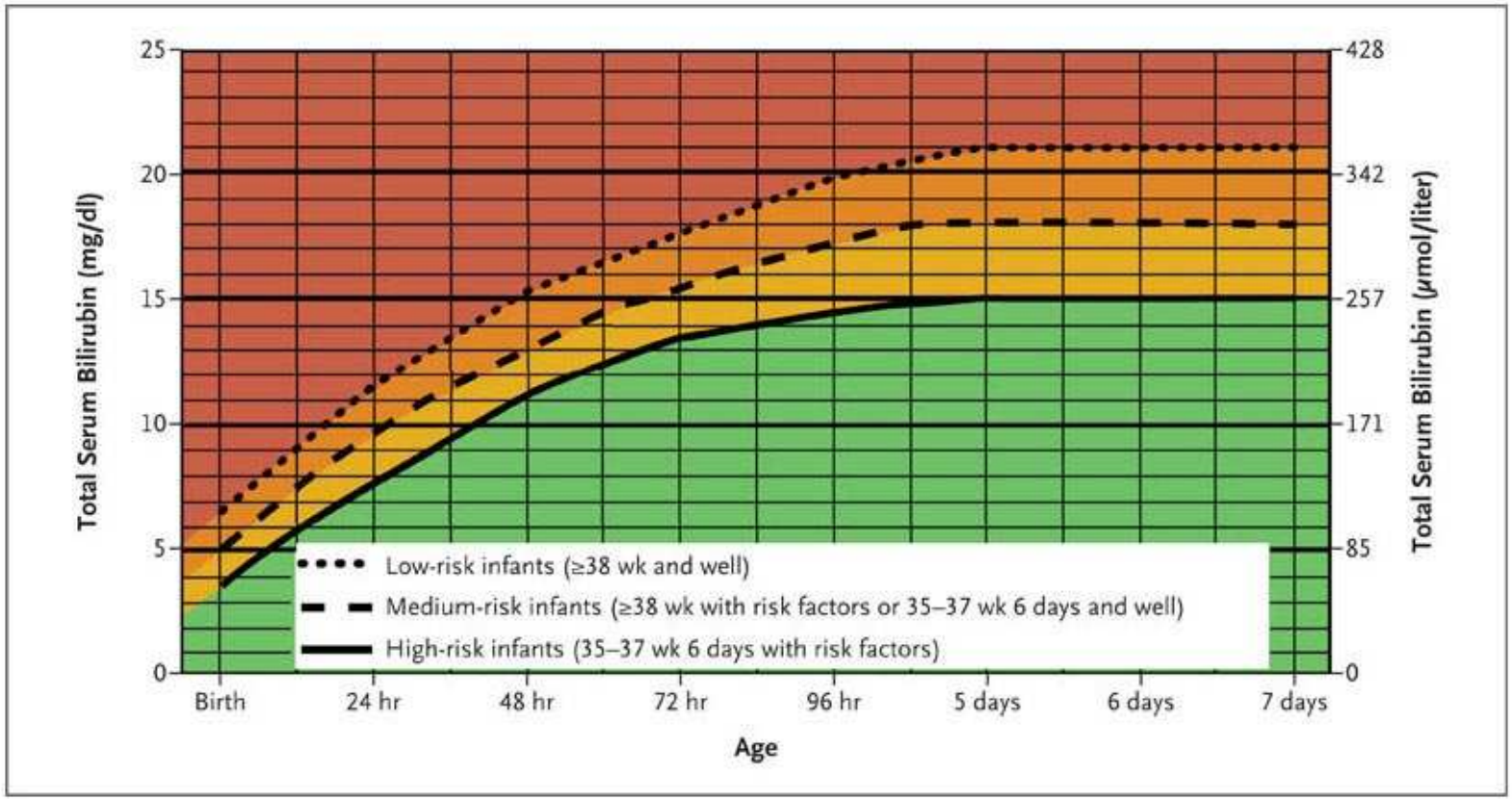
1. Cafeïnereagens (accelerator) wordt toegevoegd aan monster
2. Toevoeging gediazoteerd sulfanylzuur
3. Geconjugeerd en ongeconjugeerd reageren tot azobilirubine (rose)
4. Alkalische tartraatoplossing voor pH shift
5. Meting blauw/groene kleur bij 600nm

SRM916 gemeten op Modular en Vitros

In relatie tot meting met referentiemethode



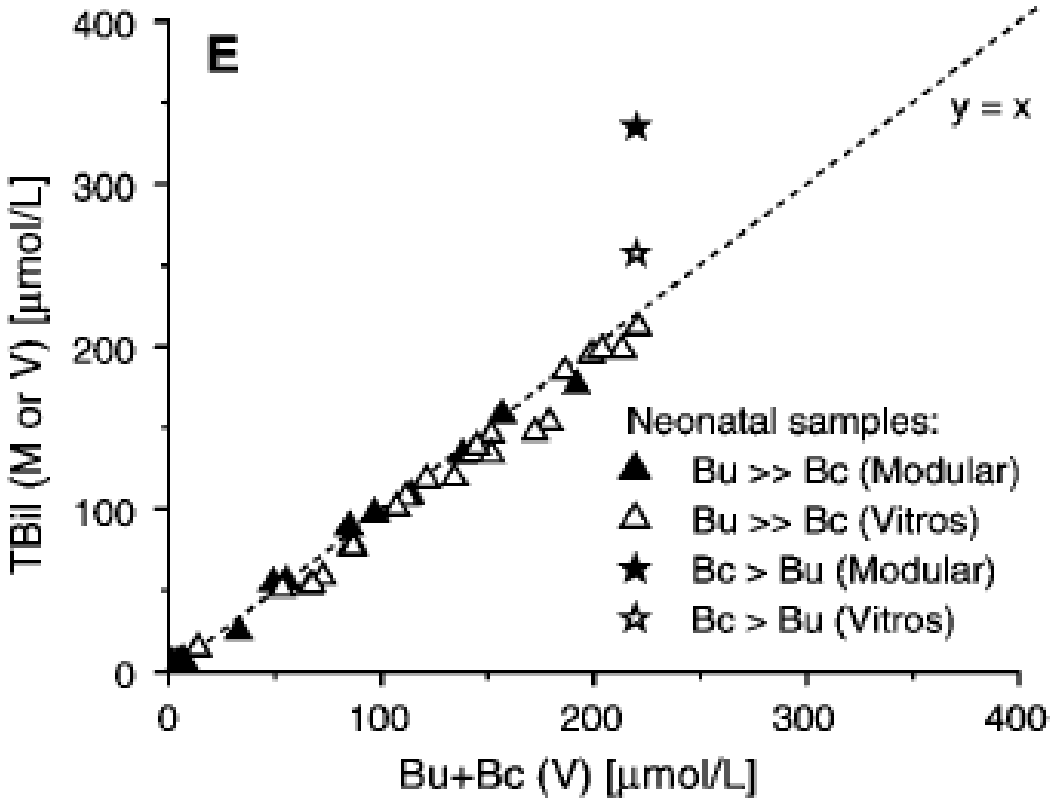
Guidelines for Intensive Phototherapy in Hospitalized Infants Born at a Gestational Age of 35 Weeks or More



Maisels M, McDonagh A. N Engl J Med 2008;358:920-928

The NEW ENGLAND JOURNAL of MEDICINE

Correlatie Vitros/Modular in neonatale monsters



Laboratory Performance in Neonatal Bilirubin Testing Using Commutable Specimens

A Progress Report on a College of American Pathologists Study

Stanley F. Lo, PhD; Bernadine Jendrzejczak, BA; Basil T. Doumas, PhD

• *Context.*—In 2003 the Chemistry Resource Committee of the College of American Pathologists introduced a commutable specimen in the Neonatal Bilirubin Surveys. This specimen was intended to help evaluate all bilirubin methods.

Objective.—To evaluate the effect of commutable specimens on the performance of selected clinical analyzers in measuring neonatal bilirubin from 2003 through 2006.

Design.—A human serum–based specimen enriched with unconjugated bilirubin in human serum has been included since 2003 in the Neonatal Bilirubin Surveys. The bilirubin values of these specimens were determined by the reference method and used to evaluate results reported by various chemistry analyzers.

Results.—Coefficients of variation for College of American Pathologists All Data ranged from 4.9% to 6.2% for the Neonatal Bilirubin Survey. However, coefficients of variation for the 4 major instrument groups (Dimension, Olympus, Synchron, and Vitros), which report 65% of all results, varied from 2% to 3%. College of American Pathologists All Data mean bilirubin values were within 0.46 mg/dL (7.8 μmol/L) of the reference method mean in 2003; in subsequent years these differences became larger, peaking at 1.87 mg/dL (32 μmol/L) in 2005.

Conclusions.—The large systematic error of bilirubin measurements is due primarily to failure of instrument manufacturers to produce reliable bilirubin calibrators. Primary calibrators should consist of human serum enriched with unconjugated bilirubin. Bilirubin values must be assigned by the reference method, the performance and robustness of which are reported in this article. Secondary calibrators distributed to users must be traceable to primary calibrators.

(*Arch Pathol Lab Med.* 2008;132:1781–1785)

Interlaboratory variability in albumin and bilirubin measurements on neonatal intensive care units.

Christian V. Hulzebos, Peter H. Dijk, Deirdre E. van Imhoff, Arend F. Bos,
on behalf of the BARTrial Studygroup
Dept. of Paediatrics, Div. of Neonatology, University Medical Center Groningen, the Netherlands

Background

Guidelines are used for the management of unconjugated hyperbilirubinemia to standardize care of jaundiced newborn infants. Treatment of unconjugated hyperbilirubinemia is based on total serum bilirubin. Measurement of albumin is recommended because low albumin is considered a risk factor for bilirubin encephalopathy. Variability in measurements of bilirubin and albumin levels may affect timing of starting or stopping treatment.
To date, it is unclear whether variability exists in bilirubin or albumin measurements on laboratories of Dutch neonatal intensive care units (NICUs).

Objective

We aimed to assess the variability in measurements of albumin and bilirubin on Dutch NICUs.

Design/Methods

Stabilized quality control samples with different levels of albumin (0, 10, 15, 20, 25 and 30 g/L) and bilirubin (100, 200, 300, 400, and 500 µmol/L) were sent to laboratories of all Dutch NICUs (n=10). The mean, standard deviation (SD) and coefficients of variations (CV) were calculated per sample.

Level	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Albumine (g/l)	30	25	20	20	20	20	20	20	15	10	10	10	10	10	10	0	0	0	0	0
Bilirubine (µmol/l)	0	0	0	100	200	300	400	500	0	0	100	200	300	400	500	0	100	200	300	400

Combinations of Albumin and Bilirubin levels in Quality Control Samples.
Values in the blue boxes are used in Figures 1A and 1B.

Results

Measured albumin levels were ~ 10% lower than levels of albumin in quality control samples. Maximal CV was 6.8 % (Table). Maximal CV of measured bilirubin levels was 9.2% (data not shown).

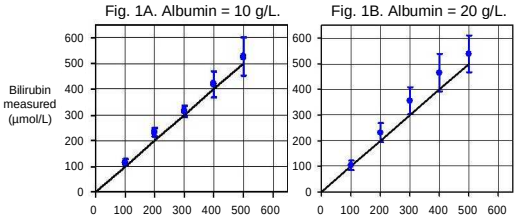
Table. Results of measurements of albumin levels.

Albumin (g/L)	Mean ± SD	CV
30	27.2 ± 1.0	3.5
25	22.6 ± 0.9	4.0
20	18 ± 0.7	3.7
15	13.3 ± 0.7	5.3
10	8.9 ± 0.6	6.8

Data represent mean ± SD, or coefficients of variations (CV=SD/ mean)

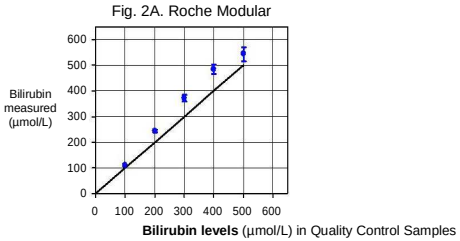
Bilirubin levels of the QC samples were overestimated and a large interlaboratory variation was found (Figure 1A & B).

Figure 1. Measured Bilirubin Levels vs. Bilirubin Levels of Quality Control Samples for Albumin Levels of 10 (Fig.1A) and 20 g/L (Fig.1B).



Differences in methodology may contribute to the observed interlaboratory variability. However, comparison of bilirubin measurements of laboratories using the same device yielded similar accuracy and variabilty (Figure 2).

Figure 2. Measured Bilirubin Levels vs. Bilirubin Levels of Quality Control Samples using the same method (Roche Modular (2A).



Conclusions

1. Accuracy of albumin and bilirubin measurements on laboratories of Dutch NICUs is poor.
2. Considerable variability in albumin and bilirubin measurements exists between laboratories of Dutch NICUs potentially affecting treatment of jaundiced newborn infants.

Recommendations to improve care of jaundiced newborn infants

1. Accuracy of albumin and bilirubin measurements needs to be improved by recalibration.
2. Quality Control Samples with age-specific ranges of albumin and bilirubin should be used to reduce the large interlaboratory variability.

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Available online at www.sciencedirect.com
ScienceDirect
Clinical Biochemistry 42 (2009) 1328–1330
CLINICAL BIOCHEMISTRY

Interlaboratory comparison of the Doumas bilirubin reference method

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Received 13 February 2009; received in revised form 11 May 2009; accepted 19 May 2009
Available online 22 May 2009

Abstract

Objectives: To assess the performance of the Doumas bilirubin reference method.

Design and methods: Ring trails using pooled patient specimens, a calibrator and human sera enriched with unconjugated bilirubin were analyzed in five laboratories using the Doumas bilirubin reference method.

Results: The coefficient of variation for the linear measurement range between laboratories ranged from 1–3%.

Conclusions: The Doumas bilirubin reference method is robust and reproducible. Bilirubin results using this method may be used in the development of more accurate and reliable calibrators.

Table 1
Ring trial #1. Specimens of unconjugated bilirubin in bovine serum albumin analyzed for total bilirubin by the reference method: results (mg/dL[a]) and statistics.

	Total bilirubin, mg/dL					Statistics		
Lab	A	B	C	D	E	Mean	SD	CV%
Specimen								
1	0.98	1.01	1.00	1.05	1.05	1.02	0.03	3.06
2	1.96	2.06	2.07	2.07	2.12	2.06	0.06	2.85
3	4.12	4.14	4.13	4.09	4.22	4.14	0.05	1.17
4	10.19	10.29	10.29	10.39	10.54	10.34	0.13	1.28
5	20.12	20.52	20.26	20.60	20.51	20.40	0.20	0.99

[a] To convert mg/dL to mmol/L, multiply by 17.1.

Na correctie voor onzuiverheid in SRM916a varieerden de resultaten in monster 5 van 344 tot 346 µmol/l

Table 2
Human serum pools analyzed for total bilirubin by the reference method: results (mg/dL [a]) and statistics.

Lab	Total bilirubin, mg/dL						Statistics		
	A	B		C	D	E	Mean [b]	SD [b]	CV% [b]
		Run #1	Run #2						
Specimen									
1	0.39	0.56	0.43	0.44	0.40	0.45	0.42	0.03	6.13
2	2.10	2.44	2.14	2.14	2.06	2.17	2.12	0.04	2.01
3	3.45	3.96	3.57	3.48	3.36	3.53	3.48	0.08	2.31
4	4.74	5.72	4.87	4.80	4.65	4.90	4.79	0.10	2.10
5	6.50	7.38	6.63	6.47	6.36	6.69	6.53	0.13	2.01
6	2.11	2.39	2.21	2.18	2.22	2.24	2.19	0.05	2.31
7 [c]	4.23	4.18	4.12	4.22	4.19	4.36	4.22	0.09	2.07

[a] To convert mg/dL to mmol/L, multiply by 17.1.
[b] Data from laboratory B, Run #1, were not included in the statistical calculations.
[c] Specimen #7 is a calibrator for Roche instruments.

Abbott Laboratories
100 Abbott Park Road
Abbott Park, IL 60064-6081

Field Safety Corrective Action
Product Correction
Immediate Action Required

Date Issued September 18, 2008

Product

Product Name	List Number	Lot Number
Clinical Chemistry Bilirubin Calibrator	1E66-04	61388M100, 57919M100 54754M100, 52632M100
Clinical Chemistry Total Bilirubin Reagent	8G62-20 6L45-20 6L45-40	All Lots

Explanation Customers have reported the following issues for Total Bilirubin (LN 8G62 and 6L45):

- Higher than expected results on proficiency survey samples
- Higher than expected Quality Control (QC) recovery
- Higher than expected patient results

An investigation was initiated for the Total Bilirubin reagents (LN 8G62 and LN 6L45) and determined that the matrix of the secondary standard used in the value assignment of the calibrator is sensitive to the Diazo method. The matrix of this secondary standard caused a positive bias.

Because of these findings, a new Total Bilirubin calibrator value assignment process will be implemented for use with the Total Bilirubin reagents listed above. The revised values will lower total bilirubin results up to 18% based on the method correlation in Attachment E.

Roche

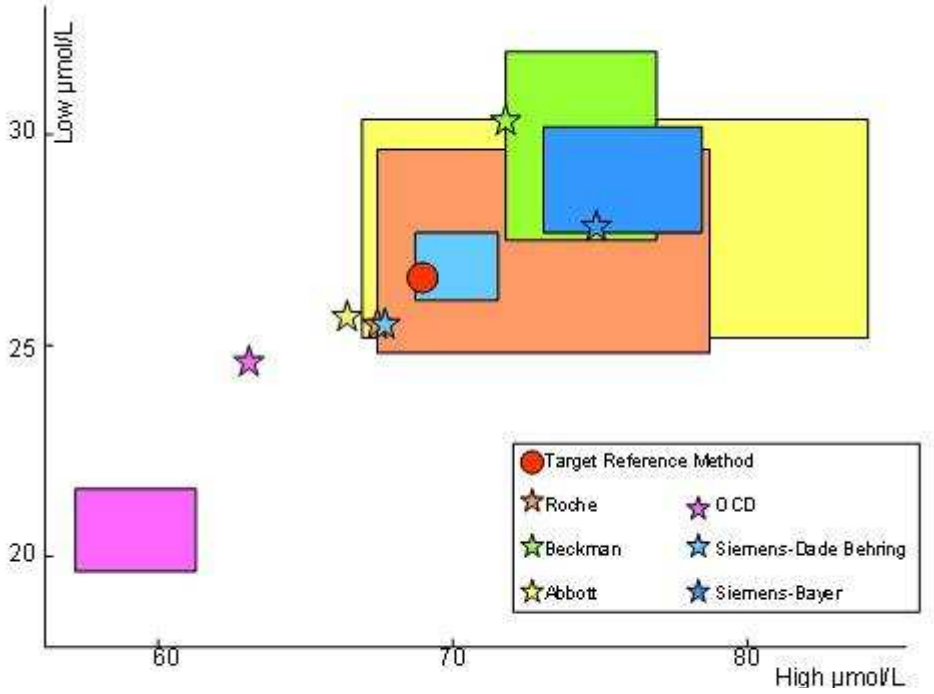
Diagnostics

Máxima Medisch Centrum Locatie Veldhoven
De hooggeleerde heer
Prof.dr.ir. H.L. Vader
Hoofd Laboratorium
Postbus 7777
5500 MB VELDHOVEN

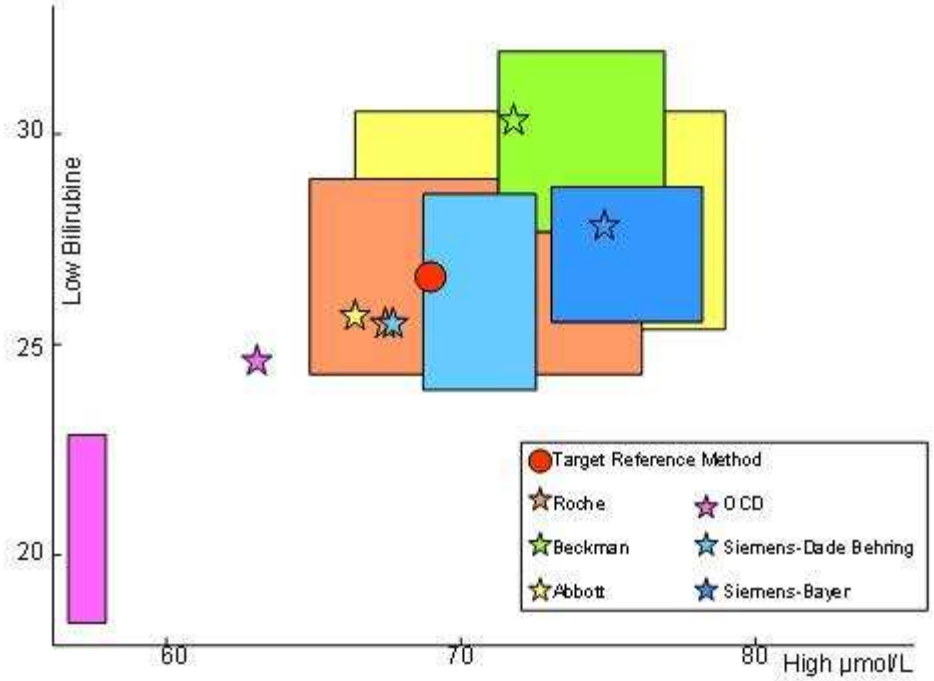
Almere, 18 december 2008
Betreft: Herstandaardisatie Totaal Bilirubine op Roche analyzers

Geachte heer Vader,

De mailing van 24 november jl. over bovengenoemd onderwerp heeft veel reacties opgeroepen. Een toelichting op deze standaardisatie lijkt dus op zijn plaats.



2009-2



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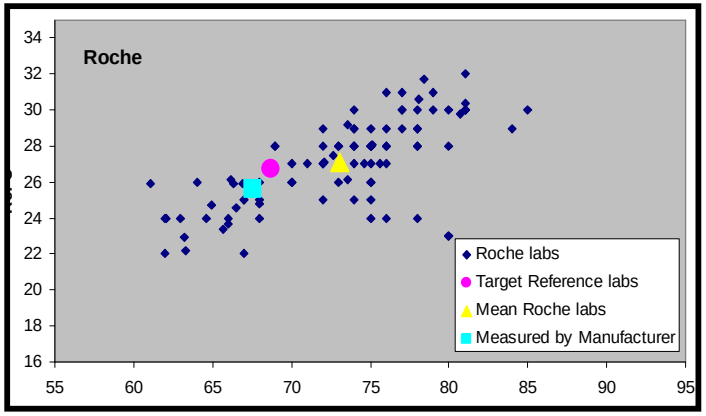
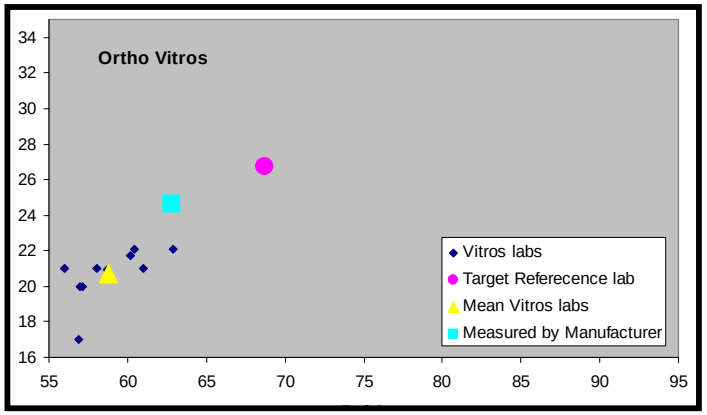
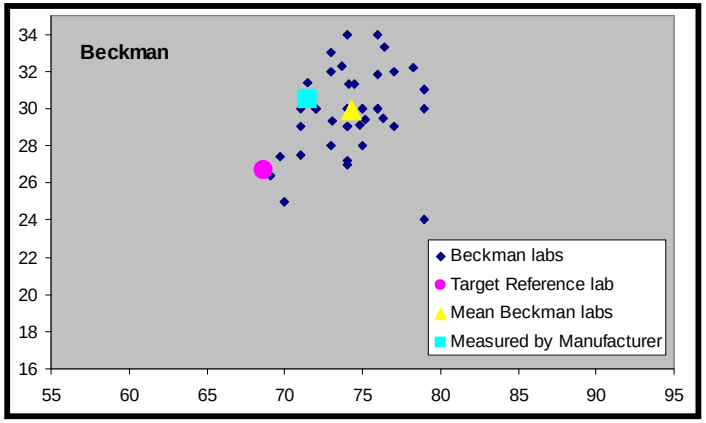
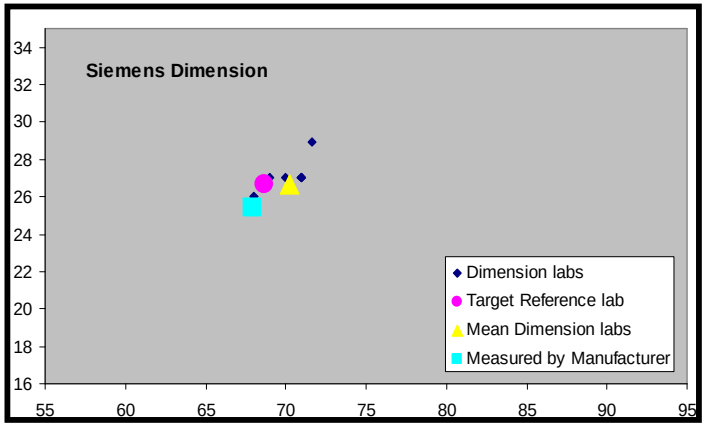
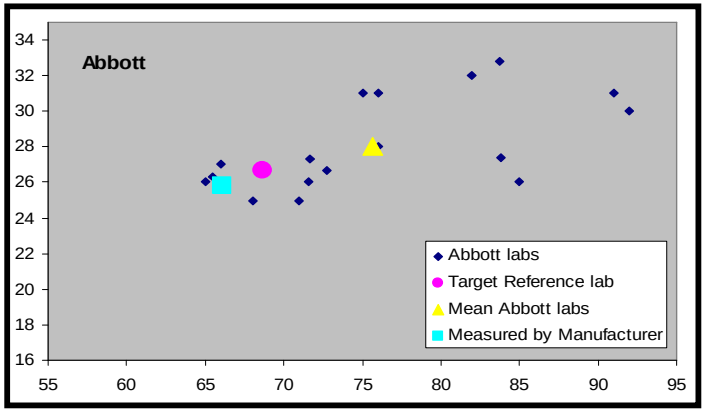

Roche
Roche labs
Target Reference labs
Mean Roche labs
Measured by Manufacturer


Ortho Vitros
Vitros labs
Target Referecence lab
Mean Vitros labs
Measured by Manufacturer


Beckman
Beckman labs
Target Reference lab
Mean Beckman labs
Measured by Manufacturer


Siemens Dimension
Dimension labs
Target Reference lab
Mean Dimension labs
Measured by Manufacturer


Abbott
Abbott labs
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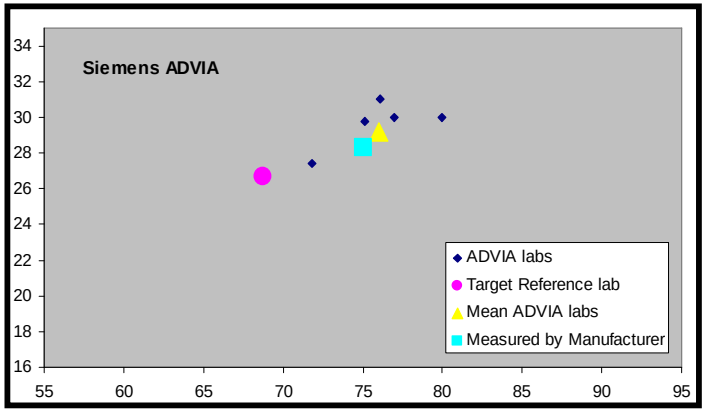

Siemens ADVIA
ADVIA labs
Target Reference lab
Mean ADVIA labs
Measured by Manufacturer

Number of participants per method, mean and SD in February 2009, September 2009 and March 2010

Methode	Number of Labs			Low Level						High level					
				Concentration			SD			Concentration			SD		
	Feb 2009	Sept 2009	Mrt 2010	Feb 2009	Sept 2009	Mrt 2010	Feb 2009	Sept 2009	Mrt 2010	Feb 2009	Sept 2009	Mrt 2010	Feb 2009	Sept 2009	Mrt 2010
Abbott	19	20	19	28.0	28.4	21.1	2.6	2.5	1.3	75.7	72.5	76.8	8.7	6.4	4.6
Siemens ADVIA	7	4	3	29.4	24.5	21.5	1.2	3.3	0.7	76.0	75.1	78.9	2.6	2.2	0.2
Siemens Dimension	7	11	17	27.1	25.8	19.5	1.0	2.0	1.4	70.2	71.6	76.2	1.3	2.7	3.9
Beckman	42	42	41	29.9	30.3	23.0	2.2	2.0	2.0	74.3	73.9	79.0	2.6	3.2	3.0
Olympus	-	-	9	-	-	22.6	-	-	2.1	-	-	78.1	-	-	2.9
Roche	99	117	120	27.1	26.4	19.2	2.4	2.2	1.9	73.1	70.6	73.0	5.6	5.6	5.8
Roche without high	-	-	103	-	-	18.8	-	-	1.6	-	-	71.6	-	-	3.8
Ortho Vitros	9	3	3	20.6	20.6	17.2	1.2	2.4	1.6	59.1	53.6	63.1	2.1	1.0	6.3
Target				26.7	26.7	20.0				68.7	68.7	72.6			

Table 2. Measured Bilirubin levels as percentage of the value of the reference laboratory.

Manufacturer	Low Bilirubin Level			High Bilirubin Level		
	SKML Labs			SKML Labs		
	February	September	March 2010	February	September	March 2010
Roche	101	99	96	106	103	101
Beckman	112	113	115	108	108	109
Olympus			113			108
Abbott	105	106	106	110	106	106
Ortho Vitros	77	77	94	86	78	87
Siemens Dimension	101	97	98	102	104	105
Siemens Advia	109	92	108	111	110	109

Green: percentages from 96 – 104%
Amber: percentages from 91 -95 and 105 – 109%
Red: percentages <91 and >109%

Clin Chem. 2010 May;56(5):869-72. Epub 2010 Mar 5.

Bovine serum-based bilirubin calibrators are inappropriate for some diazo methods.

Lo S, Jendrzejczak B, Doumas BT.

- di-taurobilirubine en BSA (gebruikt in de meeste commerciële kalibratoren) interfereren in de bilirubinebepaling
- UBIL en TBIL worden toegevoegd aan verschillende eiwit-matrices
- meting op 7 analysers met diazo methoden
- in bovine sera worden veel lagere concentraties gevonden dan in humane sera
- verschil sterker in commerciële bovine preparaten dan in abattoir serum. Inhibitoren diazoreactie / acceleratoren?

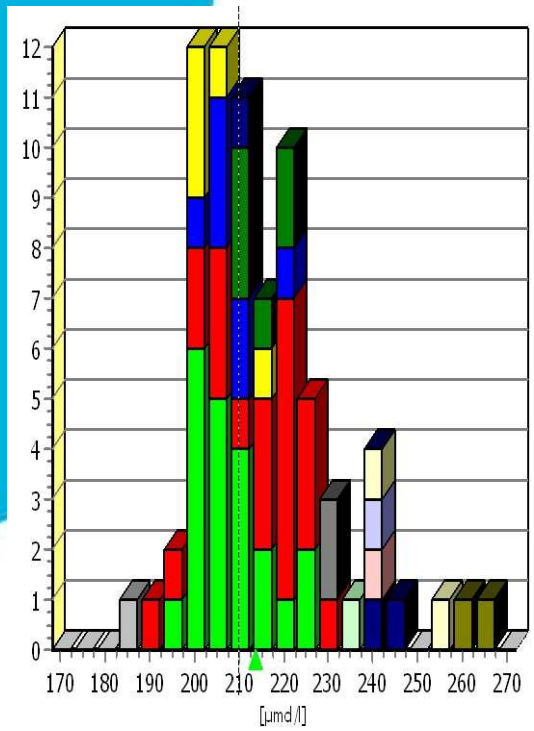
Clin Chem. 2010 May;56(5):869-72. Epub 2010 Mar 5.

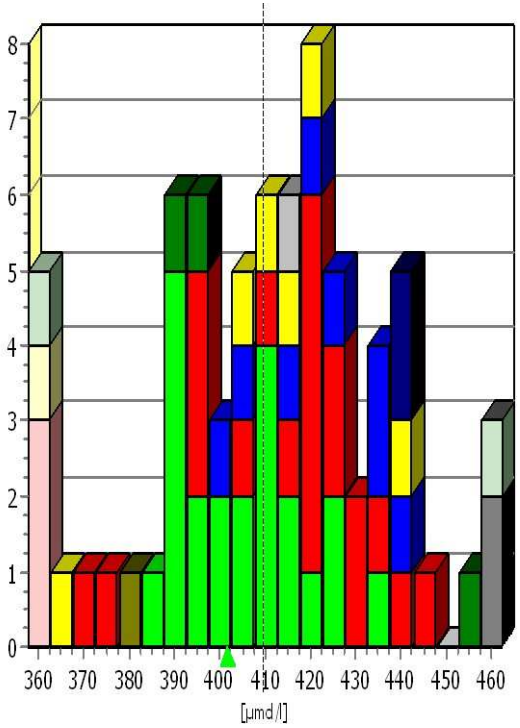
Bovine serum-based bilirubin calibrators are inappropriate for some diazo methods.

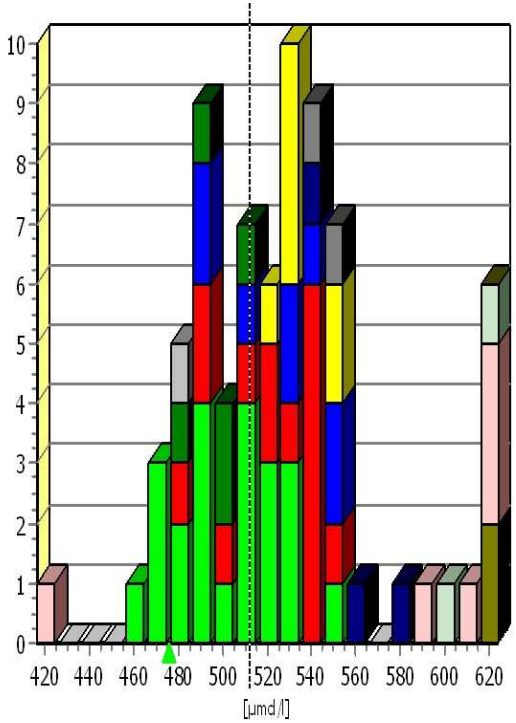
Lo S, Jendrzejczak B, Doumas BT.

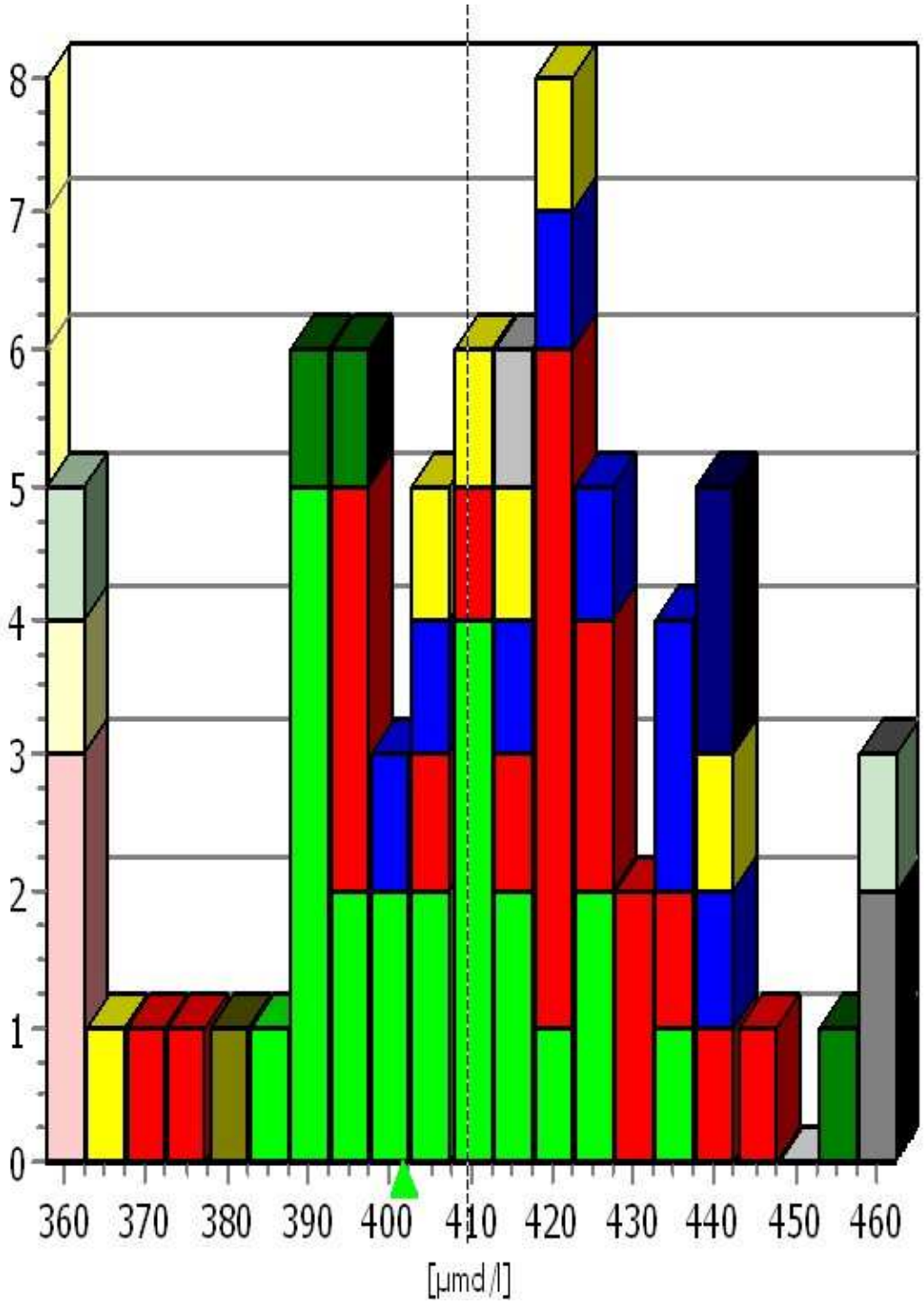
- Onvoldoende recovery DTB in humaan serum door Vitros en Architect
- In verse bovine matrix (abattoir) 5 van de 7 analysers goed
- In de commerciële bovine sera laten alle analysers een te lage recovery van DTB zien
- Auteurs gebruiken reeds 20 jaar BSA, nooit problemen
- Inhibitoren uit voeding of bij processing gebruikte containers? Azide? Aging? → auteurs vinden geen verklaring
- **“The solution to this problem is simple: Use human instead of bovine serum for preparing bilirubin calibrators”**

Resultaten SKML neonatale bilirubine 2010.1









- DiCl-Phenyl Diaz.zout (DPD)
- Jendrassik-Grof, automatisch
- Ictometer, meting gele kleur
- Diazo-p-nitraniline
- Evelyn Malloy
- Vanadaat oxidatie
- Vitros Bilirubine
- Spectrofotometrisch met verdunning
- Spectrofotometrisch zonder verdunning

SKML 2010.B

		GEM µmol/l	SD µmol/l	VC %
2010.1A		215	15	7.2
2010.1B		414	26	6.3
2010.1C		524	38	7.2
2010.1D		405	25	6.3
2010.1E		214	13	6.2
2010.1F		312	18	5.8

2010.1D	n	GEM µmol/l	SD µmol/l	VC %
Diazo-p-nitroaniline	8	409	12	2.8
Jendrassik-Grof. Autom.	23	407	25	6.0
DiCl-phenyl diaz. Zout (DPD)	25	403	18	4.4
Jendrassik-Grof achtigen	63	405	20	4.8
Ictometer	8	419	14	3.2
spectrofotometrisch	12	418	13	3.1

Wisselwerking tussen kliniek en laboratorium:

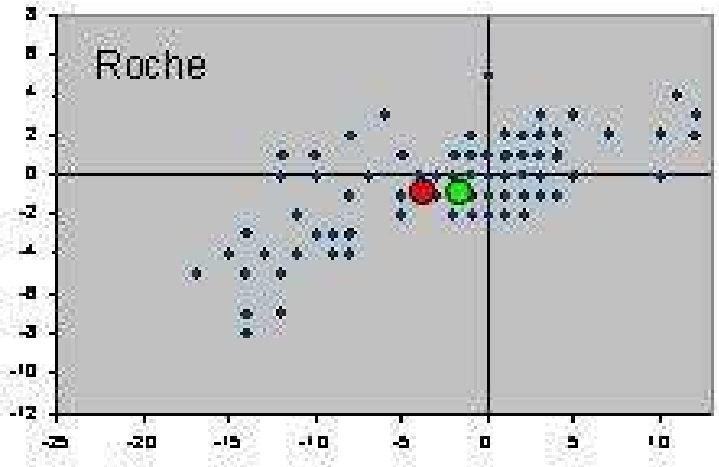
staat het sein op groen of rood ?

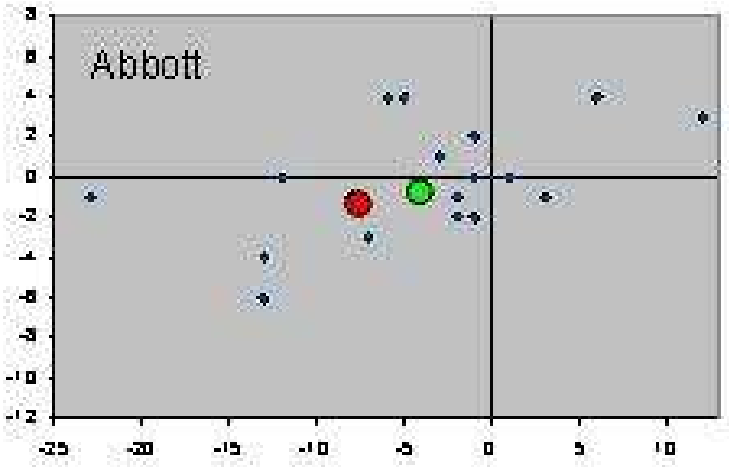
Met dank aan

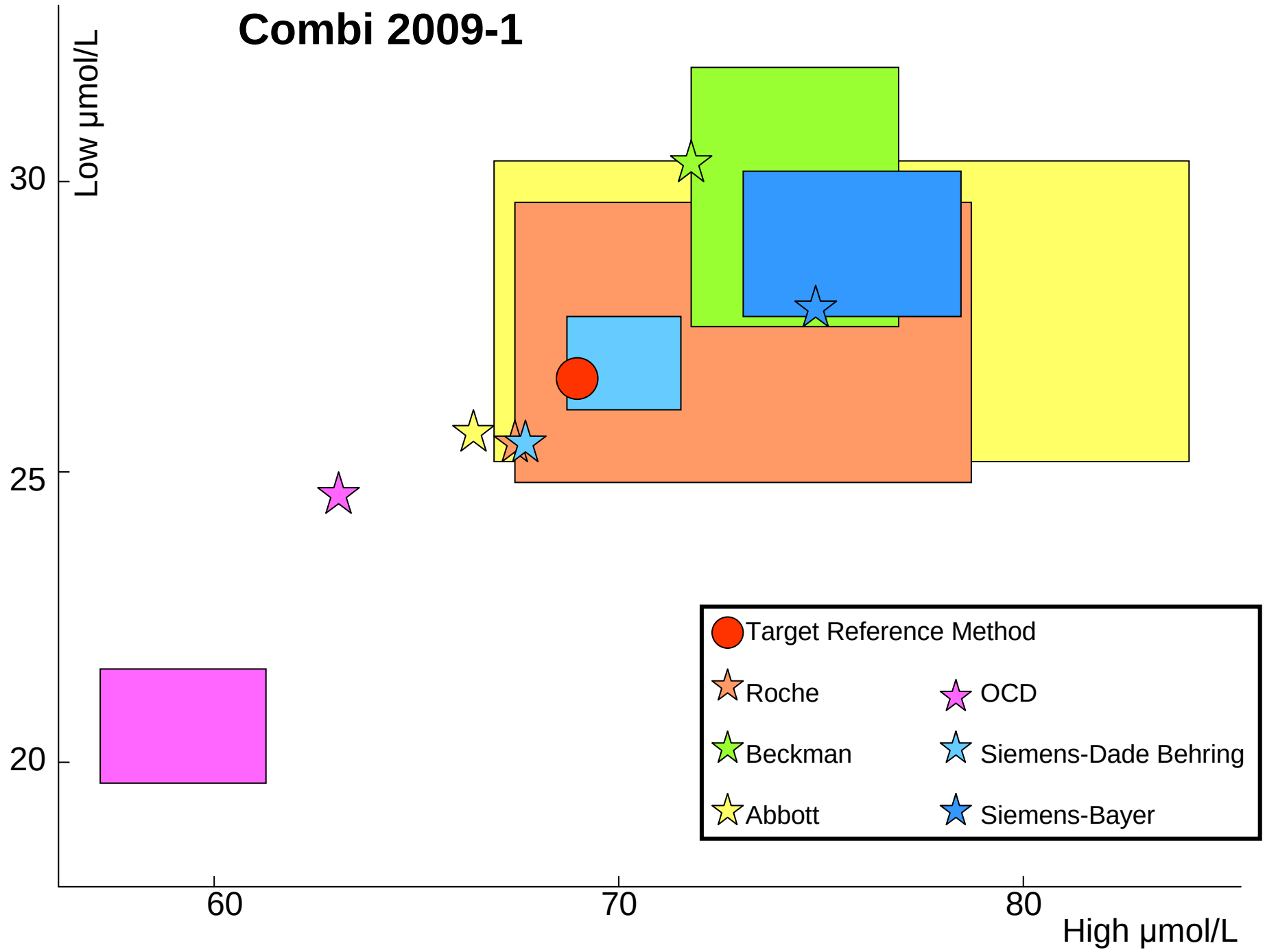
dr. Cas Weykamp

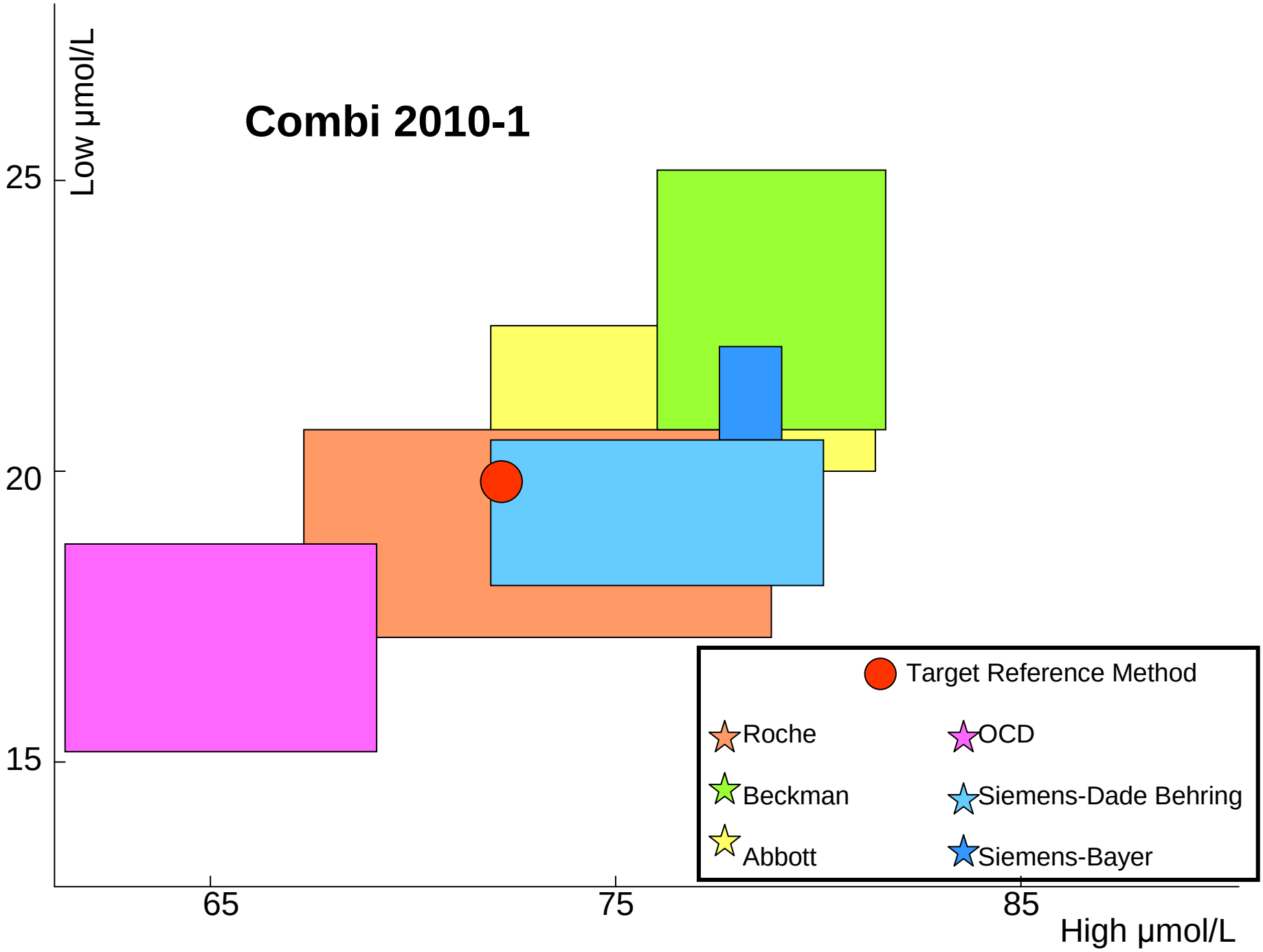
Ing. Riejean Kuylaars

dr. Joke Apperloo


Roche


Abbott


Combi 2009-1
Low µmol/L
30
25
20
60
70
80
High µmol/L
Target Reference Method
Roche
OCD
Beckman
Siemens-Dade Behring
Abbott
Siemens-Bayer


Combi 2010-1
Low µmol/L
25
20
15
65
75
85
High µmol/L
Target Reference Method
Roche
OCD
Beckman
Siemens-Dade Behring
Abbott
Siemens-Bayer