LCSI: LeadCare Situation Investigation

Anatomy of the LeadCare Product Recall

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ESA LeadCare Analyzer

- A portable device for measuring blood lead (BPb) levels.
- Based on Anodic Stripping Voltammetry (ASV).
- Uses disposable screen-printed electrodes
- Requires blood to be "treated" with a reagent that decomplexes lead bound to proteins.
- Takes around 3-4 minutes per analysis

ESA LeadCare

- Calibration using an electronic button.
- Buttons are specific to each batch of sensors
- Blood specimens are treated with reagent for 1 minute.
- Treated blood deposited on the sensor

ESA LeadCare

- Advantages:
  - Moderately complex but easy to use.
  - Dr's office use
  - Rapid results (3-4 m)
  - Low cost device (~$2K)
  - $7 a test
  - Can operate @ 9V

ESA LeadCare

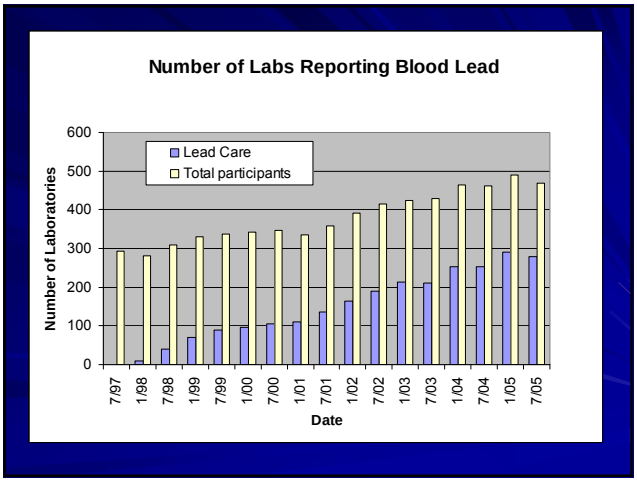
- Limitations:
  - Blood must be fresh (<24 hrs old)
  - Cannot refrigerate blood
  - Response is affected by glutathione
  - Sensor lots may vary
  - Temperature sensitive

WI Proficiency Program

- Bureau of Maternal and Child Health sponsors the PT program
- Our cows are dosed with lead, so it is biologically bound
- The samples are aliquoted and stored frozen until shipment
- Mailed to participants, who analyze the samples and report results back, which are then graded

WI Proficiency Program

- Target values are determined by a group of referee laboratories
- LeadCare targets are determined by participant mean
- Currently there ~600 labs in the program, about half are LeadCare
  - ~40 International labs
- Offer two types of Programs
  - Regulatory Program
  - Monthly Blood Lead Program



LeadCare Recall Chronology

- In May 1997, data[1] was presented comparing the LC prototype with a reference method. It was concluded that it was accurate for screening children
- In September, the LeadCare is commercially introduced
- In October, LeadCare users begin to enroll in the WI PT Program

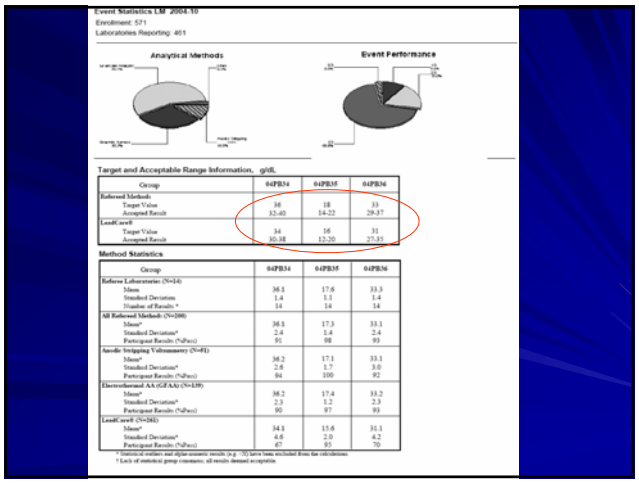
1. Shannon M and Rifai N. The Accuracy of a Portable Instrument for analysis of Blood Lead in Children. Amb Child Health 1997;3:249-254

LeadCare Recall Chronology

- It was expected that the samples would exhibit a positive bias, relative to other methods
  - Due to specimen prep and absence of glutathione
- This positive bias was observed in early PT events
- Consequently, in December 1997, it was decided that LeadCare results should be evaluated as a separate group

LeadCare Recall Chronology

- In January 2000, our enrollment had grown from 9 to approximately 100 and the positive bias had disappeared
- The LeadCare now exhibited a low bias compared to other methods
- Despite several cooperative efforts by ESA and WI, the reason for this trend was not determined


Event Statistics LM 2004.10
Enrollment: 571
Laboratories Reporting: 461

Analytical Methods

Event Performance

Target and Acceptable Range Information, g/dL

Group	04PB34	04PB35	04PB36
Referee Methods:			
Target Value	36	18	33
Accepted Result	32-40	14-22	29-37
LeadCare®			
Target Value	34	16	31
Accepted Result	30-38	12-20	27-35

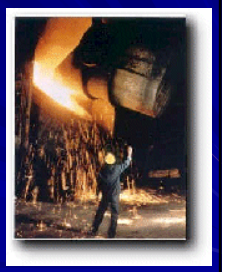
Method Statistics

Group	04PB34	04PB35	04PB36
Referee Laboratories: (N=14)			
Mean	36.1	17.6	33.3
Standard Deviation	1.4	1.1	1.4
Number of Results *	14	14	14
All Referee Methods: (N=200)			
Mean*	36.1	17.3	33.1
Standard Deviation*	2.4	1.4	2.4
Participant Results (%Pass)	91	98	93
Anodic Stripping Voltammetry (N=81)			
Mean*	36.2	17.1	33.1
Standard Deviation*	2.6	1.7	3.0
Participant Results (%Pass)	94	100	92
Electrothermal AA (GFAA) (N=139)			
Mean*	36.2	17.4	33.2
Standard Deviation*	2.3	1.2	2.3
Participant Results (%Pass)	90	97	93
LeadCare® (N=261)			
Mean*	34.1	15.6	31.1
Standard Deviation*	4.8	2.0	4.2
Participant Results (%Pass)	67	95	70

* Statistical outliers and alpha-numeric results (e.g. <5) have been excluded from the calculations.
* Lack of statistical group consensus; all results deemed acceptable.

LeadCare Recall Chronology

- In June 2001, Taylor, Jones, et all, report that a comparative study of occupationally exposed adults demonstrated a modest positive bias for the LC compared to a referee method[2]



2. Taylor L, Jones RL, Kwan L, Deddens JA, Ashley K, and Sanderson WT. Evaluation of a portable blood lead analyzer with occupational exposed populations. Am J Ind Med 2001;40:354-362

LeadCare Recall Chronology

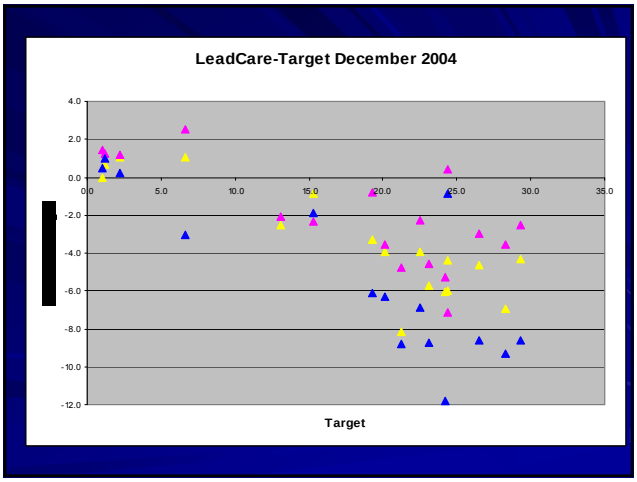
- In August 2004, the Blood Lead PT program administered by NY State reports a low bias in LeadCare results compared to other methods
  - NY provides fresh whole animal blood
  - Directly compare LeadCare with other methods
- Failure rates of 69% and 38% for the previous two PT events
  - Failure rates had previously been below 10%
- In November, there continues to be a low bias and NY gave the directive to report only qualitative results (≥10 µg/dL or <10 µg/dL)

Is the Bias Real?

- Artifact of Animal Blood?
- Artifact of the processing?

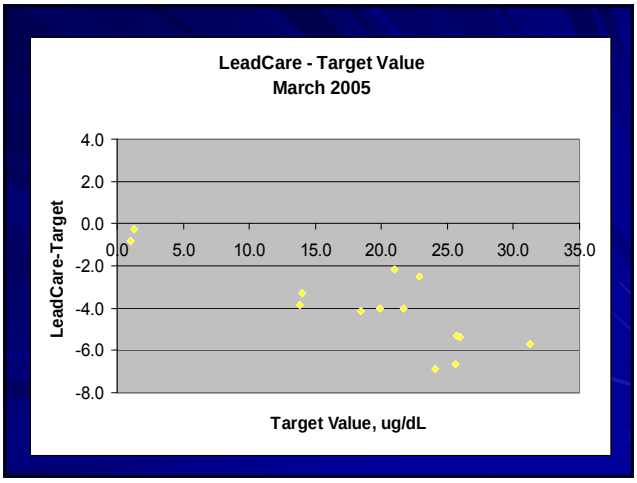
LeadCare Recall Chronology

- In December 2004, WSLH and ESA initiate a cooperative evaluation study using fresh human blood from occupationally exposed workers
- Three sensor lots were examined and all three demonstrated a low bias



What happened next?

- ESA reviewed data and requested additional studies…
- WSLH conducted a second study, using fresh human blood from exposed workers
  - The blood was placed in reagent at WSLH and shipped to ESA for analysis
  - A fourth sensor lot was used
  - Shipped to ESA in Feb. 2005



Spring 2005

- WI shared data with representatives from NY and CDC seeking comment
- Contacted Bureau of Maternal & Child Health (MCH) about the bias and shared data
  - Conference call was held with MCH, ESA, WI, and CDC to discuss issue

Spring 2005, cont'

- Correspondence from the CDC, that more data is needed, especially since the results were from occupationally exposed adults and not children
- Noted a CDC publication regarding positive bias on adult blood

Spring 2005, cont'

- Beginning in April we started asking our participants in the PT program to provide us with their sensor lot code for further investigations
- There were 2 labs using a new lot, and their results were higher than the other LeadCare labs and the referee targets
- Shared this data with ESA

Spring 2005, cont'

- May 3, WI receives the newest lot of LC sensors to evaluate.
- ESA indicates that this new lot should read higher than other lots on the PT specimens, but not on patient specimens
  - This is attributed to "different glutathione sensitivity"

Spring 2005, cont'

- May 12, Testing of the new lot is completed. And as anticipated, results on the PT specimens were higher
- May 12, WI concludes that the bias is real and recommends that LeadCare users should be notified and contacts MCH

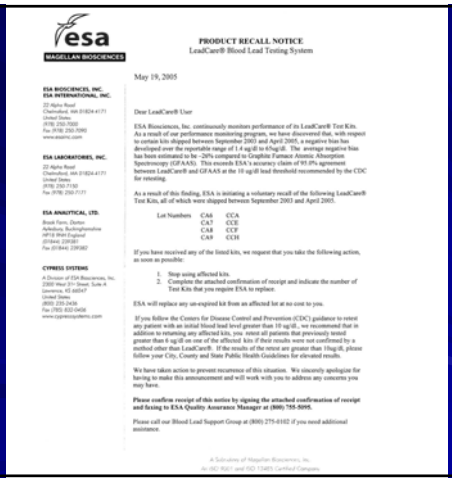
Sample #	Lot CCA Average	Referee Targets	Lot CCJ Average
0602-01	0.6	1.0	0.7
0602-02	0.9	1.5	1.0
0602-03	20.1	23.9	26.0
0602-04	23.4	28.2	28.1
0602-05	15.4	19.8	20.8
0602-06	12.2	16.2	16.9
0602-07	14.3	19.0	18.1
0602-08	18.4	25.8	26.3
0602-09	38.5	20.3	43.5
0602-10	14.8	22.2	19.3
0602-11	11.4	17.2	15.0
0602-12	11.9	17.8	17.3
0602-13	20.0	26.8	27.7

Spring 2005, cont'

- May 13, Contacted by ESA that they were voluntarily issuing a recall.
- The recall was prompted by the studies with WI and additional in-house testing

Spring 2005, cont'

- May 20, WI receives the official recall notice issued by ESA.
- The notice states that a low bias of 26% was detected for sensor lots dating back to September 2003.
- 8 lots were recalled
- Recommendation to retest children with lead levels exceeding 6 ug/dL



esa
MAGELLAN BIOSCIENCES

PRODUCT RECALL NOTICE
LeadCare® Blood Lead Testing System

May 19, 2005

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www.cypresssystems.com

Dear LeadCare® User

ESA Biosciences, Inc. continuously monitors performance of its LeadCare® Test Kits. As a result of our performance monitoring program, we have discovered that, with respect to certain kits shipped between September 2003 and April 2005, a negative bias has developed over the reportable range of 1.4 ug/dl to 65ug/dl. The average negative bias has been estimated to be ~26% compared to Graphite Furnace Atomic Absorption Spectroscopy (GFAAS). This exceeds ESA's accuracy claim of 95.0% agreement between LeadCare® and GFAAS at the 10 ug/dl lead threshold recommended by the CDC for retesting.

As a result of this finding, ESA is initiating a voluntary recall of the following LeadCare® Test Kits, all of which were shipped between September 2003 and April 2005.

Lot Numbers		
	CA6	CCA
	CA7	CCE
	CA8	CCF
	CA9	CCH

If you have received any of the listed kits, we request that you take the following action, as soon as possible:

1. Stop using affected kits.
2. Complete the attached confirmation of receipt and indicate the number of Test Kits that you require ESA to replace.

ESA will replace any un-expired kit from an affected lot at no cost to you.

If you follow the Centers for Disease Control and Prevention (CDC) guidance to retest any patient with an initial blood lead level greater than 10 ug/dL, we recommend that in addition to returning any affected kits, you retest all patients that previously tested greater than 6 ug/dl on one of the affected kits if their results were not confirmed by a method other than LeadCare®. If the results of the retest are greater than 10ug/dL please follow your City, County and State Public Health Guidelines for elevated results.

We have taken action to prevent recurrence of this situation. We sincerely apologize for having to make this announcement and will work with you to address any concerns you may have.

Please confirm receipt of this notice by signing the attached confirmation of receipt and faxing to ESA Quality Assurance Manager at (800) 755-5095.

Please call our Blood Lead Support Group at (800) 275-0102 if you need additional assistance.

A Subsidiary of Magellan Biosciences, Inc.
An ISO 9001 and ISO 13485 Certified Company

Consequences

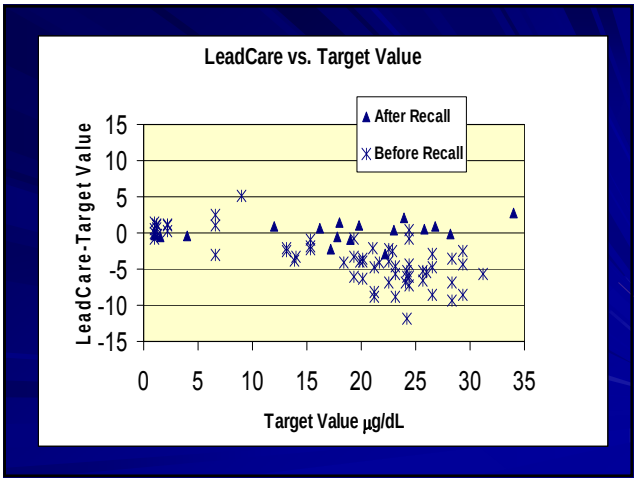
- Based on the recommendation to retest children with leads >6 μg/dL…
- State of MA, ~6000 results were affected
- State of CA, ~100,000 suspect results, ~2% will need to be retested
- Nationally …

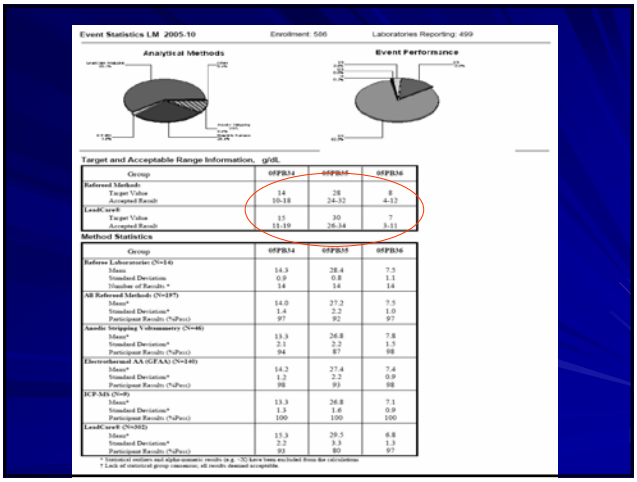
Notification

- WI agrees to provide a mailing to PT participants that includes the recall letter
- WI will also monitor the sensor lots reported, and provide information back to ESA

Performance

- Data obtained on the new test kit lots demonstrate much improved comparability on fresh human blood
- Absence of significant bias in the NY program
- Results in the monthly WI program also show a disappearance of the negative bias



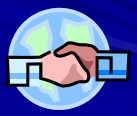


Recent Developments

- Based on recent data on the new sensor lots, NY lifted their qualitative reporting restriction on November 21st
- The official closing of the recall by the FDA was anticipated in November 2005
- In WI, the issue in the PT program was resolved by August

What Did We Learn?

- Value of PT extends beyond the evaluation of individual laboratories
- Changes in performance can provide evidence of widespread analytical issues
- Cooperation between the manufacturer and the PT providers facilitated the investigation and resolution of the problem



What's on the Horizon?

- Development of a new LeadCare analyzer that will be 'waived'
- Similar to the current LeadCare, but will not have to quantitatively measure the blood
- By being waived, this instrument would not have to participate in PT

And the bias problem?

- Rooted in human error during the calibration process and not a defect in the sensors themselves
  - An absence of glutathione
- Blood that was used to calibrate was the same as what WI uses in its PT program
  - Need to add glutathione to our blood