Effect of Bias in Hematofluorometer Measurements of Protoporphyrin in Screening Programs for Lead Poisoning

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Values for erythrocyte protoporphyrin (EP), measured in our laboratory after extraction with ethyl acetate–acetic acid, were compared with hematofluorometer measurements made in 21 other laboratories. We found that: (a) for samples of patients’ blood, hematofluorometer results were 11 to 28% lower than the extraction-based values, depending on the concentration of EP and the mathematical model used; (b) hematofluorometers had mean errors of 0 to 3% for federal proficiency-testing samples; (c) there were no performance differences between fresh and shipped blood for the six laboratories that were analyzing both; (d) a hematofluorometer with a 20% low bias at an EP concentration of 500 μg per liter of whole blood (by the extraction method) will not detect about a third of the children whose EP concentration exceeds that cutoff value; and (e) at this same cutoff value for EP, the extraction test detects about 45% of children whose blood lead exceeds 300 μg/L, whereas a 20% low-bias hematofluorometer detects only about 37%.

Additional Keyphrases: pediatric chemistry · toxicology · cutoff value · intermethod comparison · erythrocytes · interlaboratory performance

Large-scale screening for lead poisoning was begun in the United States in the early 1970s. Initially, body lead status was determined by measuring lead in 5- to 10-mL specimens of venipuncture blood. Later, tests were developed to measure both lead and erythrocyte protoporphyrin (EP) in fingerstick specimens of blood.1 The latter is usually measured by one of two methods: the protoporphyrin is extracted and measured fluorometrically (1, 2), or zinc protoporphyrin in whole blood is measured by direct fluorometry in a hematofluorometer (3, 4).

These tests allow several alternative approaches to screening for lead poisoning, including (a) measurement of both lead and EP in venipuncture blood, (b) lead plus EP in fingerstick blood, (c) EP only in either type of blood specimen by extraction (EEP), and (d) EP only in either type of blood specimen by hematofluorometry.1

The most reliable data and the most information come from combining analyses for lead and EEP in samples obtained by venipuncture. However, the laboratory costs of these determinations are high, and venipuncture is traumatic for small children. The data for lead plus EEP in fingerstick blood are almost as reliable, and specimen collection is more convenient, but laboratory costs are still high. Measuring only EEP in fingerstick blood provides less information, but costs are sharply reduced. HEP measurement is also inexpensive, and data can be provided within a few minutes, often at the blood-collection site. So far, these benefits have been somewhat negated by the data-quality problems reported below.

A hematofluorometer measures fluorescence from blood by front surface fluorometry. The instrument has important operational advantages. It measures EP in whole, untreated blood; it can be operated by non-laboratory personnel; and it directly reads out HEP concentrations within a few minutes. However, it has some important technical problems not shared by the reference method, extraction with ethyl acetate–acetic acid followed by fluorometric measurement (1, 2). In the extraction procedure, protoporphyrin is extracted into dilute acid, leaving behind the highly absorbing hemoglobin in the aeous phase; the protoporphyrin is then determined fluorometrically. The hematofluorometer, however, measures protoporphyrin fluorescence in the presence of both very strongly absorbing hemoglobin and cellular material. These are much more likely to interfere with fluorescence measurement than are the transparent solutions used in the extraction procedure.

The instrument also has calibration problems:

(a) It measures zinc protoporphyrin per erythrocyte rather than total protoporphyrin per unit of blood volume. The former index better reflects effects of lead on heme synthesis, but screening program action levels are based on the latter.

(b) The instrument is routinely calibrated with fluorescent dye standards, and these do not closely simulate blood.

(c) The instrument is difficult to calibrate with pure protoporphyrin standards, and it has not been calibrated with lyophilised blood.

Nonetheless, hematofluorometers are widely used in programs for control of lead poisoning. In the federal government’s (5) proficiency testing report for protoporphyrin for September 1983, 178 of 218 participants (82%) used this instrument. It is therefore important to know whether the problems of accuracy expected with the instrument are common and, if so, to determine their effect on lead poisoning control programs. Here we report the performance of 23 hematofluorometers used at 21 locations in the United States.

Materials and Methods

Laboratory Selection

Questionnaires were sent to 180 laboratories in the federal proficiency testing program for EP.3 Seventy laboratories returned our questionnaire, and 35 were willing to participate in the study of hematofluorometers. We selected 21 of these on the basis of diverse geographical locations, laboratory size, and lead poisoning detection rates.

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1 Nonstandard abbreviations: EP, erythrocyte protoporphyrin; EEP, erythrocyte protoporphyrin concentration as determined by extraction; HEP, erythrocyte protoporphyrin concentration as determined by hematofluorometry.

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3 This program was funded for many years by the Centers for Disease Control. Since fiscal 1982, it has been funded by the Division of Maternal and Child Health, Bureau of Health Care and Delivery Assistance.
Study Design

During six months each participating laboratory, in screening children for lead poisoning, collected an additional blood sample (in 75-μL capillary tubes, with EDTA anticoagulant) from about 300 children in all. They then mailed the samples and the HEP results to us. Most samples collected contained <500 μg of HEP per liter of whole blood. We selected at least 20 samples per participating laboratory for EEP analysis, so as to have five samples in each of four HEP ranges: <500, 500–1090, 1100–2500, and >2500 μg/L. Technicians then analyzed these samples without prior knowledge of the HEP values, by an extraction method similar to that of Piomelli (7) except that the blood was prediluted with water rather than with Celite suspended in saline. We used zinc protoporphyrin (Porphyrin Products, Logan, UT) to prepare the calibration curve, and the control standards were lyophilized blood samples, from lead-dosed cows, containing 690 and 1380 μg of EP per liter of whole blood. The target values for control standards were determined by five laboratories not participating in this study, each using the extraction method. We analyzed the two standards after every 32 test samples; results for the two controls that fell within the range of the nominal value ±50 or ±100 μg/L, respectively, indicated the analysis was in control.

Evaluation of Laboratory Performance

For each participating laboratory, we plotted HEP data vs EEP data, then used a statistical program, REGRESS (6), to calculate the least squares curves of best fit. This program calculates a first-order line and tests it for lack of fit. If there is no significant lack of fit, the program rejects outlying measurements with a kurtosis test and prints out regression data. If there is lack of fit, the program evaluates the appropriateness of a second-order curve. (Outlier rejection is important because, in our experience, about 5% of human blood samples show gross error in HEP values, much greater than the calibration error.)

In the laboratory evaluations, we used a first-order curve when there was no lack of fit, and both first- and second-order curves when there was significant lack of fit. In the former case, the second-order curve most nearly models the HEP vs EEP relation, but almost all laboratories use calibration methods based implicitly on first-order curves. We determined laboratory bias by calculating HEP values equivalent to EEP values at the key cutoff values of 500, 1100, and 2500 μg/L. We also determined HEP vs EEP relationships over several concentration ranges, dividing the data from the laboratories into three ranges: low (<350 μg EEP/L), moderately increased (350 < EEP < 1100), and high (EEP >1100). After plotting EEP values vs HEP, we calculated the mean biases at 350, 700, and 1100 μg of EEP per liter. To evaluate performance in the federal proficiency testing program, we plotted test results vs target values (5), calculated the first-order line of best fit, and then calculated predicted HEP values at 500, 1100, and 2500 μg/L.

Effects on Lead Poisoning Control Programs

To estimate the effects of hematofluorometer bias on screening programs, we studied two sets of data. Set A was for a group of 343 children screened by using data on both lead and EEP at various locations in New York State in 1977. Set B was for a group of 607 children screened by using data on both tests at a local health center in Albany, NY, in 1983 and early 1984.

All data were those obtained on initial screening; about 85% of these specimens were finger-puncture blood. All testing was performed at this laboratory, with use of the above quality-control procedures. As an additional check, all samples yielding atypical results (e.g., lead <390 μg/L with EEP >1500 μg/L) or abnormally high values for lead were reanalyzed.

Results

Analytical Variables

Validity of extraction procedure. It is important to ensure accurate data by the extraction procedure, because it is assumed to yield correct target values. Our laboratory has been determining protoporphyrin by extraction for over eight years. Staff members have several publications in the field (7–10). The laboratory is currently a reference laboratory for the federal and New York State proficiency-testing programs. During the period the present study samples were being analyzed, the laboratory analyzed 12 New York State proficiency-test samples containing 180 to 2330 μg of EEP per liter. The laboratory showed a mean low bias of 2%. For 12 federal proficiency-test samples there was a mean high bias of 3%.

The laboratory also carried out split-sample EEP analysis of 40 patients' samples submitted by the Onondaga County Health Department laboratory. This laboratory has excellent performance in EEP proficiency-testing programs. Results from the two laboratories were plotted against each other, and a first order line of best fit calculated. The line had a negligible intercept (0.24) and the slope was very close to unity (1.00), indicating excellent interlaboratory agreement on shipped samples typical of those used in this study.

Hematofluorometer data quality. Results are shown in Table 1. The laboratories studied showed a mean low bias of 11 to 28%, depending on the EEP value and the mathematical model used. These are major errors for this application. Bias was approximately independent of concentration. For the eight laboratories whose results were classified into three ranges, there was a mean low bias of 20% at 350 μg/L for the 0–350 μg/L data. There was a 23% low bias at 700 μg/L in the moderately elevated range, and a 28% low bias at 1100 μg/L (four laboratories only; the others had insufficient data). These laboratories all performed quite satisfactorily in the federal proficiency-testing program, with mean biases of 0 to ~3%.

The most logical explanation for this difference is that laboratories are using federally-provided test samples to calibrate their instruments, and that these samples do not closely simulate patients' blood.

Effect of sample age on hematofluorometer performance. Six laboratories analyzed a significant number of samples, both promptly after collection (<24 h) and after shipping (three to 15 days). Each set of results (Table 2) was evaluated as for individual laboratories. Biases are about equal for the two groups; hence these limited data show no evidence that blood age affects data quality.

Effect of Hematofluorometer Bias

Effect on efficiency of detecting children with EEP of 500 μg/L or more. The Centers for Disease Control (11) currently recommends an EEP action level of 500 μg/L, children above this level being given confirmatory testing. This standard is mainly based on research studies in which EP is measured after extraction. Use of a hematofluorometer with low bias is equivalent to setting a higher action level—unless the program sets a lower action level for hematofluorometer users only; for example, the New York State program sets a level of 350 μg of HEP per liter.

For the 23 instruments studied, the mean low bias for a first-order line was 20% at 500 μg of EEP per liter. Use of a
### Table 1. Relationship between HEP and Predicted EEP with Patients’ Samples and Proficiency Testing Samples (Values in μg/L of Whole Blood)

<table>
<thead>
<tr>
<th>Lab*</th>
<th>First-order *</th>
<th>Second-order</th>
<th>Proficiency samples, first-order</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>EEP concn</td>
<td>500</td>
<td>1100</td>
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<tr>
<td>1(A)</td>
<td>430</td>
<td>740</td>
<td>1480</td>
</tr>
<tr>
<td>2(A)</td>
<td>330</td>
<td>650</td>
<td>1390</td>
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<td>3(A)</td>
<td>300</td>
<td>730</td>
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<td>980</td>
<td>2280</td>
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<td>460</td>
<td>1000</td>
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<td>430</td>
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<td>440</td>
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<td>2020</td>
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<td>1330</td>
</tr>
<tr>
<td>25(E)</td>
<td>300</td>
<td>640</td>
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</tr>
<tr>
<td>26(A)</td>
<td>440</td>
<td>870</td>
<td>1900</td>
</tr>
<tr>
<td>28(A)</td>
<td>480</td>
<td>590</td>
<td>2060</td>
</tr>
</tbody>
</table>

| Mean | 400 | 810 | 1780 | 380 | 860 | 2230 | 500 | 1080 | 2430 |
| CV, % | 14 | 16 | 19 | 11 | 22 | 19 | 6 | 5 | 6 |
| Bias, % | -20 | -26 | -28 | -23 | -22 | -11 | 0 | -1 | -3 |

*Instrument manufacturers shown in parentheses: A, AVIV; E, Environmental Science Associates; B, Buchler.
*First-order curve: HEP = b0 + b1·EEP; second-order curve HEP = b0 + b1·EEP + b2·EEP.
*Values rejected as outliers because of too few data from one or more individual laboratories on high concentrations.
*These laboratories used two hematofluorometers.

### Table 2. Effect of Sample Age on HEP Values

<table>
<thead>
<tr>
<th>Lab.</th>
<th>Samples measured 24 h</th>
<th>Samples measured 3–15 days after collection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EEP concn, μg/L</td>
<td>HEP concn (first-order curves)</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>1100</td>
</tr>
<tr>
<td>2</td>
<td>310</td>
<td>600</td>
</tr>
<tr>
<td>6</td>
<td>490</td>
<td>910</td>
</tr>
<tr>
<td>13</td>
<td>410</td>
<td>920</td>
</tr>
<tr>
<td>16</td>
<td>290</td>
<td>700</td>
</tr>
<tr>
<td>17</td>
<td>430</td>
<td>900</td>
</tr>
<tr>
<td>22</td>
<td>420</td>
<td>790</td>
</tr>
</tbody>
</table>

| Mean | 390 | 800 | 1760 | 410 | 850 | 1860 |
| CV, % | 20 | 27 | 18 | 20 | 26 | 15 |
| Bias, % | -22 | -27 | -30 | -18 | -23 | -25 |

hematofluorometer with this bias is equivalent to setting an action level for EEP of 625 μg/L. For Set A (1977 data), 79 children had EEP levels of 500 μg/L or more. Use of a hematofluorometer that was 20% low would result in detection of 56 (71%) of these cases. For Set B (1983 data), 59 children had EEP values of 500 μg/L or more. Use of a hematofluorometer that was 20% low would detect 40 (68%) of these cases. Thus in these limited samples, 42 of 138 (30%) children with EEP concentrations high enough to be of public health concern would not have been identified by the average hematofluorometer used in this study.

**Effect on detecting children with blood lead of 300 μg/L or more.** Alternatively, we could define children at risk as those having blood lead concentrations ≥300 μg/L (II). In Set A, 111 children exceeded this value. An extraction EP test would have detected 49 (44%) of them and a hematofluorometer with a 20% low bias would detect only 40 (36%). In Set B, 61 children had blood lead concentrations of 300 μg/L or more. An extraction EP test would detect 28 (46%) of them; a hematofluorometer with 20% low bias would detect 24 (39%). Altogether, 95 of 172 (55%) cases of blood lead of 300 μg/L or more would have been missed by EEP screening, 108 (63%) by HEP screening.

**Effect on screening detection rates.** Detection rates in screening programs have dropped significantly during the last few years. For example, programs in New York State had mean detection rates of 8.2% in 1976 and 3.0% in 1983. This decline can be attributed to a combination of:

(a) Effective lead poisoning control measures. This includes education, nutrition, and environmental-abatement programs, including reduction in lead sources. Decreased use of leaded gasoline has been a major change.
(b) Change in definition of detection rate. In 1976, children with a lead of 300 μg/L or more and EP of 600 μg/L or more were targeted. In 1983, the target population had EP ≥500 μg/L and lead ≥300 μg/L.
(c) Effects of hematofluorometer bias. Use of a hematofluorometer that is 20% low is equivalent to setting an EP target of 625 μg/L rather than 500 μg/L. The relative contribution of each of these factors can be roughly calculated. Data Set A showed an 11.9% detection rate with cutoff values of lead ≥300 and EP ≥600. The detection rate would have been 14.0% with lead ≥300 and EP ≥600.
EP B=500, 11.4% with lead ≥300 and EP ≥625. In 1976, the New York State detection rate with a lead ≥300 and EP ≥600 standard was 8.2%. It would have been (8.2 × 14)/11.9, or 9.6%, with a modern lead ≥300 and EP ≥500 standard. It would have been (8.2 × 11.4)/11.9, or 7.8%, with a hematofluorometer that was 20% low. The current detection rate in New York is 3.0%. Assuming that lead poisoning control programs initially screen with a hematofluorometer that is 20% low, the decline from 9.6 to 7.8% is attributable to hematofluorometer bias. The remaining, actual improvement should be due to effective lead poisoning control. Thus 73% of the apparent improvement is actual, the rest a measurement artifact. (Note that this calculation ignores the unquantifiable effects of changes in the risk status of the screened populations.)

Effect of Laboratory Procedures on Hematofluorometer Performance

Participating laboratories reported on several factors: type of laboratory, average sample turnaround time, workloads, quality control and maintenance procedures, and instrument manufacturer.

With one exception, inspection of these data yielded no obvious relationship between procedures and performance of the hematofluorometer. Figure 1 shows months since factory calibration plotted vs bias for 500 and 1100 µg of EEP per liter. Two first-order lines were plotted. One includes data from all laboratories; the other excludes three laboratories who hadn't factory calibrated their instruments for over 20 months. In both cases, Student's t-test showed that the slope of the line differed significantly from zero (p <0.05 and p <0.01, respectively.) Similar results were observed when data for the two concentrations were plotted separately.

We saw no significant differences in performance between instruments from different manufacturers.

Discussion and Recommended Action

In most lead poisoning control programs in the United States a hematofluorometer is used in initially screening the target population. Children with HEP concentrations exceeding 500 µg/L of whole blood subsequently are tested for lead, and the EP measurement is often repeated at a central laboratory. HEP measurement is thus the primary classification step in the control program, and error at this stage will adversely affect overall program performance.

We found that almost all laboratories participating in this study are producing data with clinically significant error. These laboratorise voluntarily participated in the study, and many have excellent reputations. Thus other hematofluorometers users may well be generating data of worse quality. The problem should be corrected as soon as possible, and the procedures leading to these errors should be replaced. The following steps should decrease the problem:

* Factory overhaul and recalibrate instruments at least four-month intervals. In this study, laboratories with the most recent factory calibration had the best performance.
* As a stopgap measure until absence of bias is proven, use a minimum action level for hematofluorometers of, say, 30% below the extraction EP action level. Thus the 500 µg/L cutoff value for EEP would be reduced to 350 µg/L for the hematofluorometer. This would compensate completely for low bias in all but two of the laboratories we studied.
* Replace proficiency-testing samples and fluorescent dye slides as primary standards. Clearly, these are not working. There are several possible alternatives, although all have disadvantages: (a) Hematofluorometer users could send a few high, medium, and low samples each week to a reference laboratory for EEP analysis. Extraction EP data would be used continuously to calibrate the instrument, with fluorescent dye standards used only to monitor instrument stability. For example, if a sample read 1000 µg/L on the hematofluorometer and 1200 µg/L by EEP, the hematofluorometer dye standards would be adjusted by 20%. This approach is expensive, and hematofluorometer users may have difficulty getting high-value patients’ blood samples. Because very few samples would be analyzed, the calibration would be adversely affected by outliers. (b) Reference laboratories could analyze patients’ blood by EEP and ship the blood to hematofluorometer users for calibration. This procedure is cheaper and less prone to error from outliers. However, a typical 5-mL venipuncture sample would only provide enough blood for about 20 hematofluorometers, and the instrument may perform less satisfactorily with shipped blood (though this study suggests otherwise). (c) Develop a blood standard. For example, a group of reference laboratories could accurately calibrate their hematofluorometers by using patients’ blood and then determine HEP in blood from lead-dosed animals or humans with lead poisoning or iron-deficiency anemia. The mean value so obtained would be the target value for hematofluorometer users. Animal blood with high EP concentrations is available in quantity. However, the fractions of zinc protoporphyrin in animal blood are not the same as human blood, and individual hematofluorometers may respond differently to these specimens. Lack of a satisfactory blood standard is clearly the most urgent problem with this instrument.

* Results from proficiency-testing programs in which synthetic blood is used should be regarded as suspect unless validated by comparison with analytical data from patients' specimens.

At present, the safest procedure for validating instrument performance is to determine both HEP and EEP in freshly collected blood. If results differ from those obtained from synthetic test samples, the former will most probably be correct. For example, Balamut et al. (8) found that two instruments performed satisfactorily with proficiency test samples, but showed a 30% low bias with patients' blood.

Note that it is not necessary to use the same proficiency-test material for both HEP and EEP. In the New York State proficiency-testing program, we use blood from lead-dosed goats to control EEP, because it is both readily available and satisfactory. We use patients' blood to control HEP because
we believe it is more satisfactory than other materials used
to date.

The effects of hematofluorometer bias on the efficiency of
screening programs will vary from site to site, depending
both on instrument performance and lead concentrations in
the target population. It is worth noting that an extraction
EP screen fails to detect a large proportion of children (45% of
the 1977 data set) whose blood lead exceeds 300 μg/L. A
hematofluorometer screen misses even more (63%). The
statement of the Centers for Disease Control (11) concludes
that the children at greatest risk are those with above-
normal concentrations of EP and lead, and not those with
above-normal EP but low lead. However, this statement is
based on a study by Reigert and Whitlock (12) of a group of
children with initial lead values of 400 to 590 μg/L. Their
conclusions may not be as applicable to children with lead
values of 300 to 400 μg/L, most of whom will be missed by
current screening procedures.

If these data quality problems can be corrected, the
hematofluorometer could be the method of choice for screen-
ning for insult to erythropoiesis. It measures zinc protopor-
phyrin per unit of hemoglobin, while the extraction method
measures total protoporphyrin per unit of volume. Zinc
protoporphyrin production is an error of erythropoiesis and
the fraction of aberrant hemoglobin molecules produced is
proportional to the lead or other insult. Zinc protoporphyrin
per unit of hemoglobin should therefore best measure effects
on heme synthesis. This datum can be obtained from a
single hematofluorometer measurement or from the ratio of
two other measurements: EEP and hemoglobin or hemo-
crit. (An even better method may be to measure zinc
protoporphyrin per unit of "recently formed" erythrocytes, to
detect children with very recent lead exposure.)

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