I, Alexander R. Daniels, hereby submit this original work as part of the requirements for the degree of Master of Public Health in Epidemiology.

It is entitled:
Extreme exposure biomarker levels: do physicians want to be informed?

Student's name: Alexander R. Daniels

This work and its defense approved by:

Committee chair: Susan Pinney, Ph.D.
Committee member: Frank M. Biro, M.D.
Committee member: Jun Ying, Ph.D.
University of Cincinnati

Date: 7/16/2015

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Extreme exposure biomarker levels: do physicians want to be informed?

A thesis submitted to the
Graduate School
of the University of Cincinnati
in partial fulfillment of the
requirements for the degree of

Master of Public Health

In the Department of Environmental Health
Of the College of Medicine

By

Alexander R. Daniels

B.M.E. Wittenberg University, 2008

Committee: Susan M. Pinney, Ph.D.
Jun Ying, Ph.D.
Frank M. Biro, MD
ABSTRACT

BACKGROUND: Improving technology has allowed researchers to detect ever smaller amounts of environmental toxins in blood, serum and urine. Occasionally, participants are found to have concentrations well above national averages. There are few systems of support in place for participants to whom these results have been returned, and no guidelines for researchers or community physicians concerning how to address participants' concerns. This study aims to assess whether or not community physicians are ready and willing to assist their patients who have participated in biomonitoring studies.

METHODS: The study group recruited 100 internists, and 100 pediatricians selected via multiple online directories to ensure the greatest coverage of the Greater Cincinnati area. A survey consisting of two scenarios, with 8 or 9 multiple choice questions each, was mailed to these 200 community physicians. The scenarios presented were an 11 year old female with extremely high urinary phthalates, and a 55 year old male with extremely high urinary cadmium.

STATISTICAL ANALYSIS: Descriptive statistics were calculated for each scenario separately for strata of physician specialty, gender, and age range.

RESULTS: The majority of physicians surveyed indicated that they would like to receive the information about their patient's exposure levels (93.4%). Nearly all indicated that they did not have the knowledge base to offer their patient any guidance or treatment, and that they would require additional information. Many of the comments left on the surveys asked for the researchers to provide informational material to the physicians along with their patient's results, so that they might be able to better serve the patient.

DISCUSSION: Based on the large percentage of physicians who indicated a desire to receive this kind of information, we believe this topic warrants further study in order to address the lack of guidance for researchers and community physicians.
Acknowledgements

This study was supported by a pilot project from the Center for Environmental Genetics from the University of Cincinnati (NIEHS P30-ES006096). I would like to thank Victoria Straughn for assistance with the mailings and data entry, Yifan Zhang for statistical analysis support, and Dr. Robert Daniels for editing support.
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Background

As technology improves, researchers are finding smaller amounts of metals and environmental toxins in blood, serum, and urine. Advances in biomarker research has led to studies uncovering evidence of exposures to agents within and outside of the study scope. This information can have far reaching implications, such as in the case of lead, which was found to have no safe level of exposure[1]. In many other cases; however, the information on health effects from low-level exposures may be inadequate to support recommendations. Furthermore, incidental findings, regardless of clinical implications, present a difficult ethical dilemma. If there is no evidence of an association between the exposure and a negative health effect, then should we inform the participant of their potential exposures? Has the participant consented to receive his or her personal results?

Clinicians and researchers often have differing viewpoints on disclosure. It has been stated that the researcher’s goal is to produce generalizable knowledge for future social benefit, not to preserve the health and welfare of individual study participants[2]. This seems especially pertinent in situations where the health effects of an environmental exposure are unknown. For example, Pinney et al. monitored levels of perfluoroalkyl chemicals (PFCs) in the serum of girls ages 6-8 in the Greater Cincinnati and San Francisco Bay areas and found that 94% of the girls living in Northern Kentucky had serum PFC concentrations above the NHANES 95th percentile for perfluorooctanoic acid (PFOA)[3]. Families of the participants were informed of the results despite the lack of knowledge of the source of the exposure and impact on health at the time. Animal studies have indicated that PFOA may impact pubertal development [4, 5]. Lopez-Espinosa et al. found an association between PFOA exposure and later onset of puberty in girls in the Ohio River Valley[6]. Despite these findings, the association between PFOA exposure and adverse health effects are not fully elucidated. The disclosure of these results to participants and their families may be of little use without appropriate support, or methods to
reduce or treat exposures. In most cases, support would need to come from health care professionals.

Many research groups that return individual results to participants suggest that participants contact their physician with additional questions. Nevertheless, the knowledge and desire of community physicians to assist these study participants has not been assessed formally. Guidelines on whether or not individual results indicating personal exposure should be returned to participants are lacking, as are support systems for participants who do receive individual results.

This study assessed the willingness and confidence of community physicians to consult with a hypothetical patient about a finding of extremely high biomarkers of personal exposure, to help identify additional issues with researchers, clinicians, ethicists, lawyers, and other stakeholders to develop a set of guidelines for disclosing research results.

**Methods**

This study was conducted under the review and approval of the University of Cincinnati Institutional Review Board. A survey consisting of two scenarios, with 8 or 9 multiple choice questions each, was mailed to 200 community physicians in the Greater Cincinnati Area. The survey instruments comprised two options that were equally distributed. Option 1 presented a scenario involving an 11 year old female with extremely high urinary phthalates on the front of the sheet with accompanying questions, and a scenario concerning a 55 year old male with extremely high urinary cadmium and accompanying questions on the back. Survey Option 2 presented the scenarios with their accompanying questions in the opposite order. Physicians were selected for participation using various online directories, which were selected based on geographic location with the intent of covering the Greater Cincinnati Area. 100 pediatricians and 100 internists were selected for recruitment to the study. Participants were randomized to receive either Option 1 of the survey (11 year old female first) or Option 2 of the survey (55 year
old male first). Accompanying the surveys were pre-stamped, self-addressed return envelopes, and a $5 gift card for Starbucks as an advance “thank you”. The gift card did not require the recipient to participate in the study.

Upon return, the letters were opened and each respondent form was assigned a unique identification number. Respondent data were independently double entered into two master tables by two researchers. These tables were compared for coding accuracy and differences reconciled via visual comparison to the original survey. Descriptive statistics were calculated for each scenario separately and stratified by physician, gender, and specialty. Pearson’s chi-square tests were used to compare rates between groups. All analyses were conducted using SAS software[7].

Results

There were 61 (31%) survey forms completed and returned by respondents. Fifty-four percent of respondents indicated that they were practicing pediatricians, twenty-nine percent practicing internists and four respondents (7%) as both a pediatrician and an internist. Forty (66%) physician respondents were between the ages of 35 and 55, while 18 (31%) of respondents were 56 years or older. Three percent of the respondents did not report their age. Fifty-seven percent of respondents identified as female, and thirty-eight percent identified as male. Five percent declined to indicate their gender.

The majority of physicians surveyed indicated that they would like to receive the information about their patient's exposure levels. Overall, for the adult scenario 93.4% of respondents showed interest in receiving the information, higher than that of the 80.3% to the child scenario (p=0.032, Tables 1 & 2). All physicians who provided feedback indicated that they did not have the knowledge base to offer their patient any guidance or treatment, and that they would need additional information, regardless of scenario.
When stratified by specialty, pediatricians showed more interest in receiving information than internists. In particular for the child scenario, 31 out of 32 pediatricians would like to receive the information vs. 11 out of 14 internists \( (p=0.043) \). For the adult scenario, the rates were 31/31 and 16/18 for pediatricians and internists respectively \( (p=0.058) \).

When asked if they felt they possessed sufficient knowledge of the exposures to take further action with their patients, more than 90% of all physicians responded that they did not, regardless of scenario. Only two pediatricians \( (3.4\%) \) indicated that they had the knowledge of cadmium exposure (adult scenario) to assist their patient, and one internist \( (1.64\%) \) indicated the same for the phthalate exposure (child scenario).

Seventy-seven percent of total respondents indicated that they would contact the parent of the patient in the child scenario. More pediatricians \( (87.9\%) \) than internists \( (61.1\%) \) were likely to contact the patient's parent \( (p=0.056) \). A similar pattern was noticed in the adult scenario. More than eighty percent \( (84.9\%) \) of pediatricians were inclined to contact the patient compared to 77.8% of internists, even though the difference was not statistically significant \( (p=0.224) \). Overall, 83.61% of participants responded that they would contact the adult patient with his biomarker results.

One question unique to the Child Scenario portion of the survey was "Would the fact that the health effects of phthalate exposure are relatively unknown influence your decision to contact the patient's parents with this information?" Fifty-four percent of all respondents indicated that this fact would have no impact on their decision to contact the patient's family. Thirty-eight percent said that it would be a factor in their decision, with 8% missing (Figure 1).

Both surveys featured the question “If the patient was a child (adult), how would it affect your decision to follow up with him or her?” followed by the options more likely, less likely, and no difference (Table 3). The results showed the physician’s decision was associated with the
patient’s age (p<0.001). Specifically, twenty-One (63.6%) pediatricians indicated that if the patient in the adult scenario had been a child, it would have made no difference in their decision to follow up with the person. Ten (30.3%) would have been more likely to follow up if the patient had been a child, and none said less likely. Of the internists, a slim majority (55.56%) indicated that whether the patient was a child or adult would not have had any impact on their decision to follow up. In the opposite situation, if the patient had been an adult rather than a child, a large majority of both pediatricians (84.9%) and internists (77.8%) indicated that there would be no difference in their decision to follow up with the patient. None of the respondents indicated that if the patient had been an adult, they would have been more likely to contact her.

Discussion

This survey of community physicians found that the discrepancy between the desire to receive patient results and actual physician knowledge is wide. This is to be expected for the scenario involving the eleven year old girl with high levels of urinary phthalates. The fact that the health effects of phthalates are relatively unknown may be responsible for the difference in positive responses between the two scenarios. Interestingly, most physicians indicated they lacked the necessary level of knowledge about cadmium exposure, which is a relatively well known renal toxicant. In some of their comments, physicians asked whether kidney function tests should be administered, and others what sort of treatment exists for cadmium toxicity. For phthalates, these clinicians frequently asked what the results meant.

Many of the respondents indicated that they would contact the patient after having received the test results, but only if provided educational materials along with the result in order to effectively convey information to their patients. Respondent questions indicated a specific need for information on available treatment that could be conveyed to patients during consult.

One important limitation of the study is the low return rate of the surveys (31%). In future studies it will be necessary to develop a way to increase the rate of return in order to bolster our
power and reduce the bias introduced by the low return rate. One method of achieving this that has been suggested by physicians themselves, is to send surveys via social media. Most healthcare professionals are engaged in social media, and the ability to access study surveys from anywhere, or anytime, could increase the return rate. Though we initially considered this as an option for our study, we decided that trying to read both scenarios on a smart phone may have been prohibitively difficult. A similar issue arose in which respondents only filled out one side of the survey. Regardless of which survey option the physicians received, the question “Did you answer the questions on the other side of the page?” appeared on both sides of the sheet. Still, a number of participants only filled out the questions associated with the hypothetical patient most closely related to their own practice. Some left comments such as “I only see kids, not adults,” indicating they did not think the alternate set of questions applied to them. In hindsight, we should have perhaps made a note in the survey instructions to fill out both sets of questions regardless of the physician’s own specialty.

The financial burden of preparing and returning individual results along with the appropriate supplemental material may render many projects unfeasible. Obtaining a release to report the results to the individual’s physician may also present difficulty. Ensuring that staff are available to field questions from participants about their results requires time and money. Many times, there is inadequate staff who hold the appropriate clinical knowledge to address questions and concerns of participants. Physicians and other health professionals may have insufficient knowledge of the basic principles of environmental exposure. If the health effects of a certain exposure are unknown, or poorly understood, answering participants’ questions becomes much more difficult.

Though our results indicate an overwhelming majority of physician respondents would want to receive this information, the topic requires further study. The decision to disclose would depend on numerous factors, including participant consent, what constitutes a high or clinically
relevant level, whether or not the health effects of an exposure are known, among others. On a larger scale, researchers must consider whether or not it is feasible to reduce exposure to certain environmental chemicals without negatively impacting the affected communities [8]. Possible negative effects, such as undue stress and anxiety for the participant, must also be considered. These anxieties may be exacerbated if participants’ physicians have only limited knowledge of the effects of the exposure, and the possible management options to minimize adverse outcomes. One positive outcome of communicating these findings to physicians may be an increased awareness among the medical community of the prevalence of these types of environmental exposure levels. Understanding the likelihood of exposure may help medical professionals understand the relationship between an undiagnosed condition and an exposure. We believe our findings merit further study of this complex ethical issue in order to address the lack of guidance for researchers [9], and to establish a means of communication with participants as well as their primary caregivers.
References


[10-29]
**Appendix**

Table 1. Descriptive statistics for questions concerning the child scenario.

<table>
<thead>
<tr>
<th>Question</th>
<th>All</th>
<th>Pediatricians</th>
<th>Internists</th>
<th>Dual Specialty</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Missing</td>
<td>Yes</td>
</tr>
<tr>
<td>Would you want to receive this information about your patient?</td>
<td>49</td>
<td>7</td>
<td>5</td>
<td>31</td>
</tr>
<tr>
<td>Would you have sufficient knowledge to take further action?</td>
<td>1</td>
<td>56</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Would you want more information about the exposure?</td>
<td>53</td>
<td>4</td>
<td>4</td>
<td>32</td>
</tr>
<tr>
<td>Would you contact the patient with this information?</td>
<td>47</td>
<td>9</td>
<td>5</td>
<td>29</td>
</tr>
<tr>
<td>Do you have any questions for researchers?</td>
<td>35</td>
<td>26</td>
<td>0</td>
<td>22</td>
</tr>
</tbody>
</table>

*.weighted*
Table 2. Descriptive statistics for responses to questions concerning the adult scenario.

<table>
<thead>
<tr>
<th>Question</th>
<th>All</th>
<th>Pediatricians</th>
<th>Internists</th>
<th>Dual Specialty</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Missing</td>
<td>Yes</td>
</tr>
<tr>
<td>Would you want to receive this information about your patient?</td>
<td>57 (93.4%)</td>
<td>2 (3.3%)</td>
<td>2 (3.3%)</td>
<td>31 (93.9%)</td>
</tr>
<tr>
<td>Would you have sufficient knowledge to take further action?*</td>
<td>2 (3.3%)</td>
<td>56 (91.8%)</td>
<td>3 (4.9%)</td>
<td>2 (6.1%)</td>
</tr>
<tr>
<td>Would you want more information about the exposure?</td>
<td>55 (90.2%)</td>
<td>4 (6.6%)</td>
<td>2 (3.3%)</td>
<td>29 (87.9%)</td>
</tr>
<tr>
<td>Would you contact the patient with this information?</td>
<td>51 (83.6%)</td>
<td>7 (11.5%)</td>
<td>3 (4.9%)</td>
<td>28 (84.9%)</td>
</tr>
<tr>
<td>Do you have any questions for researchers?***</td>
<td>30 (49.2%)</td>
<td>31 (50.8%)</td>
<td>0 (0%)</td>
<td>18 (54.6%)</td>
</tr>
</tbody>
</table>

* One respondent’s gender was missing as well as the response to this question for the Child Scenario.

** For this question, empty lines were given to respondents to write their questions. For this frequency, YES indicated that they had written something, and NO that they had not.
Table 3. Descriptive statistics for question concerning the reversal of patient exposures.

<table>
<thead>
<tr>
<th>Question</th>
<th>More Likely</th>
<th>Less Likely</th>
<th>No Difference</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>If the patient was an adult, how would this affect your decision to follow up with her?</td>
<td>3 (4.92%)</td>
<td>7 (11.48%)</td>
<td>47 (77.05%)</td>
<td>4 (6.56%)</td>
</tr>
<tr>
<td>If the patient was a child, how would this affect your decision to follow up with him?</td>
<td>20 (32.79%)</td>
<td>0 (0%)</td>
<td>36 (59.02%)</td>
<td>5 (8.20%)</td>
</tr>
</tbody>
</table>
Figure 1.

"Would the fact that the health effects of phthalate exposure are relatively unknown influence your decision to contact the patient's parents?"
Eleven Year Old Female with Extremely High Urinary Phthalates

Your 11 year old female patient has been a participant in the Growing Up Female study at CCHMC since she was 7 years old. As part of that study, urine was banked at the beginning of the study and about a year ago (when she was 10 years old) sent to the CDC Environmental Laboratory for exposure biomarker analyses, including for the presence of phthalates in serum. The CDC lab is a certified CLIA lab and follows its own strict quality assurance procedures in addition to the CLIA requirements. One of your patient’s phthalate metabolites was found at a very high concentration in her urine. Methyl-ethyl phthalate (mEP) was measured at 18,000 ug/L in this girl’s urine, compared to the 95th percentile value for children in the US population, which is 522 ug/L. Since phthalates have very short half-lives, this number most likely represents her exposure in the past day. (Phthalate half-lives are generally estimated to be about 12 hours, meaning that ½ of the body burden is excreted in 12 hours if there is no additional exposure.) Existing cohort data indicate that repeat measures of urinary biomarkers for a girl, spaced over time, are likely to stay in the category of exposure (high, middle, low), but not always. Possible sources for children are shampoos, lotions, and products such as vinyl flooring used in the home. Human health effects from exposure to low levels of phthalates are unknown. Some types of phthalates have affected the reproductive system of laboratory animals.

1. As her physician, would you want to know about this girl’s high urine concentration of methyl-ethyl phthalate?
   - YES
   - NO

2. Would you have the knowledge base about phthalates needed to take any further action once you have received this information?
   - YES
   - NO

3. Would you need or want more information about phthalates?
   - YES
   - NO

4. Would you contact the girl’s parents to discuss this finding with them?
   - YES
   - NO

5. Would you only discuss the finding with them if they first contacted you?
   - YES
   - NO

6. If the patient were an adult, would you be less likely to follow-up with the patient’s parents about this finding?
   - YES
   - NO

7. Would the fact that the human health effects of exposure to low levels of phthalates are unknown affect your decision to contact or follow up with the patient about her results?
   - YES
   - NO

8. Does the length of time between when the urine sample was obtained (age 7) and when the analyses were done (age 10) affect your thinking about whether to contact your patient’s parents?
   - YES
   - NO

9. What questions would you have for the researchers?
Fifty-five Year Old Male with Extremely High Urinary Cadmium

Your 55 year old male patient was a participant in the Fernald Medical Monitoring Program from 1992 to 2008, when the examination program ended. As part of that study, urine was banked in 2008 and about a year ago (2013) sent to the CDC Environmental Laboratory for exposure biomarker analyses, including for the presence of cadmium. The CDC lab is a certified CLIA lab and follows its own strict quality assurance procedures in addition to the CLIA requirements. Cadmium was found in very high concentration in your patient’s urine, measured at 8.99 ug/L, compared to the 95th percentile value for non-Hispanic whites in the US population, which is 1.17 ug/L. Cadmium in urine can come from either a recent exposure to cadmium or from remobilization of cadmium stored in solid tissue. With a single spot urine sample, it is impossible to tell whether an acute or chronic exposure is responsible for the high concentration in urine. Urinary cadmium does have a relatively long half life (about 13 years), so the high urinary concentration could represent an adult with a large body burden for a long time. (The cadmium half life means that ½ of the body burden is excreted in 13 years if there is no additional exposure.) Persons with low iron levels absorb more cadmium. Possible sources of cadmium are occupational (painter, metal worker, printer) or hobby (pottery glazing) exposure.

Well-known health effects seen in studies of humans include renal toxicity and endocrine disrupting effects. Occupational exposure to cadmium also has been associated with low bone density.

7. As his physician, would you want to know about this man’s high urine concentration of cadmium?
   □ YES
   □ NO

8. Would you have the knowledge base about cadmium needed to take any further action once you have received this information?
   □ YES
   □ NO

9. Would you need more information about cadmium?
   □ YES
   □ NO

10. Would you contact the patient to discuss this finding with him?
    □ YES
    □ NO

11. Would you only discuss the finding with him if he first contacted you?
    □ YES
    □ NO

12. If the patient were a child, would you be more or less likely to follow-up with the patient about this finding? Please circle one:
    MORE LIKELY  NO DIFFERENCE  LESS LIKELY

13. Does the length of time between when the urine sample was obtained and when the analyses were done (5 yrs) affect your thinking about whether to contact your patient?
    □ YES
    □ NO

14. What questions would you have for the researchers?