Author’s response to reviews

Title: Development of an Environmental Health Tool Linking Chemical Exposures, Physical Location and Lung Function

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Response to Reviewers

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Development of an Environmental Health Tool Linking Chemical Exposures, Physical Location and Lung Function Diana Rohlman, PhD; Holly M. Dixon; Laurel Kincl, PhD; Andrew Larkin, PhD; Richard Evoy, MPH; Michael Barton; Aaron Phillips; Elena Peterson; Christopher Scaffidi, PhD; Katrina M. Waters, PhD; Kim A. Anderson, PhD BMC Public Health

We appreciate the comments provided by the reviewers, and below provide a point-by-point response to each comment, and reference the Section and line numbers of the changes to the
manuscript. In addition to addressing reviewer comments below, we have added another author, as denoted in the manuscript.

Hanns Moshammer (Reviewer 1)

The paper is well-written and clearly structured. But the information is neither new nor very relevant. As far as I understand the paper shows that (a) asthmatics interested in air pollution are able to adhere to a protocol including wearing a wristband and performing spirometry 2 times a day for one week, (b) spirometry is able to measure lung function, (c) GPS devices are able to read and store position data, (d) passive sampling is a valid method for measuring air pollution, and (e) mobile phones can transfer data. Which of these is new?

• We acknowledge that none of these individual components is new. The components of the ELF were carefully chosen to address community concerns around air pollution and asthma; the relevance is due to the way in which multiple components were integrated into one system. On its own, a mobile phone transferring data is not new or innovative. A mobile phone that can interact with and capture data from a hand-held spirometer, while also collecting GPS data and delivering time-sensitive questions via an application, and then securely transmitting data, is relevant and innovative, given the potential for the ELF to be used as a research tool. We designed the device to simultaneously collect multiple sources of data, and integrate that data. We have clarified this in the manuscript. Please see lines 207-208 (Materials and Methods), line 357 (Results), as well as lines 452-456 (Discussion). Future studies are being designed to utilize the ELF to evaluate correlations between exposure and health outcomes.

The authors state that their study is only a pilot or feasibility study. Which of the parts did they fear is not feasible? Even the combination of the five parts cannot be the problem. What we would be interested in as readers is exactly the combination of the parts: are there any correlations between the data sets? The authors claim their study did not have enough power to detect any effects. (Line 183f: "This study was not designed to make inferences regarding health status.” OK. But I want to point out that several panel studies have shown health effects using not many more data points. But apart from health effects: what about correlation between exposure estimates? (e.g. PAH x various estimates based on position data)

• We agree that each proposed ‘part’ is already feasible. However, integrating these different parts required the development of a new application (ELF App), and relied on a Bluetooth connection between the spirometer and the phone, and then a separate connection to upload data to the servers at PNNL. We were also uncertain about the ability for a participant to follow the protocol and generate reliable, compliant data. However, we see the confusion between feasibility of a component working as it should, versus the feasibility of all the pieces working in tandem and the ability of a participant to utilize the device with a high degree of compliance. We have added a fifth metric to our Materials and Methods, lines 207-208.
We appreciate that panel studies can be used to evaluate health effects. However, this paper was designed to demonstrate the use and feasibility of the ELF, both in terms of instrument capability and ability of study participants to collect useful, valid data. Therefore, identifying correlations between exposure estimates is outside the scope of this paper. Future studies will focus on larger study groups with sufficient statistical sampling to identify health outcomes associated with exposures.

I wonder why the authors decided to measure PAHs. They provide 6 papers as justification that "Exposure to PAHs has been linked with diminished respiratory health". Well, the first paper (12) is not about health effects. References 13 and 14 are. Reference 15 indicates an association between PAH and respiratory disease but PAH and PM are highly correlated in that study. References 16 and 17 are about prenatal exposure and indeed in my understanding PAHs are much more relevant as carcinogens and as developmental toxicants than as short-term irritants of the respiratory system.

We have added additional references that have evaluated exposure to PAHs and correlation to respiratory health. Al-Daghri et al. (2013) evaluated correlations between PAH exposure and various symptoms of respiratory distress. Liu et al. (2016) found that urinary PAHs were positively associated with asthma in US children using NHANES data. We removed the Terzi and Samara citation. (Line 92, Introduction). Furthermore, we included reference to the importance of evaluating volatile and semi-volatile PAHs (Dixon et al. 2018).

We recognize that multiple chemical classes are relevant as respiratory irritants; our future work includes analysis of 92 volatile and semi-volatile organic compounds. In recognition of this, we have updated our Discussion to acknowledge that our system is capable of analyzing far more than PAHs. Please see lines 415-417, Discussion. We included a citation showing that the wristband is currently capable of detecting and analyzing 1,530 semi-volatile and volatile chemicals (Bergmann et al. 2018).

In a panel study you would be interested in current exposure and you would prefer high temporal and spatial resolution. Passive sampling, even with a resolution of 1 day, is not the best choice. The analytical technique might be feasible, but likely not very cost-effective. Other markers of exposure are cheaper and easier to measure and might be equally relevant for respiratory health. Different PAH mixtures might be indicative of specific sources but with a 24 hour averaging time I doubt clear links to sources are possible.

The ELF was designed to collect multiple sets of data to better identify specific sources that may be increasing individual chemical exposure and/or impacting respiratory health. The research goal is to utilize location data and integrate into multiple other publicly available exposure datasets (as shown in Supplemental Table 1) to better understand the effect of potential point sources of pollution. The passive sampler allows analysis of a single day with high temporal and spatial resolution. The spatial resolution of the wristband is well described in O’Connell et al. (2014). Based on community focus groups conducted previously (Rohilman et al. 2015), community members were interested in the breadth of exposures in a full day. Community members cited differing schedules and
routines as a reason for looking at a full 7-day week, explaining that each day might represent different exposures. Therefore, daily sampling provides the necessary resolution, given our expectation that daily exposures may influence respiratory outcomes (which are also sampled daily). We have included that justification in the Introduction, lines 119-121. We chose a wristband passive sampler for the following reasons:

- Low cost: We find that silicone wristbands are cost-effective compared to other approaches. The silicone is purchased in bulk from 24hourwristbands.com (these are common silicone wristbands). The cost for silicone wristbands is primarily in analysis; the analysis cost is comparable to other types of matrices used for personal chemical exposure assessment (polyurethane foam, urine, etc.) (Anderson et al. 2017, Dixon et al. 2018). Because wristbands do not require any batteries or in-field maintenance these are additional reductions in cost from traditional air monitoring sampling equipment (Dixon et al. 2018). (lines 84-85, Introduction). Furthermore, this technology allows for intra-individual and inter-individual analyses’.

- Breadth of chemical detection: While this study evaluated 62 PAHs, we have expanded our methods to quantitatively analyze up to 1,530 chemicals in wristbands with a single analytical method (instrument run time under 1 hour), highlighting the importance of integrating this sampler in environmental health. This same breadth of chemicals cannot be captured with biological samples; there are not 1,530 organic chemical biomarkers that can be evaluated in biological samples or in other wearable devices. Researchers recently demonstrated that the wristband is a tool that can be used to efficiently screen chemical exposure of 1,530 organic chemicals on wristbands worn across three different continents (Dixon et al. 2019).

- Decreased burden on the participant (& more accurate reflection of personal chemical exposure): Wristbands do not interfere with a person’s daily activities and can be worn while swimming, working, sleeping, etc. In this study, 99% of all wristbands were returned (Table 2). Of those, 90% followed all compliance and quality assurance standards as outlined in the Materials and Methods. In comparison, traditional active air monitoring can be more burdensome and may alter a person’s behavior due to the weight (~5 pounds), humming noise produced by the sampler, and requirement to carry out the monitor during the study (Bohlin et al. 2007, Cherrie et al. 1994, Dixon et al. 2018).

- Bioavailable fraction of chemical exposures: Studies have shown that passive samplers reflect the bioavailable fraction of lipophilic organic chemicals (Paulik et al. 2016, Booij et al. 2006). In a previous study, co-authors Anderson, Kincl and Dixon compared PAH concentrations in silicone wristbands with paired PAH concentrations in active air monitoring backpack samples and PAH-metabolite concentrations in urine. There were three times more positive and significant correlations between PAH and PAH metabolite pairs in wristbands and urine samples than between PUF-filters and urine samples (Dixon et al. 2018). Similarly, other studies report strong significant correlations between concentrations in wristbands and concentrations in urine for flame retardants (Hammel
Lung function testing was restricted to the 3 easiest parameters: FVC, FEV1, and PEF. In my own experience the end-expiratory flows (MEF50, MEF25) are much more sensitive to early irritative effects and inflammatory responses of the small airways.

- We restricted our testing to these parameters, as they are the recommended metrics by the American Thoracic Society (Miller et al. 2005). Furthermore, using these established values, we are able to utilize established reference values for each participant, based on age, gender, race and height. This allows us to look at FEV1 values across the study population. We based our decision as well on previous papers that have utilized FEV1 as the main parameter (Adam et al. 2015; Baccarelli et al. 2014; Panis et al. 2017; Santos et al. 2016). We have added additional justification for the use of FEV1, FVC and PEF; please see lines 111-112, Introduction.

To sum up: (1) The choice of parameters (lung function, pollutants) is not very well argued. (2) At least some correlations would indeed increase the value of the paper. Right now it is only descriptive and therefore rather boring. I understand that this second requirement calls for additional calculations and therefore in my understanding the revision would be a major one.

- We appreciate the concerns, and have tried to best address them, as described above and in the revised manuscript.

Some minor points (language-wise):

Line 372f "...the use of cell phones … ha(s) been used…” (the use has been used???)

Line 357: "A basic assessment of compliance was assessed" (assessing an assessment?)

Line 417: "The ELF tool is now being used in a cohort study" (I assume "cohort study" is not the right term. I suggest using "panel study" instead!)

- Thank you, we have made these revisions. We appreciate the final clarification; this is a panel study, not a cohort study. We have updated the text accordingly on line 469.

Fuyuen Yip (Reviewer 2):

The authors provide a clear background on the development of the ELF and the need for improved personal exposure assessment for mixtures. One aspect that is less clear, however, is if there was interest among the community members to differentiate indoor vs. outdoor exposures? Or if the key focus was only outdoor PAH exposures? Does the GPS data assist in discerning indoor vs. outdoor exposures? Some additional information would be helpful. There is brief
mention in L181 regarding exposure to indoor pollutants, but it would be important to include language in a subsequent section so that the reader can understand how indoor exposures were assessed in addition to the outdoor exposures.

• Thank you for this clarification. This study built upon a pre-existing collaboration with a community organization called Beyond Toxics (Eugene, OR) and Carroll Concerned Citizens (Carroll County, OH). Working with these organizations, we conducted focus groups to evaluate community concerns regarding air quality (Rohlman et al. 2015). The results of the focus groups revealed that people largely wanted to know what, in total, they were being exposed to. That was one of the benefits they saw in a passive sampling wristband; it would capture both indoor and outdoor exposures. We have included this discussion in the Introduction, lines 119-121. To better understand indoor exposures, each participant completed a Daily Activity Log. Each day, they marked exposures to common air pollutants. We have included this information in the Materials and Methods (lines 158-161) and the Results section (lines 298 – 300).

Some additional information regarding the nature and frequency of participant training on spirometry would be helpful.

• We are happy to provide this. We have included the information in the Materials and Methods section, Lines 188-192.

In the recruitment of study participants, it may be helpful to provide some additional definitions for the eligibility criteria. For example, in L161, is 'asthma diagnosis' defined as currently having asthma or ever having asthma? And did the case definition include specific asthma severity levels? For 'non-smoker', does this refer to a current non-smoker or an individual who has never smoked? Based on Table 1, it is surmised that the definition is current non-smoker, but some additional clarification would be helpful, especially for future efforts in interpreting spirometry results.

• We have added this additional clarifying information, lines 182-183, Materials and Methods

For the performance of spirometry (L169 - L171), what type of feedback do the participants receive to ensure that the readings are successful?

• The spirometer does not provide feedback on if a reading is successful (i.e. valid) or not. However, participants are instructed to take 3 readings each time. Participants do receive immediate notification if the transfer of data from the spirometer to the phone is successful. As the data is received, it is analyzed using American Thoracic Society criteria to identify valid, successful readings. These criteria are included in Table 2, under the ‘Data Accuracy’ heading, and we have included a reference to this table in the text. Please see line 377, Results.

When did the participants provide feedback via telephone interview (L174) - was it at the end of the study period?
Participants provided feedback 1-2 weeks after they participated. As part of the study protocol, when an ELF device was returned, incentives were immediately mailed and the participant was contacted by telephone and asked if they would provide feedback on their experience using the ELF. Please see lines 383-385, Results.

There is a detailed summary provided on ELF Geospatial Analyses, with focus on outdoor air pollutant exposures. Perhaps some information can be added on how indoor exposures were also assessed and analyzed?

Thank you, we have provided some additional text on how we collected estimates of indoor exposures, assessing the presence or absence via participant-self report. Please see lines 298-300, Results.

How were the list of target PHAs selected?

The 62 PAHs were selected as they represent a wide breadth of physical-chemical properties, ranging from naphthalene’s two-ring structure (molecular weight of 128 and boiling point of 218°C) to dibenzo[a,l]pyrene’s six-ring structure (molecular weight of 302 and boiling point of 595°C; Anderson et al. 2015). Uniquely, this method not only includes PAHs from the U.S. Environmental Protection Agency’s (EPA’s) PAH priority list and the EPA’s list of PAHs with relative carcinogenic potency factors, but also includes PAHs that exist in complex environmental mixtures. The analytical method for the 62 target PAHs is described in-depth in Anderson et al. 2015. We added additional information on the 62 PAHs on lines 266-268, Materials and Methods.

(Table S3) For the "driving" variable, what does an average of 0.2 represent? Would it be more appropriate to treat this solely as a dichotomous variable (0/1), or were the decimal values also used in the analysis? Would this variable be treated similarly as the Wildfire smoke density variable?

We appreciate the opportunity to fix this in the manuscript. Initially, each GPS data point was analyzed to determine if a participant was driving, or not, as a dichotomous variable (0/1). Then, a percentage of all GPS points that were classified at driving was calculated. Therefore, the “driving” variable represents the percentage of GPS data points collected that were characterized as ‘driving’. However, the ELF App was programmed to collect GPS data at an increased rate when the phone was moving. As a result, a variable of 0.2 indicates that 20% of the GPS data points were characterized as ‘driving’, but this does not correlate to actual time spent driving. Therefore, we have removed the driving variable from the table, and will treat this as a dichotomous variable for future analysis. Please see an updated Table S3 (Supplementary Information).

Are there any preliminary results available regarding time spent indoors vs. outdoors?

We improved the GPS sensitivity and signal for our further data collection (to be published elsewhere); the data collected in this preliminary feasibility study was not at the proper resolution to estimate time spent indoors versus outdoors. Participants were
asked in the ELF phone app each day to estimate time spent indoors at home, work, school or transit, and time spent outdoors. We have included that information in the description of the study population. Please see lines 282-283, Results.

Were any data collected regarding possible indoor sources of PAHs (e.g., do they live with a smoker?)

• Yes, we collected data regarding possible indoor sources of PAHs. All participants were asked if they lived with a smoker or had smokers regularly visit their home. In addition, they filled out a Daily Activity Log. The log captured information about their use of and exposure to common sources of PAHs. We have included this information in the Materials and Methods section – please see lines 159-162.

The work suggests that the ELF can be a novel environmental health tool and has the capability to bring together environmental exposure and respiratory health data. It would be helpful, as part of the "proof-of-concept" discussion, to also have the authors help further address how the data collected could assist in improving one's understanding of exposures and linking that to sources (e.g., translation of Figure 2 into possible "action").

• We agree that all research should ultimately be designed to help initiate an ‘action.’ During the consent process, participants are asked if they would like to receive their data once the study is complete. While we did not discuss the return of data in this manuscript, we are preparing a manuscript discussing how we developed, in collaboration with communities, an online report-back tool. The tool uses multiple forms of charts, graphs and visuals to report the information back. This is accompanied by information on ways to reduce exposure to polycyclic aromatic hydrocarbons. We provide information regarding prior work we have done with community-engaged research using the silicone wristband, and how we used the data to improve participants understanding of exposures. We have referenced this in the Discussion, lines 463-467.

Inclusion of other potential limitations of the work, namely, other aspects in addition to the fact that current correlations are dependent on stationary air monitoring networks, would also help to strengthen the discussion.

• We appreciate the insight to include further explanation of potential limitations in the Discussion. We have added to the Discussion as appropriate, 430-436, 438-439, and lines 458-459.