Assessing the External Exposome Using Wearable Passive Samplers and High-Resolution Mass Spectrometry among South African Children Participating in the VHEMBE Study

Jeremy P. Koelmel, Elizabeth Z. Lin, Kayley DeLay, Antony J. Williams, Yakun Zhou, Riana Bornman, Muvhulawa Obida, Jonathan Chevrier, and Krystal J. Godri Pollitt*

Jeremy P. Koelmel − Department of Environmental Health Sciences, Yale School of Public Health, New Haven, Connecticut 06520, United States; orcid.org/0000-0001-9985-8901

Elizabeth Z. Lin − Department of Environmental Health Sciences, Yale School of Public Health, New Haven, Connecticut 06520, United States

Kayley DeLay − Department of Environmental Health Sciences, Yale School of Public Health, New Haven, Connecticut 06520, United States

Antony J. Williams − Center for Computational Toxicology and Exposure, Office of Research and Development, United States Environmental Protection Agency, Research Triangle Park, North Carolina 27711, United States

Yakun Zhou − Department of Environmental Health Sciences, Yale School of Public Health, New Haven, Connecticut 06520, United States

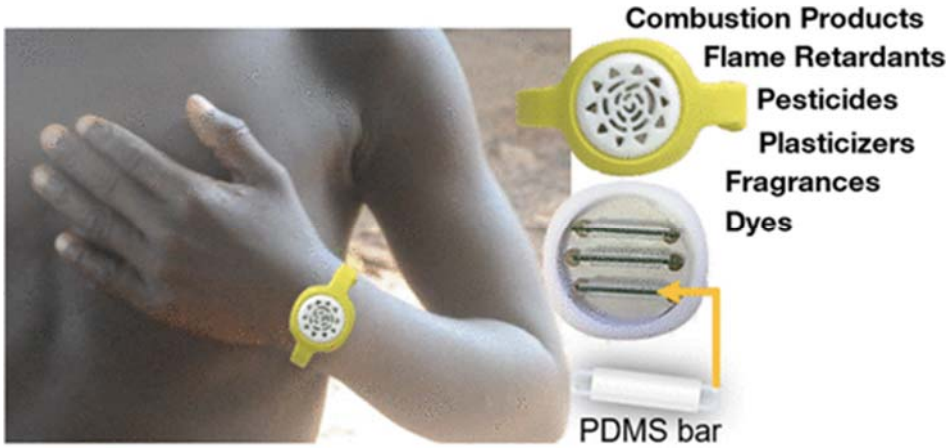
Riana Bornman − University of Pretoria Institute for Sustainable Malaria Control and School of Health Systems and Public Health, University of Pretoria, Pretoria 0028, South Africa

Muvhulawa Obida − University of Pretoria Institute for Sustainable Malaria Control and School of Health Systems and Public Health, University of Pretoria, Pretoria 0028, South Africa

Jonathan Chevrier − Department of Epidemiology, Biostatistics and Occupational Health, Faculty of Medicine, McGill University, Montréal, Québec H3A 1A2, Canada

*Corresponding Author
Krystal J. Godri Pollitt − Department of Environmental Health Sciences, Yale School of Public Health, New Haven, Connecticut 06520, United States; orcid.org/0000-0001-7332-2228; Email: krystal.pollitt@yale.edu

Abstract



Children in low- and middle-income countries are often exposed to higher levels of chemicals and are more vulnerable to the health effects of air pollution. Little is known about the diversity, toxicity, and dynamics of airborne chemical exposures at the molecular level. We developed a workflow employing state-of-the-art wearable passive sampling technology coupled with high-resolution mass spectrometry to comprehensively measure 147 children's personal exposures to airborne chemicals in Limpopo, South Africa, as part of the Venda Health Examination of Mothers, Babies, and Their Environment (VHEMBE). 637 environmental exposures were detected, many of which have never been measured in this population; of these 50 airborne chemical exposures of concern were detected, including pesticides, plasticizers, organophosphates, dyes, combustion products, and perfumes. Biocides detected in wristbands included *p*,*p*'-dichlorodiphenyltrichloroethane (*p*,*p*'-DDT), *p*,*p*'-dichlorodiphenyldichloroethane (*p*,*p*'-DDD), *p*,*p*'-dichlorodiphenyldichloroethylene (*p*,*p*'-DDE), propoxur, piperonyl butoxide, and triclosan. Exposures differed across the assessment period with 27% of detected chemicals observed to be either higher or lower in the wet or dry seasons.

KEYWORDS: exposome; wristbands; children's health; Africa; exposure assessment; chemicals

Synopsis

This study assesses hundreds of airborne chemical exposures of children in rural South Africa including previously undocumented exposures.

1. Introduction

In 2016, it was estimated that 23% of the global disease burden was attributable to environmental factors. [1,2] Enhanced vulnerability was identified in low- and middle-income countries (LMIC) due to increasing chemical production and use, lack of regulation/enforcement and education on chemical exposure risks, and differences in priorities due to the need for economic development. [3,4] Further concerns have been raised regarding the unique challenges in sub-Saharan Africa related to the lack of infrastructure for waste management and water treatment, poor availability of low-cost fuels, and high risk for malaria. [5,6] Over 90% of rural populations in Africa burn refuse or biomass for cooking or heating. This practice can generate household air pollution (HAP), with fine particulate matter ($PM_{2.5}$) levels commonly exceeding that of the World Health Organization guidelines. [7–9] Given the systemic inflammation and oxidative stress induced by $PM_{2.5}$, elevated HAP exposure is ranked as the second environmental factor of concern in global burden of disease. [10,11] In malaria endemic areas, the adverse effects of $PM_{2.5}$ may be compounded by insecticides applied on the interior walls of homes through indoor residual spraying for malaria control. This practice can result in elevated exposure to DDT and pyrethroids which may affect child development by inducing oxidative stress or by disrupting sex hormones. [12–17] Environmental exposure to insecticides from indoor residual spraying in the Limpopo province of South Africa has recently been associated with accelerated fetal growth among girls, [18] reduced social-emotional scores at 1 and 2 years of

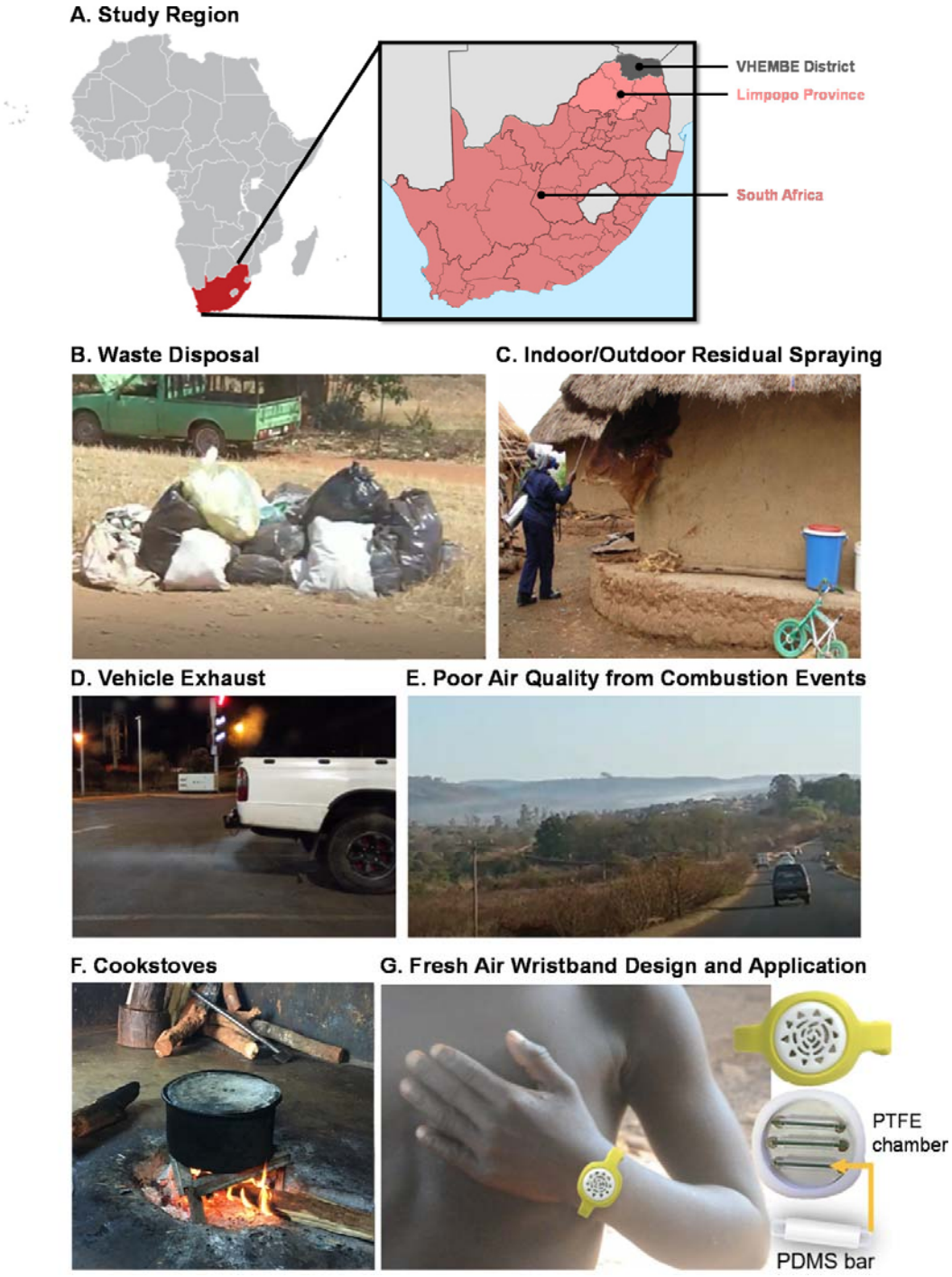


Figure 1. Map and images from across the study region. Study participants were from the VHEMBE district in the Limpopo province in South Africa (A). Examples are shown of refuse left beside roadways across the study area (B), application of residual pesticides inside and outside the homes of study participants (C), visible tailpipe emissions from diesel vehicles (D), combustion events leading to poor regional air quality (E), and a cookstove that is typical of the region where biomass, plastic, and other refuse are used as fuels (F). The Fresh Air wristband was used for personal exposure assessment of study participants (G). The wristband consists of a PTFE chamber that contains custom-fabricated PDMS sorbent bars, which passively absorb airborne contaminants.

age, [19] allergies in children at 3.5 years, [20] hypertensive disorders among pregnant mothers, [21] weight gain in girls, [22] and other health impacts. [21–26]

Children from these rural regions of Africa often spend extended periods of time indoors, near cooking fires, which can result in high exposure to airborne pollutants. [6,27] Exposure to environmental contaminants during critical windows of susceptibility coupled with poverty and malnutrition may enhance vulnerability. [28,29] Understanding the extent to which these factors contribute to poor health requires a comprehensive assessment of environmental exposures. The studies that have been conducted to date in sub-Saharan Africa have focused on a limited panel of PAHs, pesticides, or other regulated air pollutants. [19,21,25,26,30–35] The lack of an available technology which can be feasibly deployed with children in a LMIC context has presented challenges in the breadth and scale of environmental measurements that can be captured. We recently developed a lightweight, low-cost, and non-invasive device (the Fresh Air wristband) to facilitate population-scale exposure assessment in LMICs (Figure 1A). [36–42] The Fresh Air wristband is an exposomic sensor technology for evaluating an individual's personal exposure to contaminants from combustion, consumer products, clothing, and dietary (foods and additives) sources. [43] While the wristband does not directly measure the types of products and diet, mixtures of airborne chemicals measured can be used to specify what is being cooked, used, and worn. The device passively absorbs airborne chemicals into a polydimethylsiloxane (PDMS) sorbent membrane that is contained in a unique sheltered design that both minimizes the effects of wind on uptake rates [44,45] and eliminates direct dermal contact (Figure 1B). This contained design is especially important for children who are prone to play with the samplers.

Coupling the wristband technology with gas chromatography high-resolution mass spectrometry (GC-HRMS) enables evaluation of the occurrence, distribution, and magnitude of expected environmental contaminants of concern and screening for thousands of unexpected chemical exposures. [40] After chemical characterization of exposure profiles, newly introduced methods can be deployed to rapidly categorize detected compounds based on toxicity using experimental and computational evidence. [46–51]

The objective of this study was to evaluate the environmental exposures of children in the Limpopo province of South Africa and identify the exposures of most concern. While South Africa overall has the highest GDP per capita in the continent, our study region in the VHEMBE district is not reflective of this level of income with approximately 60% of the study population having a household income below 1 USD per person per day. Exposures were evaluated for children between the ages of 5 and 6.5 years enrolled in the Venda Health Examination of Mothers, Babies, and their Environment (VHEMBE) Birth Cohort using the Fresh Air wristband. Given their high breathing rates, high food consumption per body weight unit, large skin surface to volume ratios, and immature detoxifying capabilities, developing children may be more susceptible to the health impacts of chemical exposures than adults. [52–55] While the health impacts of criteria air pollutants and insecticide use are recognized, [19,21,25,26,30,31] other sources of environmental exposures may be missed in rural African populations. We determined likely chemical structures for 637 chemicals, including 50 chemical exposures of concern consisting of combustion products, insecticides and other biocides, dyes, fragrances, organophosphates, and plasticizers. This work demonstrates the feasibility of using novel exposomic sensors in a LMIC context, enabling a holistic exposure assessment approach to identify regionally specific environmental exposure signatures. Meteorological conditions, industries, consumer products, heating and cooking practices,

and residential conditions significantly differ across the African continent. Regional studies are needed to determine how environmental exposures are influenced by these factors and further explore variability with economic status and cultural practices.

2. Materials and Methods

2.1. Population, Site Characteristics, and Study Design

This study leveraged ongoing research from the VHEMBE program, a birth cohort study that originally enrolled 752 mother–child pairs from rural villages in the Vhembe district of Limpopo, South Africa. The overall aim of the VHEMBE program is to identify, understand, and manage environmental determinants of maternal and child health in rural South Africa in order to inform the development of future interventions to mitigate exposures. Pregnant women were recruited when they presented to give birth at Tshilidzini Hospital in the town of Thohoyandou between 2012 and 2013. Enrollment was restricted to women above the age of 18 years who spoke Tshivenda as their primary language at home, resided less than 20 km from the hospital and did not have intentions of moving away from the area within the following two years, were not infected with malaria during pregnancy, had contractions at least 5 minutes apart, and gave birth to a live singleton. Further information about the VHEMBE program has been published previously. [19]

Chemical exposure was assessed for 147 children ages 5 to 6.5 years participating in the VHEMBE program between October 2018 to January 2019 and July 2019 to September 2019. Some families moved away from the immediate area (>20 km from Tshilidzini Hospital), requiring extended travel times (>30 minutes). Exposures were evaluated using Fresh Air wristbands worn over a 72 h sampling period. Children were instructed to only remove samplers while bathing or swimming. At the end of the 72 h (about 3 days), wristbands were collected. There were no cases where participants self-reported that their wristband was submerged in water or experienced significant water contact.

The primary caregivers of study children were interviewed in Tshivenda (the main language spoken in the study area) by study staff based on structured questionnaires at the time of the child's birth as well as at 1 week and 1, 2, 3.5, and 5 years of age. Questionnaires were also administered to caregivers in Tshivenda at the time the Fresh Air wristband was picked up at participants' homes to collect data on exposure-related events during sampling such as the date(s) and time(s) of cooking/burning materials, which fuels were used, whether fires occurred indoors or outdoors, and whether the child was present during biomass burning. Other information was recorded based on staff observations such as the road and traffic conditions near their home, their proximity to large factories/warehouses or other major sources of pollution, the primary area of cooking, if a secondary cooking area was used, and GPS coordinates for cooking locations and the child's bedroom. All caregivers provided informed consent prior to data collection. This study was approved by Institutional Review Boards from McGill University, the University of Pretoria, the Limpopo Department of Health and Social Development, Tshilidzini Hospital and Yale University.

2.2. Wristband Preparation, Deployment, and GC-HRMS Data-Acquisition

Wristband preparation and data-acquisition have been previously described. [42,56,57] Briefly, PDMS sorbent bars were custom-fabricated and cleaned in a vacuum oven (2 h, 300 °C)

prior to use. PDMS sorbent bars were transported in airtight 2 mL amber glass vials with polydimethylsiloxane (PTFE) septa caps from Yale University to the study field office at Tshilidzini Hospital at room temperature. Immediately prior to deployment, study field staff inserted four pre-cleaned PDMS sorbent bars into the custom-designed PTFE chambers and mounted these chambers into wristband attachments.

Participants were asked to remove the wristband while bathing or swimming. At the end of the exposure assessment period, study field staff collected and stored the Fresh Air wristband in the air-tight container while being transported back to the study field office. Immediately after arrival, the field staff removed the PDMS sorbent bars from each sampler and placed them back into the airtight glass storage vials using stainless steel forceps. Samples were stored in a refrigerator at the study field office and transported using cold chain shipment to the Yale School of Public Health. Samples were then stored at −20 °C prior to analysis. Field blanks collected during the study were used to correct for potential contamination. These PDMS bars (field blanks) were processed similarly to participant samples, including both storage and placement in and out of PTFE chambers and wristband attachments (to simulate sample preparation) but were not placed on participants.

Fresh Air wristbands were designed to primarily capture chemicals in the gas phase but this sampling tool also collects particles by deposition. Given the nature of the study location and activities of the study participant, there was significant deposition of particles/dust on samples. PDMS sorbent bars were rinsed immediately prior to analysis using Optima LC/MS grade water. While this wash protocol was aimed at removing excess particulate debris in preparation for sample analysis, we acknowledge deposited ambient particulate matter may have also been removed. PDMS sorbent bars were then spiked with an internal standard mixture which contained 4,4′-dibromooctafluorobiphenyl, 5′-fluoro-2,3′,4,4′,5-pentabromodiphenyl ether, naphthalene-d_8, 1-methylnaphthalene-d_{10}, acenaphthene-d_{10}, fluorene-d_{10}, phenanthrene-d_{10}, fluoranthene-d_{10}, pyrene-d_{10}, perylene-d_{12}, phenol-d_5, and *p*-terphenyl-d_{10}. Sorbent bars were then placed into pre-cleaned glass autosampler tubes (Gerstel, Linthicum, MD, USA) on a temperature-controlled autosampler tray maintained at 10 °C (MéCour, Groveland, MA, USA). For sample analysis, an autosampler tube was transferred into a thermal desorption unit (TDU; Gerstel, Linthicum, MD, USA). The TDU was initially held at 30 °C for 1.1 min and then ramped at 720 °C per minute to 280 °C (5 min hold) under a flow rate of 350 mL/min of helium gas (99.999%). Extracted analytes were cyro-focused to −90 °C on a 2 mm glass wool deactivated liner in a cooled injection system (Gerstel, Linthicum, MD, USA) cooled to −90 °C. The transfer line between the TDU and cooled liner was maintained at 250 °C. Analytes were directly transferred to the GC column (TG-5SILMS, 30 m × 0.25 mm × 0.25 µm; Thermo Fisher Scientific, Waltham, MA). The carrier gas flow (helium) was set to 1.4 mL/min, and the GC oven was held at 70 °C for 1 min and then ramped at 7 °C/min to 300 °C. The final temperature was held for 4.0 min for a total run-time of 37.86 min. During the analysis, full-scan electron ionization (EI) mass spectra (*m*/*z* 53.4–800) were recorded at an acquisition rate of 4 Hz and at 60,000 resolution on a Q-Exactive Orbitrap mass spectrometer (ThermoFisher, Waltham, MA, USA). QCs and blanks (laboratory and transport) were run every five samples.

2.3. Suspect Screening and Data-Processing Workflow

Data-processing consisted of spectral deconvolution, compound annotation, and alignment in Compound Discoverer 3.2 (Thermo Fisher Scientific, Waltham, MA). Compound Discoverer was used for the determination of the relative abundances and possible identifications (annotations) of compounds across all participants. In-house scripts performed filtering to determine the highest confidence annotations, remove noise and measured chemicals unrelated to exposures (background signal), and normalize the signal for comparison across instrument batches and between compounds. Alkanes were used to calculate Kovat's retention indices [58] for all features. The workflow has been described in-depth previously. [40]

The raw mass spectrometry datasets were first converted to a table of aligned features (retention times and associated deconvoluted fragments) using Compound Discoverer 3.2. The table consisted of chemical abundances across all samples and field blanks, tentative annotations using a composite score of retention index (RI) matching, a dot-product search index (SI) and reverse SI (RSI), high-resolution mass filter (HRMF), and reverse HRMF (RHRMF). Tentative annotations were assigned using the NIST 2017, Wiley 11th edition, and GC-Orbitrap (Thermo Fisher Scientific) EI spectral libraries, together covering over 740,000 unique chemical structures. All tentative annotations containing a calculated RI and library RI were removed if RI differences were higher than 100.

After processing in Compound Discoverer, the dataset was exported as an Excel file, and an in-house script was used to designate annotations as "high confidence", "medium confidence," or "low confidence." High confidence annotations had molecular ions observed if in the library, RI matches within 50 units, RHRMF scores greater than 75, SI scores greater than 500, and RSI scores greater than 600. These confident annotations accurately define the exact chemical structure or a closely resembling isomer (e.g., the methyl positions for dimethyl naphthalene will not be known). Medium confidence scores were those meeting the same criteria, except for RI and molecular ion matching. All the remaining scores were designated as low confidence. Manual review of 25 high confidence annotations of interest was performed to validate the method, as well as confirmation of the top hit from the scoring method using over 70 standards. Chemicals which were determined to be the most toxic or of interest due to trends and use were validated via manual inspection of spectra and/or against standards, including various PAHs, propoxur, piperonyl butoxide, DEET, DDT, DDD, and DDE. Following ranking of confidence, blank feature filtering (BFF), [59] duplicate removal (by name and CAS-RN), batch-wise median normalization, and TIC recalculation was performed as described previously. [40] For each feature, a blank threshold was calculated using the blank feature filtering method. Specifically, $x_{75\%} > 2(\bar{b} + 3\sigma b)$, where $x_{75\%}$ is the 75 percentile of samples, $\bar{b}$ is the field blank average, and $3\sigma b$ refers to 3 times the standards deviation of the blank.

2.4. Statistics and Data Interpretation

Resulting annotations were ranked to determine the potential chemicals of most concern. Predicted acute toxicity and AMES mutagenicity for screening likely carcinogens was performed using the US-EPA CompTox Chemicals Dashboard [47] (from here on referred to as the Dashboard) batch search function (using CASRN as inputs). Chemicals were ranked by predicted mammalian acute toxicity (rat oral LD_{50}, 24 h), [49] developmental toxicity, [48] and

mutagenicity [50,60] to determine the top compounds of concern. Furthermore, chemicals were screened to determine those chemicals deemed as high priority due to human health and environmental concerns by various governmental organizations using lists contained in the Dashboard. [47] These lists included:

(1) The EPA Toxics Release Inventory, [61,62] which lists 677 chemicals which either have acute or chronic human health effects (e.g., cancer causing compounds) or significant adverse environmental effects (https://comptox.epa.gov/dashboard/chemical_lists/TRIRELEASE).

(2) The Agency for Toxic Substances and Disease Registry (ATSDR) (U.S. Department of Health and Human Services) list contained in the Toxic Substances Portal (200 chemicals deemed toxic to human health) (https://comptox.epa.gov/dashboard/chemical_lists/ATSDRLST) [63]

(3)The Minnesota Department of Health Chemicals of High Concern and Priority Chemicals list which was established under the Toxic Free Kids act (1643 chemicals of health concern, especially to vulnerable population including children and pregnant mothers) [64] (https://comptox.epa.gov/dashboard/chemical_lists/MNDOHTOXFREE) [6,64])

(4) The 20 high priority chemicals selected from the Toxic Substances Control Act Chemical (TSCA) Substance Inventory (41,587 active chemicals) which are undergoing further review based on health concerns (https://comptox.epa.gov/dashboard/chemical_lists/TSCAHIGHPRI).

(5) The NORMAN European Food Safety Authority Priority Substances (178 chemicals of 2336 chemicals assessed which were selected based on toxicity, environmental release, lack of biodegradation, and bioaccumulation in food) (https://comptox.epa.gov/dashboard/chemical_lists/EFSAPRI). [65]

(6) The NORMAN Potential Persistent, Mobile, and Toxic (PMT) substances (269 chemicals) (https://comptox.epa.gov/dashboard/chemical_lists/UBAPMT).

Furthermore, chemicals with the highest inhalation toxicity, dermal toxicity, ocular irritation, and carcinogenicity were identified using the prototype EPA Hazard Comparison Dashboard (EPA-HCD), an application resulting from adding additional data and functionality to the reported Alternatives Assessment Dashboard. [46] This dashboard compiles both experimental and predicted toxicities from various organizations and categorized chemicals from low to very high in categories spanning both health hazards and chemical properties.

Multivariable analysis (Principal Component Analysis) and univariate analysis [analysis of variance (ANOVA) and volcano plots] were performed in Metaboanalyst 5 [66] to compare exposures across seasons. Data was mean centered and log transformed prior to analysis. Participants were grouped based on date of sampling, with 99 participants falling under the dry season (July/August, with 8 of these 99 participants falling in the transition month of September). The remaining participants were classified as falling within the wetter season (October/November/December). Furthermore, levels of chemicals were compared across poverty and cooking fuel types and frequencies. For all univariate tests, p-values were adjusted using the Hochberg method to correct for multiple testing errors. Food poverty (yes or no) was defined as having a household income below R547 per person per month when children were 5 years old based on Statistics South Africa guidelines.

3. Results and Discussion

Personal exposure assessment using the Fresh Air wristband (Figure 1) is a relatively low-cost method for investigating the external exposome of vulnerable individuals including children. This study had a relatively high participation rate, attributable to the long-term partnerships between the study field staff and participants' families, as well as the comfortable and aesthetically pleasing design of the Fresh Air wristbands. Early on in this study, our study staff encountered several challenges trying to recover the wristbands. Some wristbands were lost during play or in the pit toilets, others were ripped off and some caregivers attempted to repair the bands, and some were intentionally taken off by children and hidden from study staff. There was also evidence of tampering of some wristbands such as chew marks and other children left small stones inside the PTFE chamber. To minimize loss, and increase participation rate, we prevented the chamber from being opened using Torx-headed screws. The combination of this "childproofed" design and a t-shirt offered as a reward for returning an intact wristband, increased sample recovery. A total of 194 wristbands were deployed, of which 151 (78%) were analyzed, being returned in good condition with no/minimal evidence of damage or tampering; 114 (59%) wristbands demonstrated some evidence of damage or tampering, and 37 (19%) of these wristbands were damaged such that analysis was not possible. Eight (4%) wristbands were lost by participants. These challenges were likely related to the inherent inquisitiveness of the young participants. Our team is exploring additional design modifications of the Fresh Air wristband to improve sample recovery and quality for future studies.

Exposure profiles were assessed for 147 children enrolled in the VHEMBE study between the age of 5 and 6.5 years (4 of the 151 removed due to acquisition/storage/labeling issues). Due to various sources of emissions of concerns, including cookstoves using plastic and biomass for cooking (Figure 1A,B), unfiltered vehicle exhaust (Figure 1C), open refuse disposal and biomass and refuse burning (Figure 1D), and indoor and outdoor pesticide application (Figure 1E), a diverse array of exposures were expected. Thousands of chemical signatures from various sources were detected in these children, showing the breadth of coverage of this technique. Across the children that were included in the study, 3,580 chemicals were annotated after removing any signatures from transport or other background sources. Of these, 637 were assigned a chemical structure with "high confidence", meaning that the exact structure or a close structural isomer are likely the correct annotation (see Materials and Methods). Our previous studies in different study locations areas found a similar number of annotated compounds in Jinan, China [(40)] but fewer exposures in New Haven, CT, United States, [(57)] suggesting that the diversity of chemical exposures varies geographically. These "high confidence" annotations can be considered as Level 2 annotations (probable structure), whereas "medium confidence" annotations can be considered Level 3 (tentative candidate) using the Schymanski scheme. [(67)] Comparison to over 70 standards and the 12 internal standards shows a false positive rate for these "high-confidence" annotations close to 11%, where a false positive was considered a dissimilar isomer (more than two bond positions different) or non-isomeric species. For example, the difference in methyl positions in methylated PAHs may not be discernible even with the RI matching using our GC-HRMS approach, and hence different positional isomers are not considered false positives. We have previously described our suspected screening approach and the confidence of identified exposures; no false positives

were found for chemicals validated using standards and assigned as “high confidence” annotations. [57]

A further 1,209 chemical annotations were assigned with “medium confidence”, meaning that the chemical class was likely correct, but the exact structure may not be (see the Supporting Information for all detected compounds, confidence assignments, and relative abundances). It is important to note that while the chemical coverage of this technique is extensive, sampling of airborne pollutants using the PDMS sorbent bars in the Fresh Air wristbands is limited to absorption of gases and deposition of particles. The technique presents challenges for evaluating exposure to non-volatile or very volatile compounds as well as comprehensive characterization of ambient particulate matter. To facilitate capture of the latter, study particulates wore an Ultrasonic Personal Aerosol Sampler (UPAS) in parallel with the Fresh Air wristband. [68]

Chemical exposures detected using the Fresh Air wristbands were screened against the chemical priority lists developed by various non-profit and government agencies in Europe and the United States to determine chemical exposures which may pose health risks (Figure 2). These lists consist of chemicals with acute or chronic toxic effects, or those suspected of being toxic which were under further review by government agencies. Certain lists also accounted for environmental fate and transport and the exposure potential to each chemical. Of special relevance was the Minnesota Department of Health Chemicals of High Concern and Priority Chemicals List which was established under the Toxic Free Kids (TFK) Act and consists of 1,643 chemicals (referred to here on out as the “TFK list”). [64] The TFK list contains chemicals of health concern, especially to vulnerable populations such as children. Forty-six of the 637 chemical exposures assigned with high confidence were found in at least one of the six priority lists, with 20 occurring in 2 or more lists and 37 occurring on the TFK list (Figure 2). These chemicals were found across multiple uses including pesticides (e.g., insecticides), plasticizers (e.g., phthalates), combustion products (polycyclic aromatic hydrocarbons (PAHs) and furans), flame retardants, fragrances, dyes, and personal care products (Figure 2). This shows the diverse sources of chemicals of potential health concern in this rural population of South Africa.

The lists of chemicals of concern screened in this study were developed by government agencies and organizations in the United States and Europe. Interestingly, these children in remote South African villages are exposed to a plethora of synthetic chemicals also impacting children in developed countries, including flame retardants, (e.g., tris(2-carboxyethyl) phosphine (TCEP), tris(2-chloroisopropyl) phosphate (TCPP), and triphenyl phosphate) (Figure 2). The priority lists developed in high income countries may not reflect the chemical risks of those living in developing countries because exposure potential in the two settings may be different.

Production of manmade chemicals is increasing and changing overtime, and local communities often do not have the funding to characterize these chemical exposures in a non-targeted fashion. [3] Expanding our exposure assessment approach using a wearable passive air sampling technology to other locations spanning diverse economies, industries, environments, and cultures, will provide data leading to a global understanding of the type of exposures people are exposed to and factors influencing these exposures. Furthermore, priority lists should account for these diverse populations, so that region-specific lists of chemicals of concern can be more effectively deployed, without missing chemicals which do not appear in Western countries with different regulations, for example. Finally,

experimental toxicity values can then account for a wide range of chemicals which are not prioritized in the West.

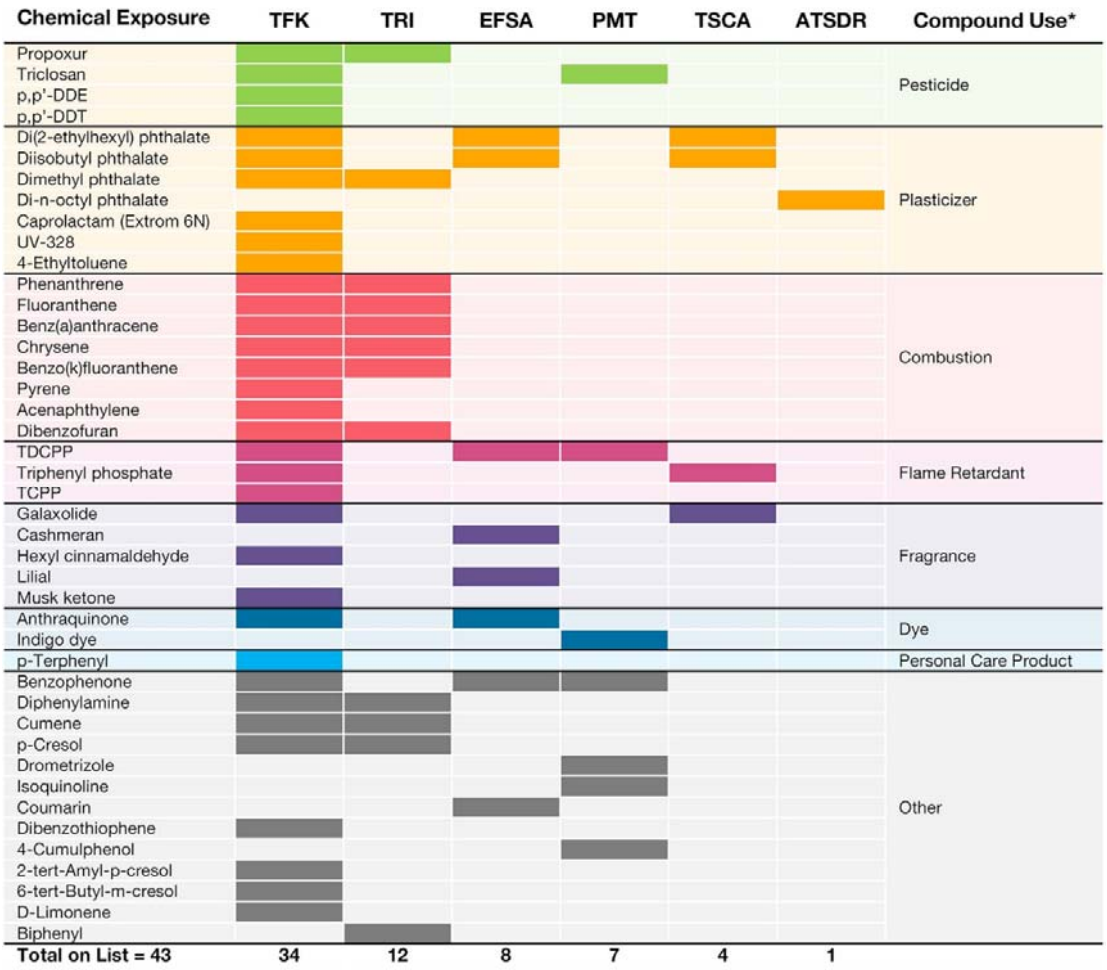


Figure 2. Forty-six chemical exposures detected in South African children which are listed in the following priority lists: NORMAN Potential Persistent, Mobile, and Toxic (PMT) substances (269 chemicals), the NORMAN European Food Safety Authority (EFSA) Priority Substances (178 chemicals), the 20 high priority chemicals selected from the Toxic Substances Control Act Chemical (TSCA) Substance Inventory, EPA Toxics Release Inventory (TRI), which lists 677 chemicals which either have acute or chronic human health effects, The Agency for Toxic Substances and Disease Registry (ATSDR), which lists 200 chemicals deemed toxic to human health, and the Minnesota Department of Health Chemicals of High Concern and Priority Chemicals list, which was established under the Toxic Free Kids (TFK) act (1,643 chemicals of health concern, especially to vulnerable populations). Other acronyms: *p*,*p*'-dichlorodiphenyltrichloroethane (*p*,*p*'-DDT), *p*,*p*'-dichlorodiphenyldichloroethylene (*p*,*p*'-DDE), tris(2-carboxyethyl)phosphine (TCEP), and tris(2-chloroisopropyl)phosphate (TCPP). *Note that common sources/uses of chemicals are provided, but these are not the only source of these chemicals and may not be the main sources of these chemicals in this population.

The Fresh Air wristband collects airborne contaminants, primarily representative of inhalation exposures. Pollutants in the air can lead to ocular exposures, deposit and be absorbed by the skin, and partition to the particle phase which may settle as dust that is ingested. Chemicals were additionally screened by predicted toxicity for these various routes of exposure, including oral acute toxicity and mutagenicity, as well as compiled

experimental evidence of “very high” acute inhalation toxicity, dermal toxicity, carcinogenicity, and ocular irritation using the EPA-HCD [46] (Figure 3).

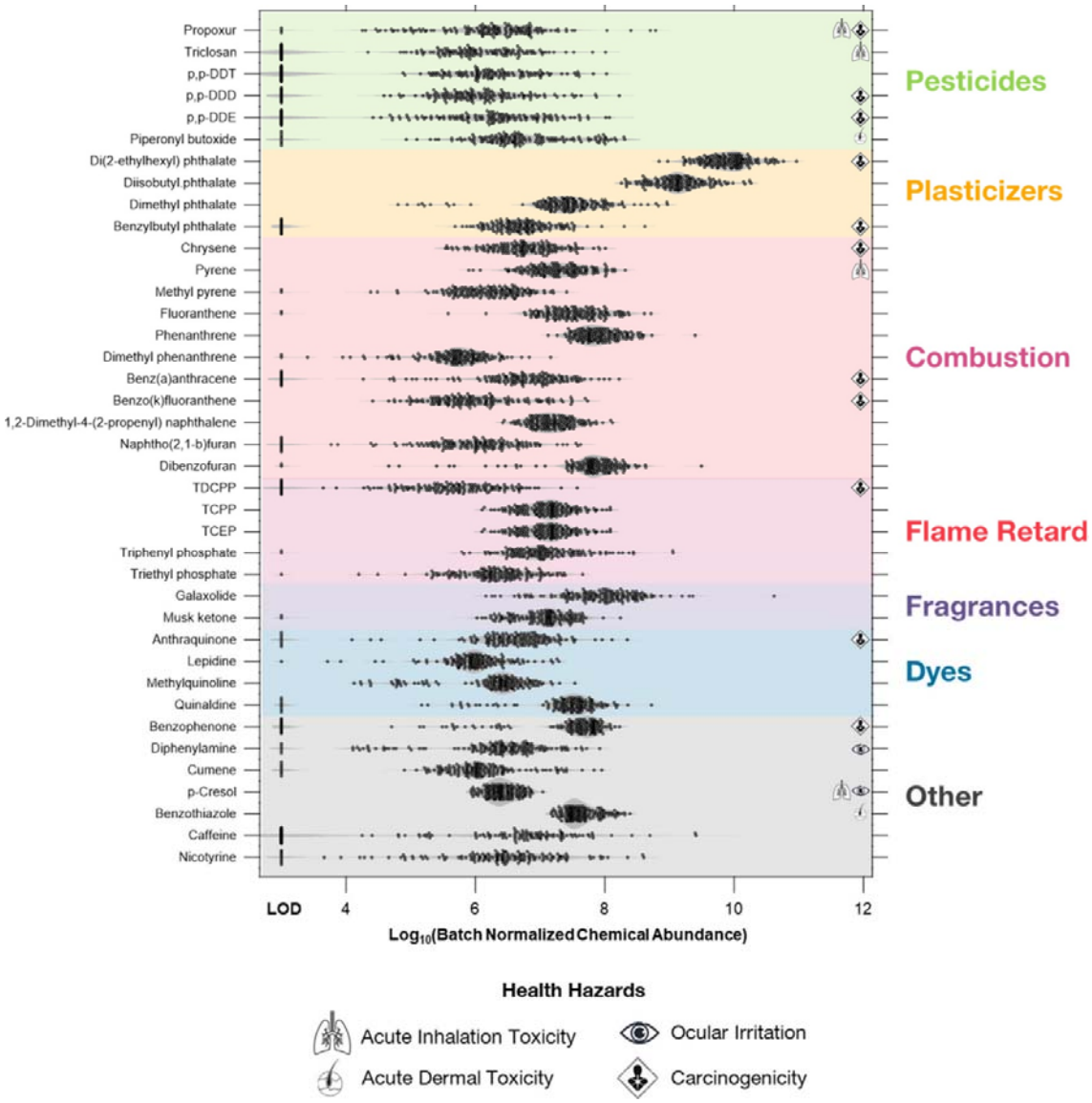


Figure 3. Thirty-five chemicals of potential concern. These chemical exposures of concern were highlighted based on occurrence in two or more priority lists (see Materials and Methods) and/or the top 10 compounds with the highest predicted acute toxicity (inhalation, dermal), ocular irritation, and carcinogenicity (predicted AMES mutagenicity). Normalized, transformed relative abundances are shown. This measure is unitless. Chemicals are grouped by common sources/uses; chemicals may also be derived from other sources. Acronyms: dichlorodiphenyltrichloroethane (*p*,*p*’-DDT), dichlorodiphenyldichloroethane (*p*,*p*’-DDD), dichlorodiphenyldichloroethylene (*p*,*p*’-DDE), tris(2-carboxyethyl)phosphine (TCEP), tris(2-chloroisopropyl)phosphate (TCPP), and limit of detection (LOD).

The hazard scores of low (L), moderate (M), high (H), or very high (VH) hazard represented in the EPA-HCD are based on the DfE Alternatives Assessment Criteria for Hazard Evaluation, which provides guidance for converting values from a variety of different sources and formats into the consistent L, M, H, and VH scores (US EPA Design for the

environment program alternatives assessment criteria for hazard evaluation Version 2.0. https://www.epa.gov/sites/production/files/2014-01/documents/aa_criteria_v2.pdf.). "Very high" is the highest category of toxicity on the EPA-HCD. Carcinogenic compounds that the children were exposed to that were categorized as "very high" toxicity included those from combustion products (PAHs: chrysene, benzo(*k*)fluoranthene, and benz(*a*)anthracene), phthalates, and components of insecticides used to control malaria in the villages including *p*,*p*'-DDT and its degradation product, *p*,*p*'-DDE (dichlorodiphenyl dichloroethylene) (Figure 3). Chemicals with exceedingly high acute dermal toxicity detected included benzothiazole (used in car tires and found in other consumer/industrial products) and piperonyl butoxide (used as a synergist to enhance insecticide efficacy against malaria carrying mosquitoes in South Africa [69]). Inhalation toxicity is of special relevance in this study. The Fresh Air wristband design has a perforated chamber that eliminates direct contact of the PDMS sorbent bar with the skin; any chemicals monitored were volatile or semi-volatile chemicals in the air. Therefore, all chemicals detected are likely being inhaled by the children to some degree. Of great concern are the five chemicals detected with very high acute inhalation toxicity (*p*-toly(4-methylbenzyl) sulfide (ot shown), pyrene, *p*-cresol, triclosan, and propoxur; Figure 3).

Insecticides are sprayed on the interior walls of residences in the study region to control malaria through indoor residual spraying practices; DDT is primarily applied to the interior walls of unpainted mud dwellings, and the pyrethroids deltamethrin or cypermethrin are primarily applied to homes with painted walls. [70] DDT and its breakdown product, DDE has been detected in serum collected from the mothers of VHEMBE participants. [71] *p*,*p*'-DDT and *p*,*p*'-DDE were also detected by Fresh Air wristbands worn by children in the current study. *p*,*p*'-DDD, *N*,*N*-diethyl-*meta*-toluamide (DEET), piperonyl butoxide, [69] and propoxur [72] were additionally observed, which are all active ingredients in insecticides, insecticide transformation products, or used in mosquito-repellant products. Most children had detectable levels of these insecticides and insecticide synergists (Figure 3), with, for example, all insecticides, insecticide synergists, and insecticide transformation products being detected in 75% or more of the participants (Figures 3 and 4C). The distributions of these chemicals were similar across participants (Figure 3), with most children having pesticide exposure within 2 orders of magnitude of each other (Figure 3). To our knowledge, while over 40 pesticide exposures have been measured in Africa, [73–75] including airborne exposures to *p*,*p*'-DDT and *p*,*p*'-DDE, this is the first study to measure exposures to propoxur, piperonyl butoxide, and DEET, as well as triclosan, another biocide, in rural Africa. These unique surrogate measurements of inhaled chemical exposures in children raise concern, as both propoxur and triclosan likely have very high acute inhalation toxicity as determined by the EPA-HCD.

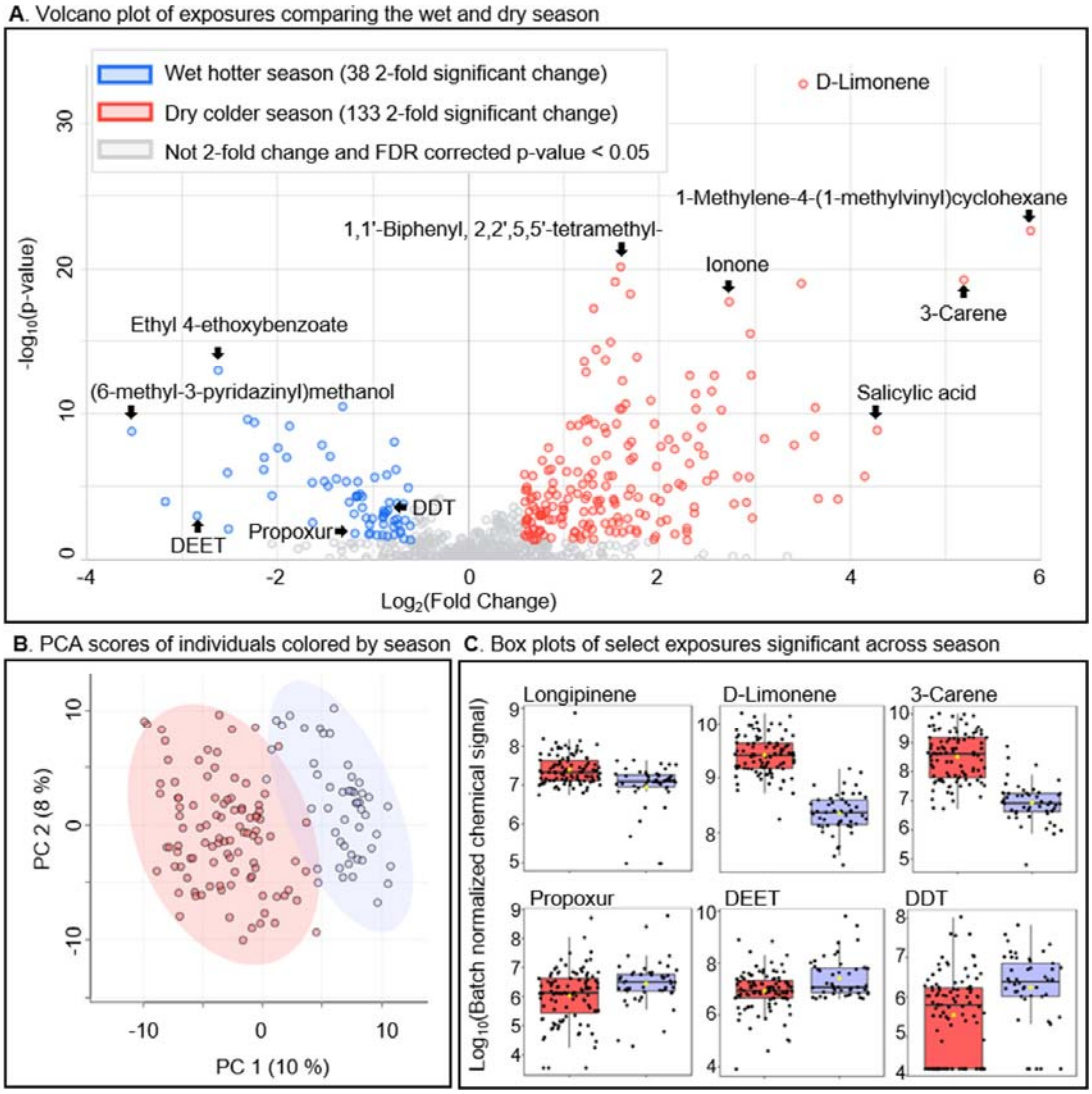


Figure 4. Comparison of chemical exposures in the wet, hot and dry, and cold season. (A) The volcano plot shows most exposures were increased during the dry season and that a significant portion of chemical exposures was dramatically different depending on the season. On the *x*-axis is $\log_2$ of the fold change, and therefore, the further to the right or the left, the bigger the difference (magnitude of difference) between wet and dry seasons. The *y*-axis represents $-\log_{10}$ of the *p*-value, and therefore data points with larger values on the *y*-axis are more significantly different. (B) PCA of exposures indicating distinct chemical profiles by season. (C) Specific chemicals of interest are shown which were significant across season, specifically insecticides and insect repellant-related chemicals and wood emission-related chemicals. Acronyms: Dichlorodiphenyltrichloroethane (*p*,*p*'-DDT), *N*,*N*-diethyl-*meta*-toluamide (DEET), and false-discovery rate (FDR).

Another source of chemical exposure for these children was from combustion of wood and refuse used for cooking in huts with little ventilation (Figure 2). Overall, over 10 plasticizers (including phthalates) and over 150 potential PAHs were detected (see Supporting Information), showing the vast diversity of exposures children have to chemicals falling under these classes of compounds. A substantial portion of PAHs were significantly higher in abundance for children whose parents reported longer durations of cooking time (>8 h) compared to those with no cooking or shorter cooking times (<4 h) during the

sampling period. Plasticizer exposures, on the other hand, were not correlated to cooking time, suggesting that combustion may not be the major source. It is interesting to note that when comparing poverty across individuals for each seasonal period, participants with higher poverty had higher exposure to certain combustion products (e.g., benzo[k] fluoranthene), suggesting that poverty may play a role in exposure to these toxic chemicals (Figure S1). While the exposure assessment to select PAHs identified as carcinogens has been monitored in past studies based in rural regions of Africa, exposures to most of the 150 PAHs detected in this study have not been previously reported. [35,76–78] Hence further work looking into the complex array of individual PAHs and their potential combined health impacts on these children is warranted, as PAH toxicity can drastically differ depending on chemical species. [79,80]

Exposures of concern among the children differed from child to child, often ranging across several orders of magnitude in abundance (Figure 3). Distributions of chemical abundances across participants enable discernment of whether or not exposures uniquely differ across individuals. Some of the chemicals with the highest variance in exposure levels across children were chemicals with specific uses to which children may not be universally exposed: these included active ingredients of pesticides, nicotyrine (a metabolite of nicotine), and caffeine. Caffeine had the widest range in exposure levels across children, ranging across 7 orders of magnitude. Comparing between chemicals, the phthalates had the highest signal of all detected compounds. For example, the average signal across all participants for all 637 chemicals was highest for di(2-ethylhexyl) phthalate, followed by butyl isobutyl phthalate ranked as 7th and diisobutyl phthalate as 8th highest exposure compound. Chemicals with tighter distributions such as benzothiazole and *p*-cresol suggest a common source for which all children were exposed similarly.

The study region has two main seasons: the wet, hotter season and the dry, colder season. The average temperature measured at the Limpopo Polokwane weather station across the study period differed by 5.7 °C between the sampling months categorized as wet [October 2018 to January 2019 (maximum monthly average of 23 °C)] and those categorized as dry [July to September 2019 (maximum monthly average of 18 °C)]–the maximum monthly average during the wet season was 23 °C, and 18 °C across the dry season. There was greater variability in precipitation across seasons with a difference of 81 mm between dry versus hot periods. On average, there was less than 6 mm of rain fall during July to September and more than 100 mm of rain on average during October to January.

Exposures were found to differ across seasons. Principal components analysis (PCA) showed distinct personal exposure profiles as a factor of season, suggesting that seasonality may be related to variation in exposure profiles (Figure 4A). Of the 637 chemicals confidently annotated, 27% (171) varied significantly across seasons (Hochberg corrected *p*-value < 0.05 and a greater than 2-fold change difference) (Figure 4B). The vast majority of these 171 chemicals were higher in the dry season (78%).

During the dry season, dust may be dispersed by wind, vehicles, and by other means, increasing the load of particulate captured by the passive samplers. Furthermore, the lower level of numerous chemicals during the wet season, including certain chemicals of concern, is attributed to wet deposition of airborne pollutants by precipitation. [81,82] An example is shown for the exposure levels of common volatile wood and plant emissions (longipinene, d-limonene, and 3-carene) with d-limonene and 3-carene decreasing by at least an order of magnitude on average during the wet season (Figure 4C). In contrast, certain chemicals of concern were elevated during the wet season, suggesting environmental changes and/or

seasonal changes in behaviors enhancing their emission or exposure. Active ingredients in insecticides (e.g., propoxur and *p*,*p*'-DDT) and mosquito repellants (e.g., DEET) were all significantly increased during the warmer wet season when mosquito populations are higher, suggesting increased insecticide use in the wet season (Figure 4C). Field observations also show that this the wet season is when indoor residual spraying is conducted.

While this study focused on chemicals of potential health hazard for the children in the villages studied, the chemical profiles measured could be used to answer several questions related to the children's behavior and environment. For example, numerous flavor-related compounds were measured, as well as active ingredients in beverages (e.g., caffeine) and a metabolite in cigarettes (nicotyrine) which could help assess the children's or family's diet/activities. Certain chemicals detected (e.g., nylon-6) could determine the type of plastics used or combusted by the community or family (depending on proximity to other villagers). Detected dye-related chemicals (e.g., indigo dye, quinaldines, and quinolines) and fragrances (e.g., musk ketone and galaxolide) could provide information on social factors and behaviors. Compounds such as dimethyl indole which was detected could be related to the exposure to fecal matter (the major odor of fecal matter).

Indeed, certain compounds which may have specific emission sources were found to correlate with poverty in either the wet or dry season. For example, lilial, a compound used in perfumes and laundry detergents, was detected at higher levels in participants classified as less poor during the dry season. During the wet season, lilial abundances approached significance for those less poor versus remaining children (Figure S1). Camphor exposure was also higher in the dry season for participants classified as above the poverty threshold (Figure S1). Chloroxylenol, an antiseptic used in soaps and other consumer products to kill bacteria, was higher in participants in the wet season classified as below the poverty threshold (Figure S1). Several combustion products (e.g., dimethyl-naphthalene, acenaphthylene, 2-ethenyl-napthalene, benzo(*k*)fluoranthene, and pyrroles) were higher in participants classified as below the poverty threshold in one or both seasons (Figure S1). This is likely due to the higher use of solid fuel for cooking used by this group and lower level of ventilation.

In summary, we show that the Fresh Air wristbands, a low-cost technology, can be used to passively capture airborne contaminants, [42] enabling measurement of a portion of the chemical exposome of vulnerable populations in LMICs. More research is needed to assess the exposure profiles of children in developing countries. This work highlights the range of chemicals of concern to which children in rural regions of South Africa are exposed. Bridging this technology together with state-of-the-art gas chromatography high-resolution mass spectrometry enables the screening of hundreds of thousands of chemicals to determine both expected and unexpected exposures in different populations. Personal exposures to 637 chemicals assigned with relatively high confidence were measured in the VHEMBE birth cohort, many of which have not previously been measured as airborne exposures in Africa at large. Fifty were deemed as potential health concern based on priority lists developed by governments based on human health hazards, predicted toxicity values, and experimentally derived toxicity values. These chemicals of concern include components of insecticides used for malaria control (e.g., *p*,*p*'-DDT, *p*,*p*'-DDD, *p*,*p*'-DDE, and piperonyl butoxide), PAHs from combustion (with over 150 individual PAHs detected), and plasticizers including phthalates, organophosphate compounds, fragrances, dyes, and biocides (e.g., triclosan). Because the wristband is designed to primarily detect airborne chemicals (gases and particles), it is of additional concern that several chemical exposures measured are

classified as having very high acute inhalation toxicity. These chemicals included pyrene, *p*-toly(4-methylbenzyl) sulfide, *p*-cresol, triclosan, and propoxur. Furthermore, many chemicals do not have data pertaining to inhalation toxicity or the data is inconclusive, showing the need for efforts to assign inhalation toxicity values for these airborne chemicals.

Individual exposure profiles for chemicals of concern ranged across orders of magnitude from individual to individual and were significantly dependent on the season. Twenty-seven percent of the confidently annotated chemicals significantly differed across seasons, with most chemicals decreasing in abundance during the wet–hot season. Certain chemicals, such as *p*,*p*'-DDT, DEET, and propoxur used for mosquito control increased in the wet-hot season, which is aligned with the increased use of insecticides and mosquito repellants during the wetter warmer season to deal with malaria. Furthermore, chemical exposures varied by cooking fuel and residential characteristics, which were associated with household poverty. This study assessed the breadth of environmental exposures of children in rural regions of South Africa including numerous chemicals which have not previously been measured in the air for this geographic area; however, this likely represents only the tip of the iceberg. Other complimentary analysis such as liquid chromatography high-resolution mass spectrometry could further extend the coverage of assessed exposures. Follow-up quantitative analysis and analysis of chemicals in the Fresh Air wristband as well as urine and blood collected from study participants are planned to assess whether the levels of these chemicals are of substantial concern. Furthermore, linking exposure data to specific participant activities, consumer product use, housing characteristics, and environmental factors will be helpful to determine the potential interventions for reducing exposure. Understanding factors that influence chemical exposures, such as seasonality, residual spraying, waste management systems, transportation, and cooking practices, is a critical step in establishing interventions both through education, policy, and industry.

Supporting Information

Additional results presenting a comparison of personal exposures stratified by season and poverty levels and spectral evidence supporting caffeine identification (PDF)

Processed mass spectrometry datasets (XLSX). Raw mass spectrometry data is available upon request.

Assessing the External Exposome Using Wearable Passive Samplers and High-Resolution Mass Spectrometry among South African Children Participating in the VHEMBE Study

Funding

This work was supported by the Canadian Institute for Health Research and a Canada Research Chair in Global Environmental Health and Epidemiology (to JC).

Notes

The authors declare no competing financial interest.

The views expressed in this paper are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency or the Canadian Institute of Health Research. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

Abbreviations

ANOVA	analysis of variance
ATSDR	the agency for toxic substances and disease registry
BFF	blank feature filtering
DDD	dichlorodiphenyldichloroethane
DDE	dichlorodiphenyldichloroethylene
DDT	dichlorodiphenyltrichloroethane
DEET	*N*,*N*-diethyl-*meta*-toluamide
EFSA	European food safety authority
EI	electron ionization
EPA-HCD	environmental protection agency hazard comparison dashboard
FDR	false discovery rate
GC-HRMS	gas chromatography high resolution mass spectrometry
HRMF	high-resolution mass filter
NORMAN	network of reference laboratories, research centres and related organisations for monitoring of emerging environmental substances
PCA	principle components analysis
PDMS	polydimethylsiloxane
PM	particulate matter
PMT	potential persistent, mobile and toxic substances
PTFE	polytetrafluoroethylene
RHRMF	reverse high resolution mass filter
RI	retention index
RSI	reverse search index
SI	search index
TCEP	tris(2-carboxyethyl) phosphine
TCPP	tris(2-chloroisopropyl) phosphate
TDU	thermal desorption unit
TFK	toxic free kids
TRI	environmental protection agency toxics release inventory
TSCA	toxic substances control act
VHEMBE	Venda health examination of mothers, babies and their environment

References

1. Prüss-Ustün, A.; Corvalán, C. How much disease burden can be prevented by environmental interventions?. *Epidemiology* **2007**, *18*, 167, DOI: 10.1097/01.ede.0000239647.26389.80

2. Prüss-Ustün, A.; Wolf, J.; Corvalán, C.; Bos, R.; Neira, M. *Preventing Disease through Healthy Environments: a Global Assessment of the Burden of Disease from Environmental Risks*; World Health Organization, 2016.

3. Trasande, L.; Massey, R. F.; DiGangi, J.; Geiser, K.; Olanipekun, A.F.; Gallagher, L. How developing nations can protect children from hazardous chemical exposures while sustaining economic growth. *Health Aff.* **2011**, *30*, 2400, DOI: 10.1377/hlthaff.2010.1217

4. Gordon, S. B.; Bruce, N. G.; Grigg, J.; Hibberd, P. L.; Kurmi, O. P.; Lam, K.-b. H.; Mortimer, K.; Asante, K. P.; Balakrishnan, K.; Balmes, J.; Bar-Zeev, N.; Bates, M. N.; Breysse, P. N.; Buist, S.; Chen, Z.; Havens, D.; Jack, D.; Jindal, S.; Kan, H.; Mehta, S.; Moschovis, P.; Naeher, L.; Patel, A.; Perez-Padilla, R.; Pope, D.; Rylance, J.; Semple, S.; Martin, W. J., 2nd Respiratory risks from household air pollution in low and middle income countries. *Lancet Respir. Med.* **2014**, *2*, 823– 860, DOI: 10.1016/s2213-2600(14)70168-7

5. Fayiga, A. O.; Ipinmoroti, M. O.; Chirenje, T. Environmental pollution in Africa. *Environ. Dev. Sustain.* **2018**, *20*, 41– 73, DOI: 10.1007/s10668-016-9894-4

6. Masekela, R.; Vanker, A. Lung Health in Children in Sub-Saharan Africa: Addressing the Need for Cleaner Air. *Int. J. Environ. Res. Public Health* **2020**, *17*, 6178, DOI: 10.3390/ijerph17176178

7. Petkova, E.; Jack, D.; Volavka-Close, N.; Kinney, P. Particulate matter pollution in African cities. *Air Qual., Atmos. Health* **2013**, *6*, 603, DOI: 10.1007/s11869-013-0199-6

8. Vanker, A.; Barnett, W.; Nduru, P. M.; Gie, R. P.; Sly, P. D.; Zar, H. J. Home environment and indoor air pollution exposure in an African birth cohort study. *Sci. Total Environ.* **2015**, *536*, 362, DOI: 10.1016/j.scitotenv.2015.06.136

9. Vanker, A.; Barnett, W.; Workman, L.; Nduru, P. M.; Sly, P. D.; Gie, R. P.; Zar, H. J. Early-life exposure to indoor air pollution or tobacco smoke and lower respiratory tract illness and wheezing in African infants: a longitudinal birth cohort study. *Lancet Planet Health* **2017**, *1*, e328– e336, DOI: 10.1016/s2542-5196(17)30134-1

10. Landrigan, P. J.; Fuller, R.; Acosta, N. J. R.; Adeyi, O.; Arnold, R.; Basu, N. N.; Baldé, A. B.; Bertollini, R.; Bose-O'Reilly, S.; Boufford, J. I.; Breysse, P. N.; Chiles, T.; Mahidol, C.; Coll-Seck, A. M.; Cropper, M. L.; Fobil, J.; Fuster, V.; Greenstone, M.; Haines, A.; Hanrahan, D.; Hunter, D.; Khare, M.; Krupnick, A.; Lanphear, B.; Lohani, B.; Martin, K.; Mathiasen, K. V.; McTeer, M. A.; Murray, C. J. L.; Ndahimananjara, J. D.; Perera, F.; Potočnik, J.; Preker, A. S.; Ramesh, J.; Rockström, J.; Salinas, C.; Samson, L. D.; Sandilya, K.; Sly, P. D.; Smith, K. R.; Steiner, A.; Stewart, R. B.; Suk, W. A.; van Schayck, O. C. P.; Yadama, G. N.; Yumkella, K.; Zhong, M. The

Lancet Commission on Pollution and Health. *Lancet* **2018**, *391*, 462, DOI: 10.1016/S0140-6736(17)32345-0

11. Bigna, J. J.; Noubiap, J. J. The rising burden of non-communicable diseases in sub-Saharan Africa. *Lancet* **2019**, *7*, 1295, DOI: 10.1016/s2214-109x(19)30370-5

12. Pérez-Maldonado, I. N.; Batres, L. E.; González-Amaro, R.; Díaz-Barriga, F.; Yáñez, L. DDT-induced oxidative damage in human blood mononuclear cells. *Environ. Res.* **2005**, *98*, 177, DOI: 10.1016/j.envres.2004.11.001

13. Nasuti, C.; Gabbianelli, R.; Falcioni, M. L.; Di Stefano, A.; Sozio, P.; Cantalamessa, F. Dopaminergic system modulation, behavioral changes, and oxidative stress after neonatal administration of pyrethroids. *Toxicology* **2007**, *229*, 194, DOI: 10.1016/j.tox.2006.10.015

14. Han, Y.; Han, J.; Zhou, J.; Wang, S.; Zhu, P.; Zhao, R.; Jin, N.; Song, L.; Wang, X. The relationship of 3-PBA pyrethroids metabolite and male reproductive hormones among non-occupational exposure males. *Chemosphere* **2008**, *72*, 785, DOI: 10.1016/j.chemosphere.2008.03.058

15. Meeker, J. D.; Barr, D. B.; Hauser, R. Pyrethroid insecticide metabolites are associated with serum hormone levels in adult men. *Reprod. Toxicol.* **2009**, *27*, 155– 160, DOI: 10.1016/j.reprotox.2008.12.012

16. Molina, E. M.; Kavazis, A. N.; Mendonça, M. T. Chronic Exposure to Environmental DDT/DDE in 2 Species of Small Rodents: Measures of Contaminant Load, Immune Dysfunction, and Oxidative Stress. *Environ. Toxicol. Chem.* **2021**, *40*, 1619– 1629, DOI: 10.1002/etc.5007

17. Yoshinaga, J.; Imai, K.; Shiraishi, H.; Yoshiike, M.; Mieno, M. N.; Andersson, A. M.; Iwamoto, T. Pyrethroid insecticide exposure and reproductive hormone levels in healthy Japanese male subjects. *Andrology* **2014**, *2*, 416, DOI: 10.1111/j.2047-2927.2014.00202.x

18. Chevrier, J.; Rauch, S.; Crause, M.; Obida, M.; Gaspar, F.; Bornman, R.; Eskenazi, B. Associations of Maternal Exposure to Dichlorodiphenyltrichloroethane and Pyrethroids with Birth Outcomes Among Participants in the Venda Health Examination of Mothers, Babies and Their Environment Residing in an Area Sprayed for Malaria Control. *Am. J. Epidemiol.* **2019**, *188*, 130, DOI: 10.1093/aje/kwy143

19. Eskenazi, B.; An, S.; Rauch, S. A.; Coker, E. S.; Maphula, A.; Obida, M.; Crause, M.; Kogut, K. R.; Bornman, R.; Chevrier, J. Prenatal Exposure to DDT and Pyrethroids for Malaria Control and Child Neurodevelopment: The VHEMBE Cohort, South Africa. *Environ. Health Perspect.* **2018**, *126*, 047004, DOI: 10.1289/ehp2129

20. Huq, F.; Obida, M.; Bornman, R.; Di Lenardo, T.; Chevrier, J. Associations between prenatal exposure to DDT and DDE and allergy symptoms and diagnoses in the Venda Health Examination of Mothers, Babies and their Environment (VHEMBE), South Africa. *Environ. Res.* **2020**, *185*, 109366, DOI: 10.1016/j.envres.2020.109366

21. Murray, J.; Eskenazi, B.; Bornman, R.; Gaspar, F. W.; Crause, M.; Obida, M.; Chevrier, J. Exposure to DDT and hypertensive disorders of pregnancy among South African women from an indoor residual spraying region: The VHEMBE study. *Environ. Res.* **2018**, *162*, 49–54, DOI: 10.1016/j.envres.2017.12.006

22. Coker, E.; Chevrier, J.; Rauch, S.; Bradman, A.; Obida, M.; Crause, M.; Bornman, R.; Eskenazi, B. Association between Prenatal Exposure to Multiple Insecticides and Child Body Weight and Body Composition in the VHEMBE South African Birth Cohort. *Environ. Int.* **2018**, *113*, 122, DOI: 10.1016/j.envint.2018.01.016

23. Coker, E.; Chevrier, J.; Rauch, S.; Obida, M.; Crause, M.; Bornman, R.; Eskenazi, B. Sex and poverty modify associations between maternal peripartum concentrations of DDT/E and pyrethroid metabolites and thyroid hormone levels in neonates participating in the VHEMBE study, South Africa. *Environ. Int.* **2019**, *131*, 1873– 6750, DOI: 10.1016/j.envint.2019.104958

24. Eskenazi, B.; An, S.; Rauch, S. A.; Coker, E. S.; Maphula, A.; Obida, M.; Crause, M.; Kogut, K. R.; Bornman, R.; Chevrier, J. Prenatal exposure to DDT and pyrethroids for malaria control and child neurodevelopment: The VHEMBE cohort, South Africa. *Environ. Health Perspect.* **2018**, *126*, 047004, DOI: 10.1289/EHP2129

25. Huang, J.; Eskenazi, B.; Bornman, R.; Rauch, S.; Chevrier, J. Maternal Peripartum Serum DDT/E and Urinary Pyrethroid Metabolite Concentrations and Child Infections at 2 Years in the VHEMBE Birth Cohort. *Environ. Health Perspect.* **2018**, *126*, 067006, DOI: 10.1289/ehp2657

26. Huang, J. Y.; Eskenazi, B.; Bornman, R.; Rauch, S.; Chevrier, J. Maternal peripartum urinary pyrethroid metabolites are associated with thinner children at 3.5 years in the VHEMBE birth cohort (Limpopo, South Africa). *Environ. Epidemiol.* **2018**, *2*, e026 DOI: 10.1097/ee9.0000000000000026

27. Shezi, B.; Wright, C. Y. Household air pollution exposure and respiratory health outcomes: a narrative review update of the South African epidemiological evidence. *Clean Air J.* **2018**, *28*, 43, DOI: 10.17159/2410-972x/2018/v28n1a11

28. Suk, W. A.; Murray, K.; Avakian, M. D. Environmental hazards to children's health in the modern world. *Mutat Res.* **2003**, *544*, 235, DOI: 10.1016/j.mrrev.2003.06.007

29. Sly, P. D.; Flack, F. Susceptibility of children to environmental pollutants. *Ann. N. Y. Acad. Sci.* **2008**, *1140*, 163, DOI: 10.1196/annals.1454.017

30. Bornman, M. S.; Chevrier, J.; Rauch, S.; Crause, M.; Obida, M.; Sathyanarayana, S.; Barr, D. B.; Eskenazi, B. Dichlorodiphenyltrichloroethane Exposure and Anogenital Distance in the Venda Health Examination of Mothers, Babies and Their Environment (VHEMBE) Birth Cohort Study, South Africa. *Andrology* **2016**, *4*, 608, DOI: 10.1111/andr.12235

31. Verner, M. A.; Chevrier, J.; Ngueta, G.; Rauch, S.; Bornman, R.; Eskenazi, B. Early-life exposure to p,p'-DDT and p,p'-DDE in South African children participating in the VHEMBE

study: An assessment using repeated serum measurements and pharmacokinetic modeling. *Environ. Int.* **2018**, *119*, 478, DOI: 10.1016/j.envint.2018.07.010

32. Salaudeen, I.; Sonibare, O. O.; Sojinu, S. O.; Ekundayo, O. Polycyclic aromatic hydrocarbons in air from industrial areas in Lagos an0d Ogun states, Nigeria. *Pollution* **2017**, *3*, 561, DOI: 10.22059/POLL.2017.62773

33. Essumang, D. K.; Ofori, J.; Dodoo, D. K.; Adjei, J. K. Polycyclic aromatic hydrocarbons in settled dust particles in selected Ghanaian environments: Levels, source characterization, and assessment of inhalational health risks. *Indoor Built Environ.* **2014**, *25*, 242– 253, DOI: 10.1177/1420326x14544530

34. Muendo, M.; Hanai, Y.; Kameda, Y.; Masunaga, S. Polycyclic Aromatic Hydrocarbons in Urban Air: Concentration Levels, Patterns, and Source Analysis in Nairobi, Kenya. *Environ. Forensics* **2006**, *7*, 147– 157, DOI: 10.1080/15275920600667112

35. Mwachiro, M. M.; Pritchett, N.; Calafat, A. M.; Parker, R. K.; Lando, J. O.; Murphy, G.; Chepkwony, R.; Burgert, S. L.; Abnet, C. C.; Topazian, M. D.; White, R. E.; Dawsey, S. M.; Etemadi, A. Indoor wood combustion, carcinogenic exposure and esophageal cancer in southwest Kenya. *Environ. Int.* **2021**, *152*, 106485, DOI: 10.1016/j.envint.2021.106485

36. O'Connell, S. G.; Kincl, L. D.; Anderson, K. A. Silicone Wristbands as Personal Passive Samplers. *Environ. Sci. Technol.* **2014**, *48*, 3327– 3335, DOI: 10.1021/es405022f

37. Hammel, S. C.; Hoffman, K.; Webster, T. F.; Anderson, K. A.; Stapleton, H. M. Measuring Personal Exposure to Organophosphate Flame Retardants Using Silicone Wristbands and Hand Wipes. *Environ. Sci. Technol.* **2016**, *50*, 4483– 4491, DOI: 10.1021/acs.est.6b00030

38. Hammel, S. C.; Phillips, A. L.; Hoffman, K.; Stapleton, H. M. Evaluating the Use of Silicone Wristbands To Measure Personal Exposure to Brominated Flame Retardants. *Environ. Sci. Technol.* **2018**, *52*, 11875– 11885, DOI: 10.1021/acs.est.8b03755

39. Wang, S.; Romanak, K. A.; Stubbings, W. A.; Arrandale, V. H.; Hendryx, M.; Diamond, M. L.; Salamova, A.; Venier, M. Silicone wristbands integrate dermal and inhalation exposures to semi-volatile organic compounds (SVOCs). *Environ. Int.* **2019**, *132*, 105104, DOI: 10.1016/j.envint.2019.105104

40. Koelmel, J. P.; Lin, E. Z.; Guo, P.; Zhou, J.; He, J.; Chen, A.; Gao, Y.; Deng, F.; Dong, H.; Liu, Y.; Cha, Y. e.; Fang, J.; Beecher, C.; Shi, X.; Tang, S.; Godri Pollitt, K. J. Exploring the external exposome using wearable passive samplers - The China BAPE study. *Environ. Pollut.* **2021**, *270*, 116228, DOI: 10.1016/j.envpol.2020.116228

41. Koelmel, J. P.; Lin, E. Z.; Nichols, A.; Guo, P.; Zhou, Y.; Godri Pollitt, K. J. Head, shoulders, knees, and toes: Placement of wearable passive samplers alters exposure profiles observed. *Environ. Sci. Technol.* **2021**, *55*, 3796– 3806, DOI: 10.1021/acs.est.0c05522

42. Lin, E. Z.; Esenther, S.; Mascelloni, M.; Irfan, F.; Godri Pollitt, K. J. The Fresh Air Wristband: A Wearable Air Pollutant Sampler. *Environ. Sci. Technol. Lett.* **2020**, *7*, 308– 314, DOI: 10.1021/acs.estlett.9b00800

43. Doherty, B. T.; Koelmel, J. P.; Lin, E. Z.; Romano, M. E.; Godri Pollitt, K. J. Use of Exposomic Methods Incorporating Sensors in Environmental Epidemiology. *Curr. Environ. Health Rep.* **2021**, *8*, 34, DOI: 10.1007/s40572-021-00306-8

44. Seethapathy, S.; Górecki, T.; Li, X. Passive sampling in environmental analysis. *J. Chromatogr. A* **2008**, *1184*, 234– 253, DOI: 10.1016/j.chroma.2007.07.070

45. Zhang, X.; Brown, T.; Ansari, a.; Yeun, B.; Kitaoka, K.; Kondo, A.; Lei, Y.; Wania, F. Effect of Wind on the Chemical Uptake Kinetics of a Passive Air Sampler. *Environ. Sci. Technol.* **2013**, *47*, 7868, DOI: 10.1021/es401486f

46. Vegosen, L.; Martin, T. M. An automated framework for compiling and integrating chemical hazard data. *Clean Technol. Environ. Policy* **2020**, *22*, 441– 458, DOI: 10.1007/s10098-019-01795-w

47. Williams, A. J.; Grulke, C. M.; Edwards, J.; McEachran, A. D.; Mansouri, K.; Baker, N. C.; Patlewicz, G.; Shah, I.; Wambaugh, J. F.; Judson, R. S.; Richard, A. M. The CompTox Chemistry Dashboard: a community data resource for environmental chemistry. *J. Cheminf.* **2017**, *9*, 61, DOI: 10.1186/s13321-017-0247-6

48. Cassano, A.; Manganaro, A.; Martin, T.; Young, D.; Piclin, N.; Pintore, M.; Bigoni, D.; Benfenati, E. CAESAR models for developmental toxicity. *Chem. Cent. J.* **2010**, *4*, S4, DOI: 10.1186/1752-153X-4-S1-S4

49. Zhu, H.; Martin, T. M.; Ye, L.; Sedykh, A.; Young, D. M.; Tropsha, A. Quantitative structure-activity relationship modeling of rat acute toxicity by oral exposure. *Chem. Res. Toxicol.* **2009**, *22*, 1913– 1921, DOI: 10.1021/tx900189p

50. Benfenati, E.; Benigni, R.; Demarini, D. M.; Helma, C.; Kirkland, D.; Martin, T. M.; Mazzatorta, P.; Ouédraogo-arras, G.; Richard, A. M.; Schilter, B.; Schoonen, W. G. E. J.; Snyder, R. D.; Yang, C. Predictive Models for Carcinogenicity and Mutagenicity: Frameworks, State-of-the-Art, and Perspectives. *J. Environ. Sci. Health, Part C: Environ. Carcinog. Ecotoxicol. Rev.* **2009**, *27*, 57– 90, DOI: 10.1080/10590500902885593

51. Martin, T. M.; Venkatapathy, R.; Das, S.; Young, D. M. A hierarchical clustering methodology for the estimation of toxicity. *Toxicol. Mech. Methods* **2008**, *18*, 251, DOI: 10.1080/15376510701857353

52. Salvi, S. Health effects of ambient air pollution in children. *Paediatr. Respir. Rev.* **2007**, *8*, 275– 280, DOI: 10.1016/j.prrv.2007.08.008

53. Wilson, R.; Jones-Otazo, H.; Petrovic, S.; Mitchell, I.; Bonvalot, Y.; Williams, D.; Richardson, G. M. Revisiting Dust and Soil Ingestion Rates Based on Hand-to-Mouth Transfer. *Hum. Ecol. Risk Assess.* **2013**, *19*, 158– 188, DOI: 10.1080/10807039.2012.685807

54. Moya, J.; Bearer, C. F.; Etzel, R. A. Children's Behavior and Physiology and How It Affects Exposure to Environmental Contaminants. *Pediatrics* **2004**, *113*, 996– 1006, DOI: 10.1542/peds.113.s3.996

55. Zhou, J.; Tierney, N. K.; McCarthy, T. J.; Black, K. G.; Hernandez, M.; Weisel, C. P. Estimating infants' and toddlers' inhalation exposure to fragrance ingredients in baby personal care products. *Int. J. Occup. Environ. Health* **2017**, *23*, 291– 298, DOI: 10.1080/10773525.2018.1475446

56. Guo, P.; Lin, E. Z.; Koelmel, J. P.; Ding, E.; Gao, Y.; Deng, F.; Dong, H.; Liu, Y.; Cha, Y. e.; Fang, J.; Shi, X.; Tang, S.; Godri Pollitt, K. J. Exploring personal chemical exposures in China with wearable air pollutant monitors: A repeated-measure study in healthy older adults in Jinan, China. *Environ. Int.* **2021**, *156*, 106709, DOI: 10.1016/j.envint.2021.106709

57. Koelmel, J. P.; Lin, E. Z.; Nichols, A.; Guo, P.; Zhou, Y.; Godri Pollitt, K. J. Head, Shoulders, Knees, and Toes: Placement of Wearable Passive Samplers Alters Exposure Profiles Observed. *Environ. Sci. Technol.* **2021**, *55*, 3796– 3806, DOI: 10.1021/acs.est.0c05522

58. Kováts, E. Gas-chromatographische Charakterisierung organischer Verbindungen. Teil 1: Retentionsindices aliphatischer Halogenide, Alkohole, Aldehyde und Ketone. *Helv. Chim. Acta* **1958**, *41*, 1915– 1932, DOI: 10.1002/hlca.19580410703

59. Patterson, R. E.; Kirpich, A. S.; Koelmel, J. P.; Kalavalapalli, S.; Morse, A. M.; Cusi, K.; Sunny, N. E.; McIntyre, L. M.; Garrett, T. J.; Yost, R. A. Improved experimental data processing for UHPLC–HRMS/MS lipidomics applied to nonalcoholic fatty liver disease. *Metabolomics* **2017**, *13*, 142, DOI: 10.1007/s11306-017-1280-1

60. Sushko, I.; Novotarskyi, S.; Körner, R.; Pandey, A. K.; Cherkasov, A.; Li, J.; Gramatica, P.; Hansen, K.; Schroeter, T.; Müller, K.-R.; Xi, L.; Liu, H.; Yao, X.; Öberg, T.; Hormozdiari, F.; Dao, P.; Sahinalp, C.; Todeschini, R.; Polishchuk, P.; Artemenko, A.; Kuz'min, V.; Martin, T. M.; Young, D. M.; Fourches, D.; Muratov, E.; Tropsha, A.; Baskin, I.; Horvath, D.; Marcou, G.; Muller, C.; Varnek, A.; Prokopenko, V. V.; Tetko, I. V. Applicability Domains for Classification Problems: Benchmarking of Distance to Models for Ames Mutagenicity Set. *J. Chem. Inf. Model.* **2010**, *50*, 2094– 2111, DOI: 10.1021/ci100253r

61. Lynn, F. M.; Kartez, J. D. Environmental democracy in action: The Toxics Release Inventory. *Environ. Manage.* **1994**, *18*, 511– 521, DOI: 10.1007/bf02400856

62. EPA, U. S. *Toxics Release Inventory (TRI), Reporting Year 2017*: Washington, DC, 2018.

63. ATSDR Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/index.html (December 21, 2021).

64. Department of Health. Toxic Free Kids Act: Chemicals of High Concern. https://www.health.state.mn.us/communities/environment/childenvhealth/tfka/index.html (accessed December 1, 2021).

65. Oltmanns, J.; Bohlen, M.-L.; Escher, S.; Schwar, M.; Licht, O. *Final Report: Applying a tested procedure for the identification of potential emerging chemical risks in the food chain to the substances registered under REACH–REACH 2*, OC/EFSA/SCER/2016/01-CT1 EN-1597; EFSA Supporting Publication, 2019; p 263.

66. Chong, J.; Soufan, O.; Li, C.; Caraus, I.; Li, S.; Bourque, G.; Wishart, D. S.; Xia, J. MetaboAnalyst 4.0: towards more transparent and integrative metabolomics analysis. *Nucleic Acids Res.* **2018**, *46*, W486, DOI: 10.1093/nar/gky310

67. Schymanski, E. L.; Jeon, J.; Gulde, R.; Fenner, K.; Ruff, M.; Singer, H. P.; Hollender, J. Identifying Small Molecules via High Resolution Mass Spectrometry: Communicating Confidence. *Environ. Sci. Technol.* **2014**, *48*, 2097– 2098, DOI: 10.1021/es5002105

68. Volckens, J.; Quinn, C.; Leith, D.; Mehaffy, J.; Henry, C. S.; Miller-Lionberg, D. Development and evaluation of an ultrasonic personal aerosol sampler. *Indoor Air* **2017**, *27*, 409– 416, DOI: 10.1111/ina.12318

69. Gleave, K.; Lissenden, M.; Richardson, M.; Choi, L.; Ranson, H. Piperonyl Butoxide (PBO) Combined with Pyrethroids in Insecticide-Treated Nets to Prevent Malaria in Africa. **2018**, 5 CD012776 DOI: 10.1002/14651858.CD012776.pub3 (1469-493X).

70. Bouwman, H.; Sereda, B.; Meinhardt, H. M. Simultaneous presence of DDT and pyrethroid residues in human breast milk from a malaria endemic area in South Africa. *Environ. Pollut.* **2006**, *144*, 902– 917, DOI: 10.1016/j.envpol.2006.02.002

71. Gaspar, F. W.; Chevrier, J.; Quirós-Alcalá, L.; Lipsitt, J. M.; Barr, D. B.; Holland, N.; Bornman, R.; Eskenazi, B. Levels and Determinants of DDT and DDE Exposure in the VHEMBE Cohort. *Environ. Health Perspect.* **2017**, *125*, 077006, DOI: 10.1289/EHP353

72. Gericke, A.; Govere, J. M.; Durrheim, D. N. Insecticide susceptibility in the South African malaria mosquito Anopheles arabiensis (Diptera : Culicidae) : research letter. *S. Afr. J. Sci.* **2002**, *98*, 205– 208

73. Anderson, K. A.; Hobbie, K. A.; Traore, A. N.; McCartney, M. A.; Ndaye, A.; Forsberg, N. D.; Haigh, T. A.; Sower, G. J. Passive Sampling Devices Enable Capacity Building and Characterization of Bioavailable Pesticide along the Niger, Senegal and Bani Rivers of Africa. *Philos. Trans. R. Soc., B* **2014**, *369*, 2013110, DOI: 10.1098/rstb.2013.0110

74. Donald, C. E.; Scott, R. P.; Blaustein, K. L.; Halbleib, M. L.; Sarr, M.; Jepson, P. C.; Anderson, K. A. Silicone wristbands detect individuals' pesticide exposures in West Africa. *R. Soc. Open Sci.* **2016**, *3*, 160433, DOI: 10.1098/rsos.160433

75. Jepson, P. C.; Blaustein, K.; Sow, M.; Sarr, M.; Mineau, P.; Kegley, S. Measuring Pesticide Ecological and Health Risks in West African Agriculture to Establish an Enabling Environment for Sustainable Intensification. *Philos. Trans. R Soc. Lond. B Biol. Sci.* **2014**, *369*, 20130491, DOI: 10.1098/rstb.2013.0491

76. Chimuka, L.; Sibiya, P.; Amdany, R.; Cukrowska, E.; Forbes, P. B. C. Status of PAHs in Environmental Compartments of South Africa: A Country Report. *Polycyclic Aromat. Compd.* **2016**, *36*, 376– 394, DOI: 10.1080/10406638.2014.988276

77. Munyeza, C. F.; Rohwer, E. R.; Forbes, P. B. C. A review of monitoring of airborne polycyclic aromatic hydrocarbons: An African perspective. *Trends Environ. Anal. Chem.* **2019**, *24*, e00070 DOI: 10.1016/j.teac.2019.e00070

78. Ofori, S. A.; Cobbina, S. J.; Doke, D. A. The occurrence and levels of polycyclic aromatic hydrocarbons (PAHs) in African environments–a systematic review. *Environ. Sci. Pollut. Res.* **2020**, *27*, 32389– 32431, DOI: 10.1007/s11356-020-09428-2

79. Gao, B.; Wang, X.-M.; Zhao, X.-Y.; Ding, X.; Fu, X.-X.; Zhang, Y.-L.; He, Q.-F.; Zhang, Z.; Liu, T.-Y.; Huang, Z.-Z.; Chen, L.-G.; Peng, Y.; Guo, H. Source apportionment of atmospheric PAHs and their toxicity using PMF: Impact of gas/particle partitioning. *Atmos. Environ.* **2015**, *103*, 114– 120, DOI: 10.1016/j.atmosenv.2014.12.006

80. Geier, M. C.; Chlebowski, A. C.; Truong, L.; Massey Simonich, S. L.; Anderson, K. A.; Tanguay, R. A.-O. Comparative Developmental Toxicity of a Comprehensive Suite of Polycyclic Aromatic Hydrocarbons. *Arch. Toxicol.* **2018**, *92*, 571, DOI: 10.1007/s00204-017-2068-9

81. Jayamurugan, R.; Kumaravel, B.; Palanivelraja, S.; Chockalingam, M. P. Influence of Temperature, Relative Humidity and Seasonal Variability on Ambient Air Quality in a Coastal Urban Area. *Int. J. Atmos. Sci.* **2013**, *2013*, 264046, DOI: 10.1155/2013/264046

82. Olszowski, T. Changes in PM10 concentration due to large-scale rainfall. *Arabian J. Geosci.* **2016**, *9*, 160, DOI: 10.1007/s12517-015-2163-2