Canaries in the Coal Mine, Canines on the Couch - A Model for Investigating Contaminant Exposures to Support Human Health Research

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ABSTRACT

Only 5-10% of human cancers can be explained by genetics alone, suggesting the environment plays a strong role in disease etiology. Quantifying the impacts of exposures remains challenging due to latency issues that can take years to manifest after exposure. Dogs may provide valuable insights as a sentinel species for exposure-related human disease because they experience similar environment exposures, have a 6-8 fold shorter lifespan, share many clinical and biological behaviors, and have closely related genomes. We evaluated individual exposures among pet dogs and their paired human companions using silicone dog-tags and wristbands as personal passive samplers (n=30 pairs). Silicone samplers were analyzed for a suite of chemicals across multiple compound classes, including organophosphate esters (OPEs), polybrominated diphenyl ethers, polychlorinated biphenyls, phthalates, and pesticides. As a validation pilot study, we collected urine samples from each study participant and dog, and measured levels of OPE metabolites. 32 of the 41 compounds measured, with a detection frequency >50%, were significantly correlated between dog and human wristbands (r_s = 0.38-0.90; p <0.05), indicating the dog could be a valuable One Health model and potential sentinel species for examining how exposure to consumer product chemicals impact health. The concentrations of several OPEs parent compounds measured on the dog tags were significantly correlated with their respective metabolites in urine (r_s = 0.50-0.71; p <0.01). These data support the value of using the domestic dog as a sentinel species to investigate the potential long-term health impacts on humans from shared exposures.

Can investigation of environmental exposure and health outcomes in our pets enhance traditional methods to understand disease etiology?

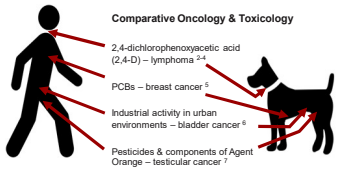
INTRODUCTION

Key advances have already been made in cancer genetics, diagnostics and therapy using a comparative approach.

Humans and dogs have over 360 shared diseases. [1]

- Pathobiological & genomic characteristics
- Clinical manifestations & progression
- Clinical management & response to therapeutics

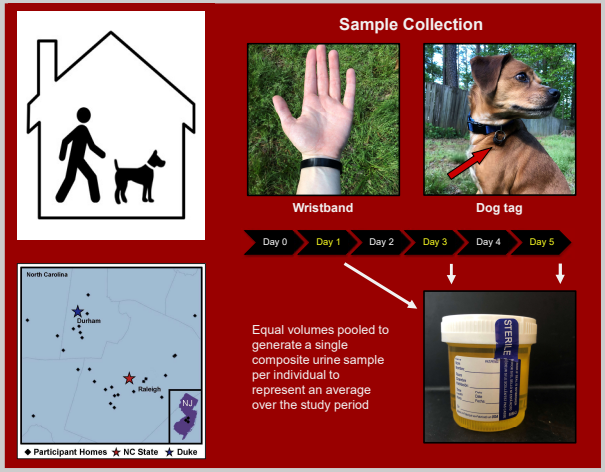
Although there are few studies investigating links between environmental exposure and spontaneous disease in pet dogs, independent studies in humans and dogs have shown associations between shared environmental risk factors for similar cancers across species.



Investigating these links in the domestic dog population may provide insight into the etiology, trends and prevention of cancer outcomes.

Silicone personal passive exposure monitoring devices can be used to capture exposures with levels detected correlating well with serum biomarkers and urinary metabolites [8,9].

STUDY DESIGN



Methods

- 30 people and their pet dogs were recruited to participate in North Carolina and New Jersey
- Silicone monitoring devices were worn for 5 concurrent days by people and their pet dogs
- First morning void urine samples were collected on days 1, 3 and 5
- Questionnaires were used to assess lifestyle and environmental factors
- Wristbands and dog tags were extracted and cleaned up using column chromatography and analyzed with mass spectrometry for organophosphate esters (OPEs), polychlorinated biphenyls (PCBs), brominated flame retardants (BFRs), pesticides and phthalates
- Equal volumes from each daily urine sample were pooled to create a single sample per individual
- Specific gravity was measured for each composite urine sample used for extraction
- Urine samples were extracted using solid-phase extraction and analyzed with LC-MS/MS for OPE metabolites
- All urinary metabolite data presented here are specific gravity corrected values, no differences were observed using these compared to raw values
- Spearman's correlations were used to determine associations between matrices and species

RESULTS

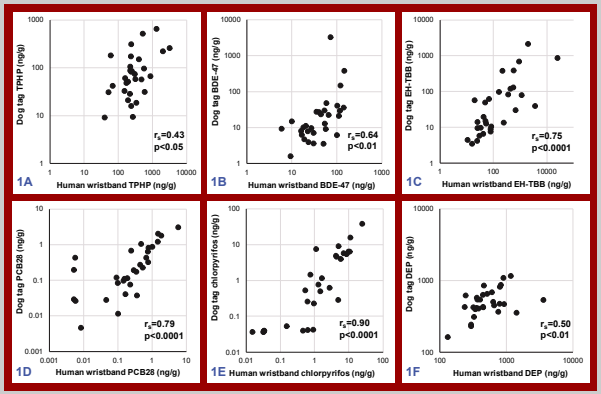


Figure 1. Example scatterplots for each chemical class for paired human wristband and dog tag samples

Spearman's correlation coefficients were calculated to estimate the association between chemical concentrations measured on wristbands and dog tags. Correlations are shown for: (**2A**) Triphenyl phosphate (TPHP), (**2B**) Polybrominated diphenyl ether congener 47 (BDE-47), (**2C**) 2-ethylhexyl-2,3,4,5 tetrabromobenzoate (EH-TBB), (**2D**) Polychlorinated biphenyl congener 28 (PCB28), (**2E**) Chlorpyrifos, (**2F**) Diethyl phthalate (DEP). Chemical concentrations are reported as ng/g for those measured on all silicone monitoring devices. Data are log transformed, Spearman's correlation coefficients (r_s) and p-values for each association are provided.

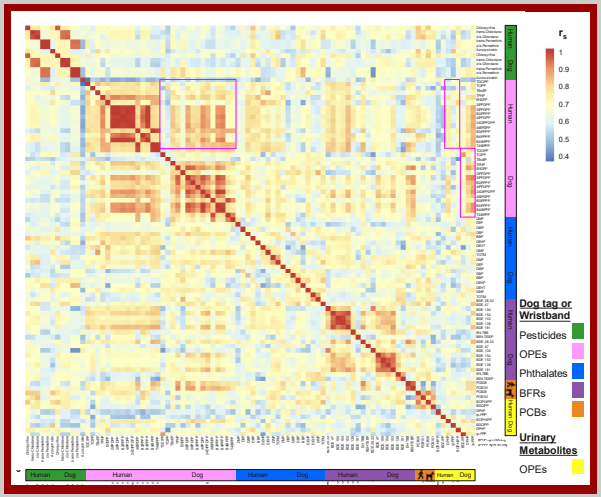
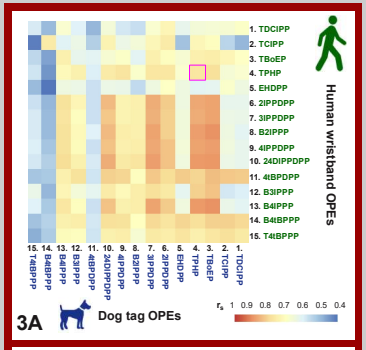


Figure 2. Spearman's correlation coefficient heatmap grouped by chemical class

The relationship of all chemical concentrations are represented as a heatmap of Spearman's correlation coefficients (r_s) to show associations between chemicals within and across species. Both dog and human data, grouped by chemical class, are represented on each axis in the same order (top to bottom and left to right). On silicone monitoring devices, for the 41 chemicals that had detection frequencies ≥50% in both species, r_s ranged from 0.06 to 0.9. Of those 41 chemicals, 32 (78%) had significant correlations when tested by linear regression (p<0.05). The pink outlined sections are OPEs and urinary OPE metabolites enlarged and explained in Figure 3.

Figure 3. Heatmap of Spearman's correlation coefficients for organophosphate esters

The pink outlined sections from Figure 2 are expanded to show (**3A**) correlations between OPEs measured on wristbands and dog tags, and (**3B**) correlations between OPE chemicals measured on the silicone monitoring devices and urinary OPE metabolites for each species. The pink outlined sections are TPHP and DPHP, which are featured in detail in Figure 4.



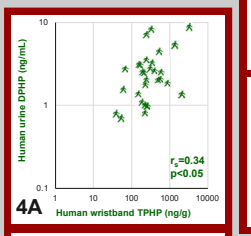


Figure 4. Example scatterplots for wristband/dog tag associated with urinary metabolites

Spearman's correlations were used to determine the relationship between concentrations measured on the wristbands/dog tags and urinary metabolites. Correlation are shown for triphenyl phosphate (TPHP) measured on wristbands and dog tags and its urinary metabolite diphenyl phosphate (DPHP) for (**4A**) humans, and (**4B**) dogs. Urinary metabolite concentrations are ng/mL specific gravity corrected values. Data are log transformed. Spearman's correlation coefficients (r_s) and p-values for each association are provided.

CONCLUSIONS

Dog

- Silicone dog tags are a reliable noninvasive tool to measure chemical exposure in pet dogs
- Silicone dog tags can be used as a surrogate for urine, which can be challenging for owners to obtain, although further validation of more chemical classes is necessary

Human vs. Dog

- Of the chemical classes measured pesticides had the highest correlations between humans and dogs
- Less than 50% of phthalates measured had significant correlations between species
- Similar concentrations were measured and had significant correlations across species for the two PCB congeners
- Despite humans generally having higher levels of OPEs and BFRs measured on wristbands, the majority have significant correlations with dog tags
- All urinary metabolites measured had greater magnitude of correlation to parent compounds on dog tags compared to human urine and wristbands

Overall

- The abundance of significant correlations between exposures in people and their pet dogs indicate the dog may be an ideal model system to investigate potential links between environmental exposures and health outcomes
- It is imperative that environmental exposure monitoring continues to occur in our pets

Silicone dog tags used as passive monitoring devices accurately capture environmental exposure in pet dogs and their owners, supporting the value of the dog as a sentinel species for environmental health research.

FUTURE DIRECTIONS

We are using this study design to conduct a case-control study with pet dogs to investigate associations between environmental exposures and health outcomes. We are validating urinary biomarkers of exposure for additional chemicals.

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