Biomonitoring of Environmental Chemical Exposures: Companion Animals as Sentinels

Kurunthachalam Kannan

Departments of Pediatrics and Environmental Medicine
New York University School of Medicine
New York

Pets as sentinels of human exposure

- Use of canaries to indicate lethal concentrations of CO in coal mines – dates back to the late 19th century.

- The neurobehavioral symptoms displayed by the "dancing cats" that consumed methylmercury contaminated fish from Minamata Bay in Japan in the 1950s before a similar disease appeared in people.

- Melamine exposure related kidney diseases – 2007 pet food >39,000 cats and dogs developed renal failure; 2008 infant formula contamination in China

Pets as sentinels of human diseases

BLADDER CANCER IN PET DOGS: A SENTINEL FOR ENVIRONMENTAL CANCER?

Am. J. Epidemiol (1981) 114, 229-233

HOWARD M. HAYES, JR.,[1] ROBERT HOOVER,[1] AND ROBERT E. TARONE[2]

Mesothelioma in Pet Dogs Associated with Exposure of Their Owners to Asbestos[1,2]

Environ. Res (1983) 32, 305-313

LAWRENCE T. GLICKMAN,*[,3] LINDA M. DOMANSKI,* TOBI G. MAGUIRE,* RICHARD R. DUBIELZIG,† AND ANDREW CHURG‡

The dog as a sentinel species for environmental effects on human fertility

Reproduction (2020) 159, R265-R276

Rebecca Nicole Sumner[1,*], Imogen Thea Harris[1,*], Morne Van der Mescht[2], Andrew Byers[2], Gary Crane William England[2] and Richard Graham Lea[2]

Companion animals when similarly exposed to toxic substances as humans regarding route, dose and chronicity often mount symptoms and signs in advance of humans

Suitability of pet animals as sentinels of environmental health

- Pet dogs and cats share a common living space with humans and exposed to similar indoor environments/contaminants (through air, water, diet and in contact with home/garden products)
- Develop similar environmentally induced diseases by the same pathogenetic mechanisms, but more rapidly than humans
- High basal metabolic rates, shorter (physiologically compressed) life spans
- Shorter latency of disease development
- Behavioral patterns resemble toddlers (mouthing/self-grooming/licking, staying close to ground)
- Greater ease of obtaining tissue at necropsy; collection of biospecimens

NRC report 1991

Heavy metal exposure in cats and dogs

- **Hg, Pb and Cd: Pets exhibit neurological symptoms, neurodegeneration from metal exposures.**

- **Mercury in cerebrum, liver and kidney of a Minamata dancing cat: 40, 126, 49 µg/g.**

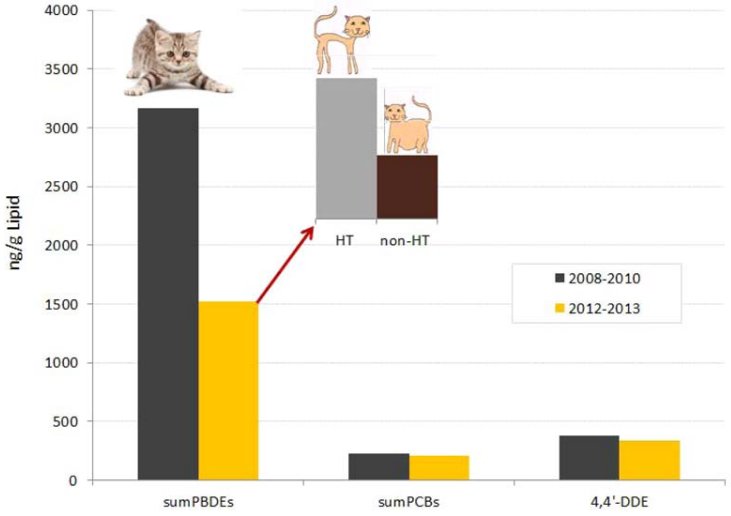
- **Mercury has been measured frequently in blood and hair of pets (blood conc >6 µg/mL ; urine conc >1.5 µg/mL acute-subacute toxicity in cats).**

- **Association between Pb concentrations in dogs and children from the same family and socioeconomic status is shown. Dogs in homes near mining areas had elevated Pb concentrations. Liver conc 5 µg/g, blood conc 3 µg/L for clinical signs in pets.**

- **Cd has been measured in pets; blood levels >100 µg/dL reflect acute exposures**

Persistent organic pollutants in cats and dogs

- **PCBs, DDT and their metabolites have been widely found in cat and dog tissues – adipose, serum, hair and pet food.**
- **Dogs had lower concentrations than cats, although diet had similar concentrations.**
- **OH-PCB levels were higher than those of parent PCBs in serum and the concentrations were linked to diabetes, disruption of thyroid homeostasis (mostly hypothyroidism)**
- **PBDEs levels in cats were associated indoor dust levels; median feline serum PCB, PBDE and DDT concentrations in 2012-2013 in the US were 206, 1520, 400 ng/g lipid wt, respectively.**
- **Concentrations varied and no systematic study exists; sample size mostly <50.**



Guo et al. 2015 EST
CA cats

Perfluoroalkyl substances in cats and dogs

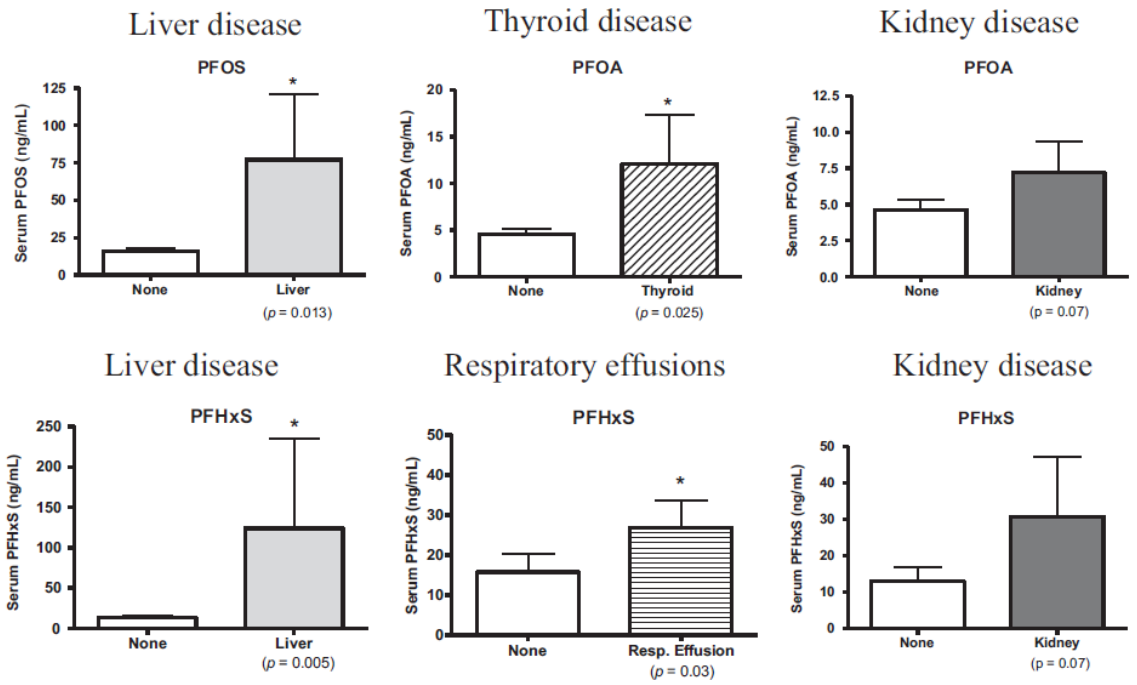
U.S. domestic cats as sentinels for perfluoroalkyl substances: Possible linkages with housing, obesity, and disease

Environ. Res (2016) 151, 145-153

Phillip C. Bost [a], Mark J. Strynar [b,1], Jessica L. Reiner [c], Jerry A. Zweigenbaum [d], Patricia L. Secoura [e], Andrew B. Lindstrom [b,1], Janice A. Dye [f,*,1]

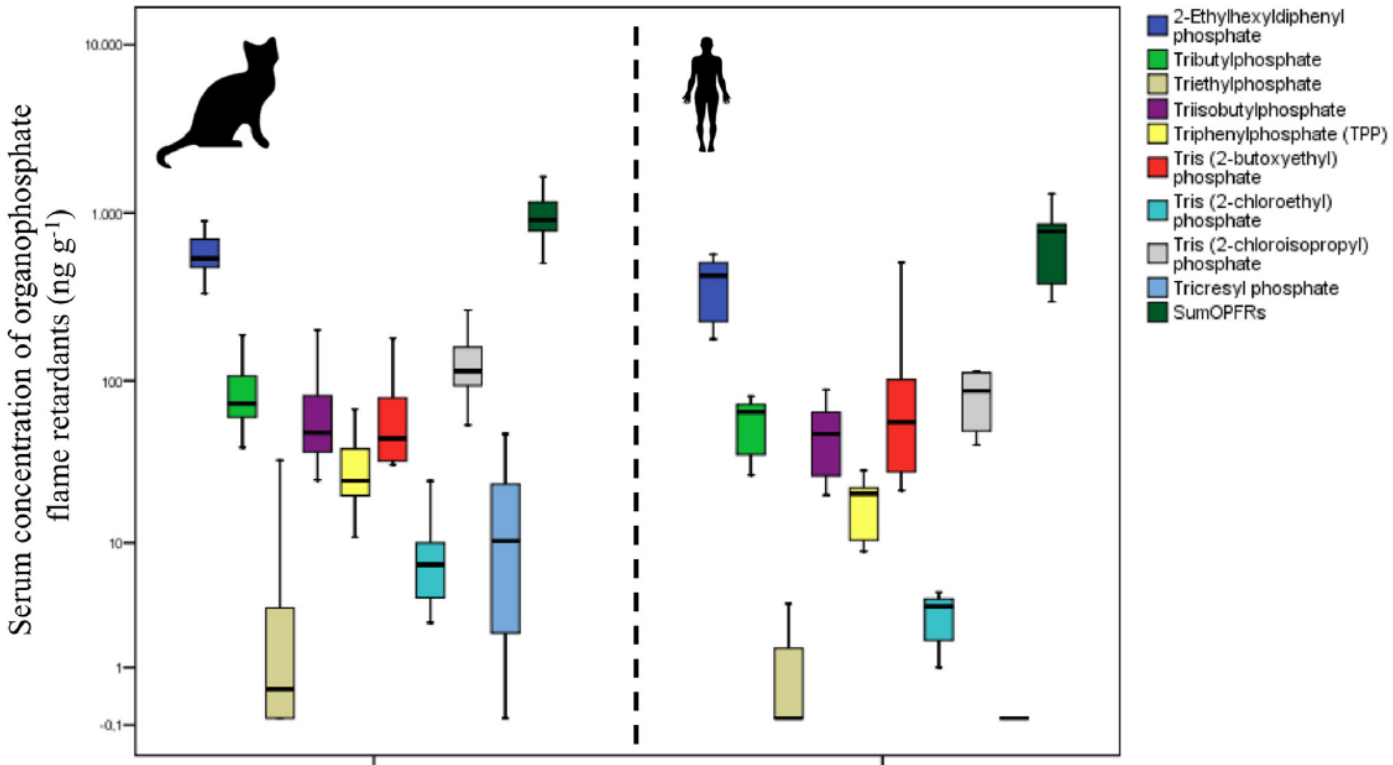
ng/ml serum	Cat	Humans
PFHxS	6.91	1.96
PFOS	8.89	13.2
PFOA	3.28	4.13
PFNA	1.72	1.49
PFDA	0.67	0.29
PFUnDA	0.5	0.2

- PFAS levels increased with body weight
- Dust as the source of exposure
- Several disease conditions were positively associated



OPEs and pesticides in cats and dogs

- **OPEs: Flame retardants and plasticizers**
- **OPE levels in serum of cats from Spain were similar to those in humans (Henriquez-Hernandez et al. 2017). Median total for OPEs in cats = 909 ng/g lw and humans = 878 ng/g lw (no difference)**
- **By contrast, PBDE levels were 20-100 fold higher in cats than humans and PCB levels were lower in cats than humans (Dye et al. 2007)**



Sci. Total Environ. (2013) 456-457, 34-41

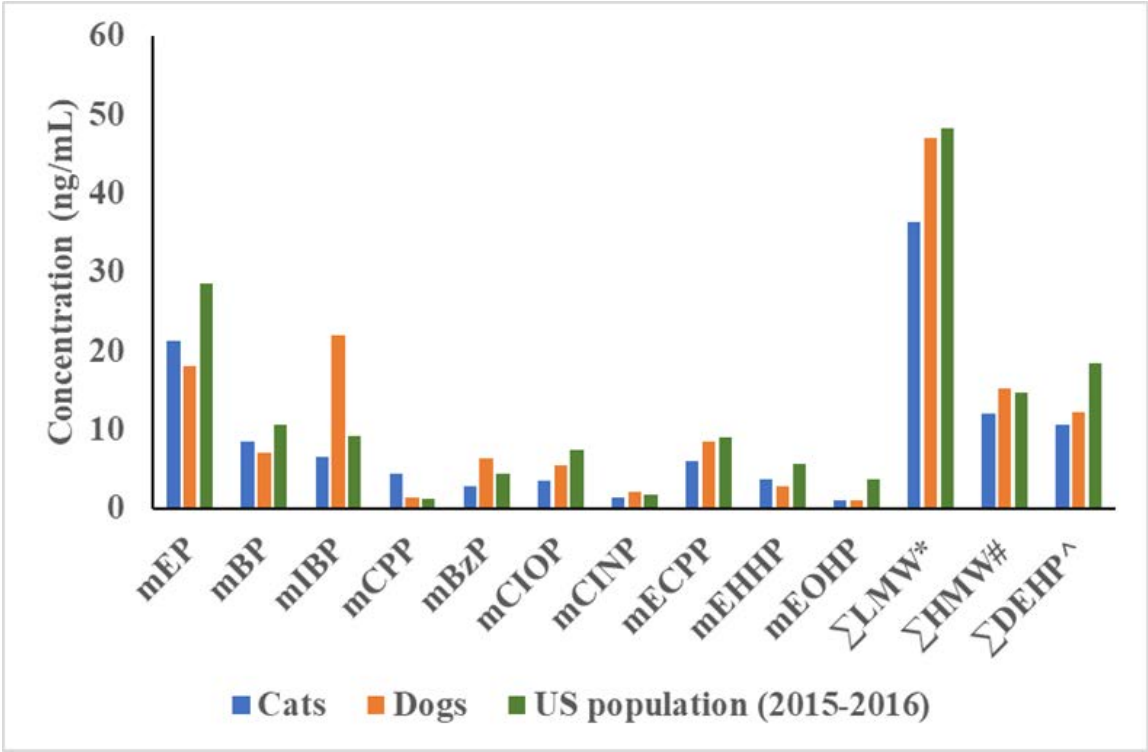
Detection of herbicides in the urine of pet dogs following home lawn chemical application

Deborah W. Knapp [a,b,*,1], Wendy A. Peer [c,2], Abass Conteh [c,3], Alfred R. Diggs [c], Bruce R. Cooper [d], Nita W. Glickman [e], Patty L. Bonney [a], Jane C. Stewart [a], Lawrence T. Glickman [e,1], Angus S. Murphy [c,1,4]

Phthalate metabolites in cat and dog urine (1)

- Widely used as plasticizers; toys, cosmetics
- 50 cats, 50 dogs, (n=100), May-Aug 2017
- Pet owners, veterinary hospitals, animal shelters in the Albany area of New York state
- Age, gender, breed information obtained
- HPLC-MS/MS method; enzymatic deconjugation; 21 metabolites
- Cats > dogs > humans; profiles similar with HMW phthalates being predominant

ng/mL	Cat	Dog	Humans
Median sum	630	186	92*
Range	80-5800	22-1600	



*Geomean from NHANES

Karthikraj, Kannan et al. 2019; STOTEN, 690, 70-75

Phthalate metabolites in cat and dog urine (2)

- **Concentrations slightly higher in females than males (not significant); concentrations decreased with age of dogs, but increased with age of cats.**
- **Samples from shelter pets were approx. 2 times lower than those of homes**
- **Slightly higher exposure doses for cats than dogs**
- **DEHP exposure doses were only 2-fold less than the RfD for humans**

Daily exposure dose to 4 phthalates (µg/kg bw/d) estimated based on urinary concentrations (reverse dosimetry)

Dose	DEP	DBP	DIBP	DEHP
RfD	800	100	100	20
Cat				
Small	4.02	1.14	1.07	7.9
Medium	8.88	1.41	1.33	8.33
Large	6.91	2.1	2.87	14.4
Dog				
Small	4.93	0.85	8.74	12.1
Medium	1.44	1.43	5.61	15.8
Large	6.83	0.59	2.41	6.44

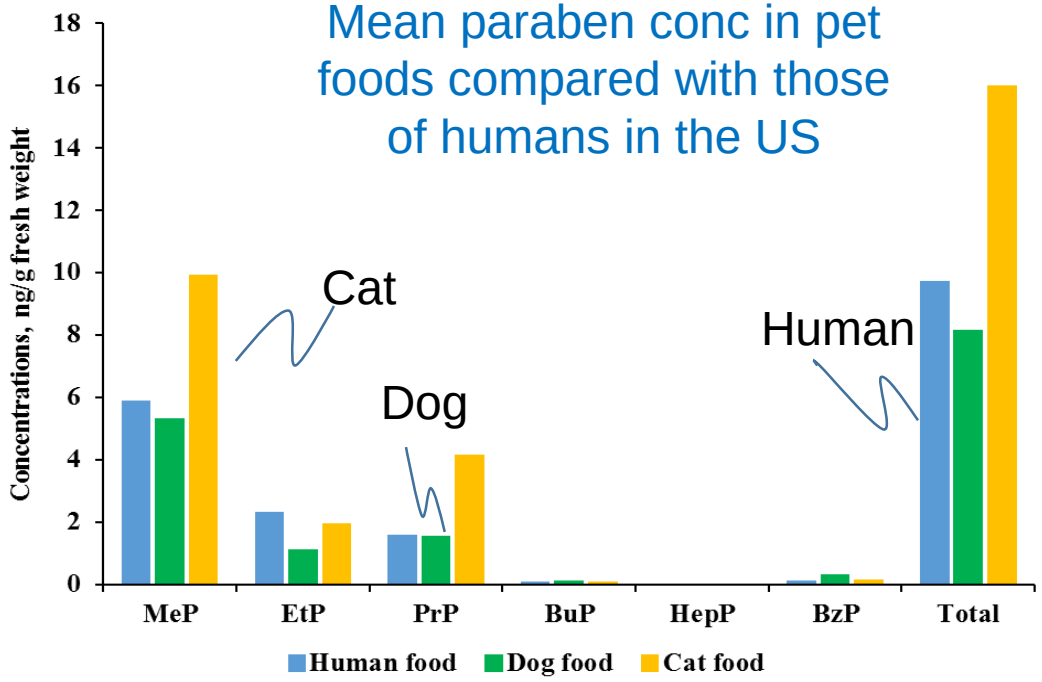
Karthikraj, Kannan et al. 2019; STOTEN, 690, 70-75

Parabens in cat and dog food and urine (1)

- **Antimicrobial preservatives used in PCPs, foods and pharmaceuticals**
- **23 dog food (10 brands); 35 cat food (13 brands), (n=58) Albany, NY, in 2017 (chicken meat common ingredient)**
- **30 cat and 30 dog urine analyzed (6 parent and 5 metabolites)**
- **Dry foods > Wet foods; Cat food > Dog food**
- **Food: MeP is the major parent compound; 4-HB is the metabolite and a preservative used on foods**
- **Profiles similar to human food: mean concentrations in cat, dog and humans at 16, 8.1 and 9.7 ng/g fresh wt, respectively.**

Median (ng/g)	Cat	Dog
Parent parabens	2.0 (<0.1-200)	3.5 (<0.1-41)
Metabolites	495 (154-5510)	695 (205-5200)

Mean paraben conc in pet foods compared with those of humans in the US



Karthikraj, Kannan et al. 2018; EST, 52, 3727-3737

Parabens in cat and dog food and urine (2)

- **Urine: MeP and 4-HB found in 100% samples.**
- **Dogs >> Humans >> Cats.**
- **MeP is a sex pheromone in canine/ veterinary drugs/flea control?**
- **Exposures are in the range of several 10s of ug/kg bw /d.**
- **Diet only accounted for <10% of the total exposures in dogs; For cats, diet contributed 30-50% of exp.**
- **TDI is 10 mg/kg bw/d for humans.**

Median conc (ng/mL)	Cat urine	Dog urine	Humans
Parent parabens	2 (0.4-65)	82.4 (21-600)	36*
Metabolites	1010 (317-1790)	6760 (1690-18700)	

Dose (µg/kg bw/d)	Cat CDI (urinary)	Cat dietary	Dog CDI (urine)	Dog dietary
MeP	0.19	0.19	5.6	0.08
4-HB	21.4	12	233	9.4
BA	40	11.4	81	6.7

*Geomean from NHANES

Karthikraj, Kannan et al. 2018; EST, 52, 3727-3737

Bisphenols in cat and dog food and urine

Biomonitoring of exposure to bisphenols, benzophenones, triclosan, and triclocarban in pet dogs and cats

Environ. Res (2020) 180, 108821

Rajendiran Karthikraj[a], Sunmi Lee[a], Kurunthachalam Kannan[a,b,c,*]

- **Bisphenols were detected in a range (<0.1-57 ng/mL) similar to that found in human populations, but medians were below that of humans for both digs and cats.**

- **Exposure doses calculated from reverse dosimetry showed (mean) values below 1 ug/kg bw/d, 2-3 orders of magnitude below the TDI.**

Dose µg/kg bw/d	BPS	BP-3
Dog	0.17	0.2
Cat	0.26	0.22

Median conc (ng/mL)	Cat (N=50)	Dog (n=50)	Humans (n=2651)
BPA	<LOQ	<LOQ	1.1*
BPS	1.1	1	0.47*
BP-3	0.9	1.4	19.3*
TCS	<LOQ	<LOQ	5.8*

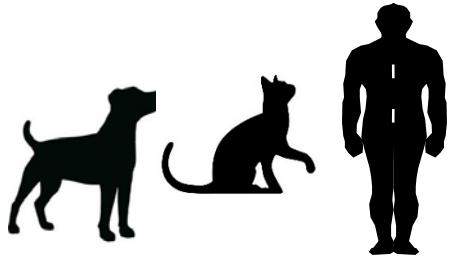
*Geomean from NHANES

Biomonitoring of melamine in pets

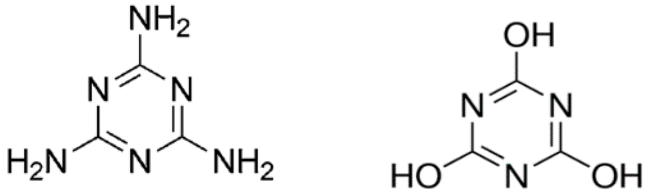
Environmental Pollution 238 (2018) 248–254

Melamine and its derivatives in dog and cat urine: An exposure assessment study☆

Rajendiran Karthikraj [a], Rasya Bollapragada [a], Kurunthachalam Kannan [a, b, c, *]



Flame retardant, dinnerware, molding; kidney toxicant



CYA > MEL

Median urinary concentrations (ng/mL); n=30/30 for cats and dogs; n=19/213 samples for humans: Detection frequency: >99% for MEL and CYA in humans

	Humans	Dog	Cat
Melamine	1.6	7.4	15
CYA	8.7	29	74
Ammeline	0.37	0.5	<1
Ammelide	0.75	6.4	4.8

Total Conc Range (ng/mL)

Humans : 3.5-190; > in children
Dogs : 13-510
Cats : 5.8-760

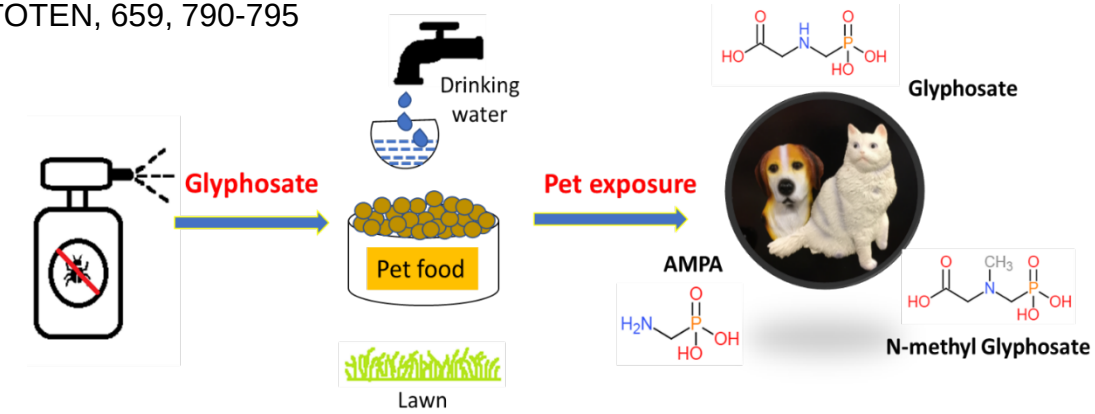
Tentative melamine reference: 63 ug/g Cr; our values 0-25 ug/g Cr (approx. 31.5 ng/mL and our values nd-57 ng/mL)

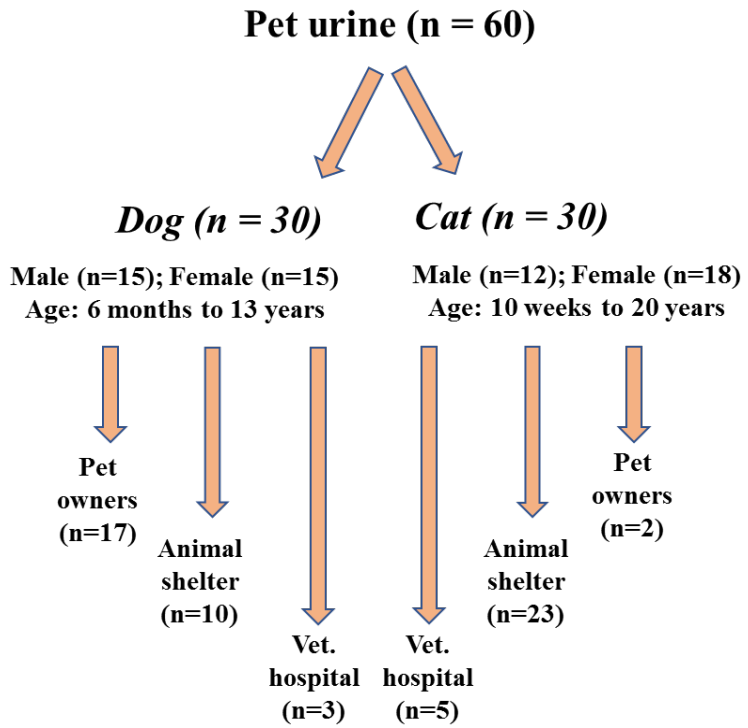
Cat and dog food also contain MEL/CYA at mean conc: 41/52 and 26/30 ng/g, respectively

Glyphosate in cat and dog urine (1)

Karthikraj/Kannan 2019; STOTEN, 659, 790-795

- **Widely used herbicide**, **used on lawns**
- **Non-hodgkins lymphoma, chronic kidney injuries**



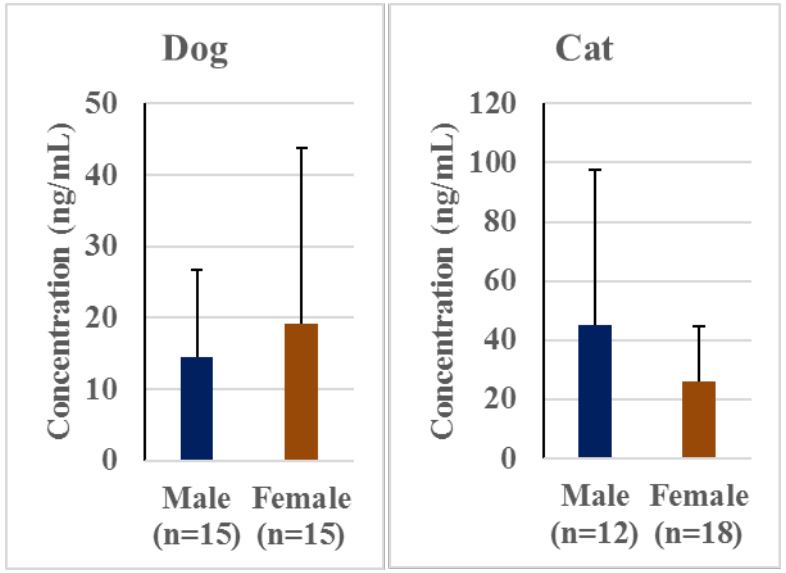


Urine (ng/mL)	Cat	Dog	Humans
Gly-Mean	21±24	13±13	3.4 (0.5-7.2)*
Gly-Median	17.8	7.0	

- **Cats > Dogs**
- **Besides Glyphosate, its metabolites AMPA, and methyl glyphosate were found in pet urine**

Glyphosate in cat and dog urine (2)

- **Glyphosate concentrations in urine decreased with increasing age, with puppies and kittens exhibiting higher concentrations than older animals.**
- **Female dogs had slightly higher concentrations than males, whereas an opposite pattern was observed for cats.**
- **Daily intake of glyphosate was 2.5-fold lower in dogs than cats**
- **ADI for glyphosate was 1750 and 500 µg/kg bw/d for humans as proposed by the EPA and EFSA, respectively.**

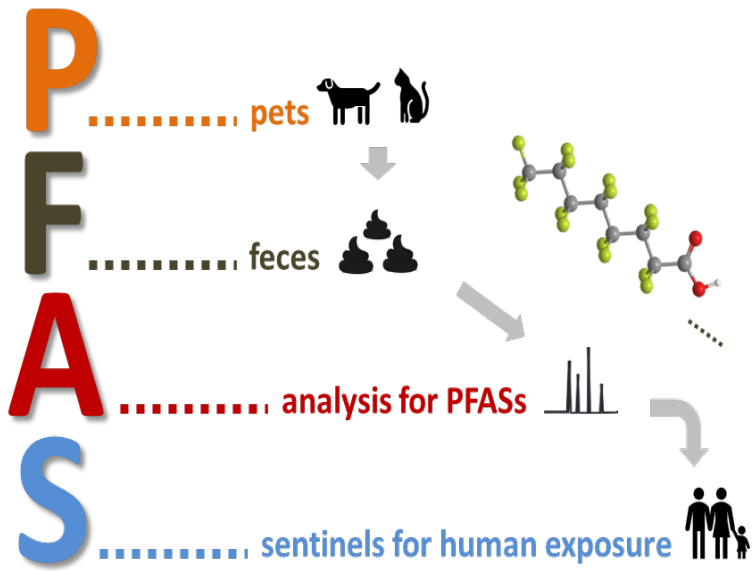


Intake µg/kg bw/d	Cat	Dog
Mean	1.37	0.57

Karthikraj/Kannan 2019; STOTEN, 659, 790-795

Fecal excretion of PFASs in cats and dogs (1)

- **PFAS elicit hepatotoxicity, immunotoxicity, metabolic disorders, reproductive and developmental effects.**
- **PFAS accumulates in bile, liver, kidney and serum; structure resembles bile acids; go through enterohepatic circulation.**
- **Urinary levels are very low; fecal excretion suspected.**
- **41 cat and 37 dog fecal samples (n=78) were collected during Jan-Mar 2019 from pet owners and animal shelters in Albany, New York.**
- **15 PFAS were analyzed in feces and fecal excretion was calculated:**



$$\frac{fecal\ concentration\ (ng/g) \times feces\ excretion\ rate\ (g/day)}{average\ body\ weigh\ (kg)}$$

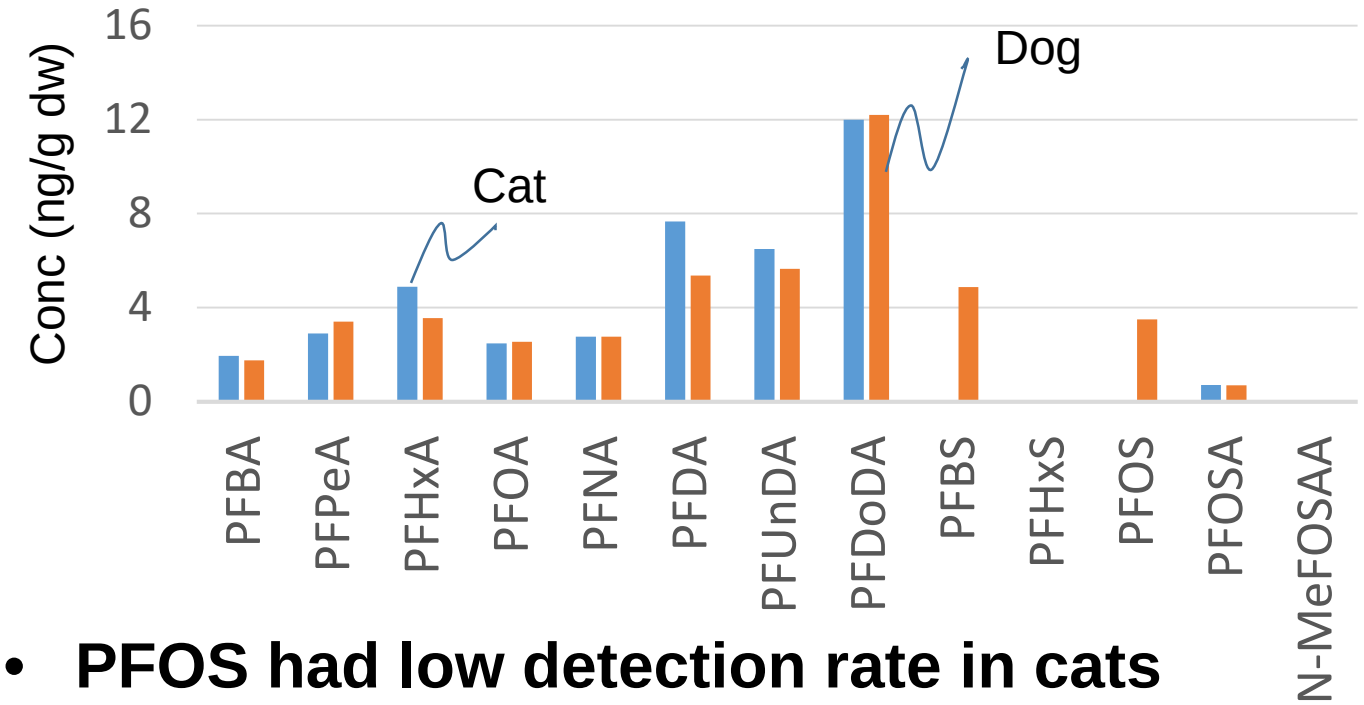
Ma and Kannan 2020; EST Lett, 7, 135-142

Fecal excretion of PFASs in cats and dogs (2)

- **Sum concentrations of PFAS in cat and dog feces were 18-165 and 22-474 ng/g dw, respectively:**
  Cat = Dog

- **PFDoDA, PFDA, PFUnDA, PFNA dominated (>60% of total) in both dogs and cats.**

- **FTOHs as the major source of exposure; biliary clearance high.**



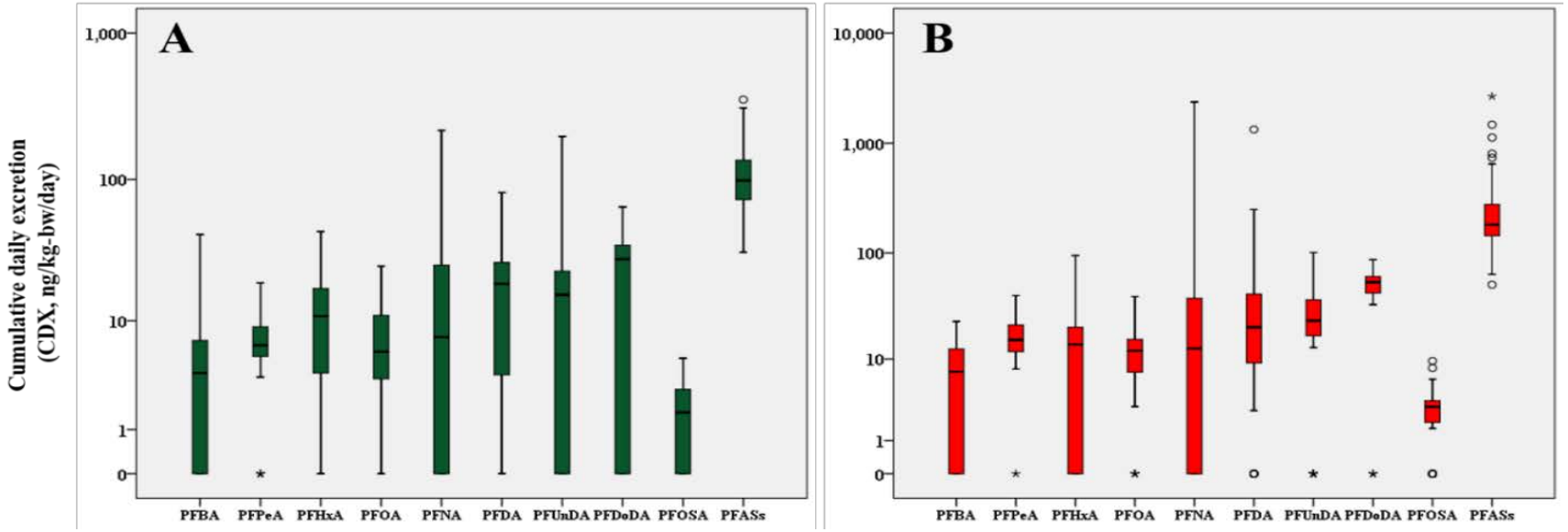
- **PFOS had low detection rate in cats (27%) and high detection rate in dogs (81%).**

- **No age or gender related differences.**

Ma and Kannan 2020; EST Lett, 7, 135-142

Fecal excretion of PFASs in cats and dogs (3)

- **Sum PFAS excretion rates in cats: 31-351 (mean: 118) ng/kg bw/d**
- **Dogs: 51-2660 (mean: 357) ng/kg bw/d**



- **ATSDR provisional minimum risk level for PFAS exposure 2, 3, 20 and 3 ng/kg bw/d for PFOS, PFOA, PFHxS and PFNA, respectively**
- **Excretion rates are 1-3 orders of magnitude above the MRLs.**

Ma and Kannan 2020; EST Lett, 7, 135-142

Microplastics in feces and food of cats and dogs (1)

78 dog feces and 58 per food samples were analyzed for PET and PC microplastics (MPs).

Food: Cat food and dog food had similar concentrations of MPs: dry food had higher levels than wet food. Few hundred to few thousand ng/g dw.

Feces:

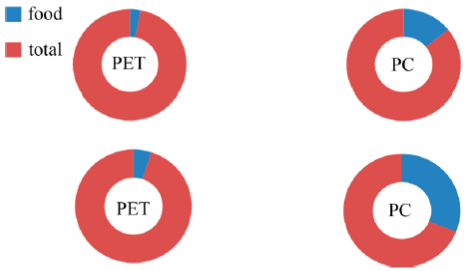
Median ng/g dw	TPA	PET	BPA	PC
Cat	260	61000	44	230
Dog	230	30000	20	160
Infants	1200	36000	<LOQ	78
Adults	410	2600	<LOQ	110

Zhang and Kannan 2019; EST, 53, 12035-12042

Microplastics in feces and food of cats and dogs (2)

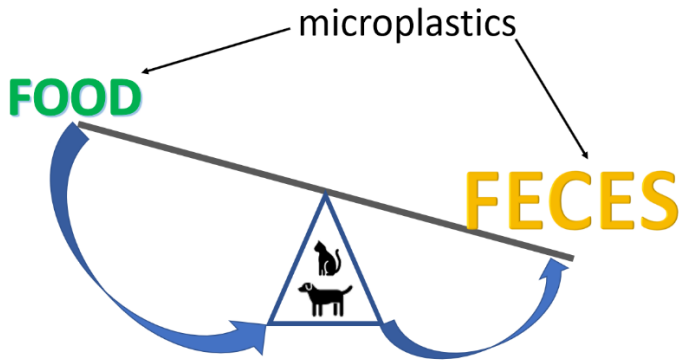
- **Exposure doses, in general, higher in cats than dogs.**

- **The contribution of pet food to MP exposure was <5% of the total dose.**



- **Concentrations of MPs in pets were similar to those found in the feces of 1-yr old infants**

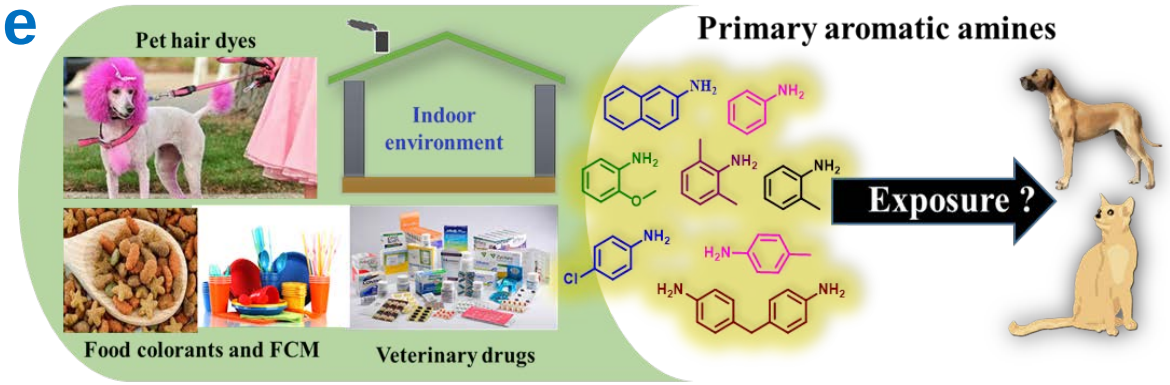
Exposure dose	Cat		Dog	
ng/kg bw/d	Dietary	Fecal dosimetry	Dietary	Fecal dosimetry
PET	35	1200	19	380
PC	1.7	12	1.8	5.8



Zhang and Kannan 2019; EST, 53, 12035-12042

Aromatic amines in feces and urine of cats and dogs

- Used in dyes, rubbers, polyurethane
- Many are known carcinogens



- **Median conc in cat and dog urine: 31 and 8 ng/mL, respectively**

- **Median conc in cat and dog feces were 240 and 278 ng/g dw, respectively; 2,6-DMA abundant, used in lidocaine, topical drugs**

- **Fecal excretion 10-100 times higher than intake.**

- **Many azo dyes oxidized or reduced by intestinal microorganisms and/or hepatic enzymes that can lead to the formation of AAs.**

Median µg/kg bw/d		Aniline	2,6-DMA
Intake	Cat	0.013	0.166
	Dog	0.002	0.007
Excretion	Cat	0.079	0.256
	Dog	0.261	0.921

Chinthakindi and Kannan 2021; EST, submitted

Summary

- **Widespread exposure of dogs and cats to contaminants; biomonitoring methods exist to assess exposures and risks (interdisciplinary collaboration will advance research; opportunities for discoveries in environmental health exists)**

- **Exposure levels are frequently higher in pets, especially cats, than in humans; nevertheless, the patterns of exposure are similar.**

- **Pet dogs and cats are excellent sentinels of environmental sources of exposure, especially to indoor contaminants.**

- **Exposure doses of some toxicants are at or above the risk levels; cumulative risks are uncertain; sensitivity of pets needs to be assessed.**

- **Biomonitoring exposures along with (1) health assessment (clinical biomarkers) in pets and (2) paired human – pet biomonitoring ("One Health") provide information on pets as sentinels of environmental health.**

NYU Langone Health

Biomonitoring/exposure analysis grants

CDC

NIEHS

Thank you