Endüstriel Hijyen Uygulamaları, ABD den Araştırma Örnekleri

Berrin Serdar, MD PhD

Colorado School of Public Health,
University of Colorado Denver
Environmental Health Associates, LLC

colorado school of public health

UNIVERSITY OF COLORADO
COLORADO STATE UNIVERSITY
UNIVERSITY OF NORTHERN COLORADO

Environmental Health Associates

What is Industrial Hygiene?

"Industrial hygiene is the science of anticipating, recognizing, evaluating, and controlling workplace conditions that may cause workers' injury or illness.

Industrial hygienists use environmental monitoring and analytical methods to detect the extent of worker exposure and employ engineering, work practice controls, and other methods to control potential health hazards..."

https://www.osha.gov/Publications/OSHA3143/OSHA3143.htm

Exposure

The contact between a person and one or more contaminant (biological, chemical or physical) over time and space

- Exposure can happen through different
  - Routes
  - Sources

Aspects of exposure

- Exposure *carrier media*: Air, water, soil, dust, food, etc.
- Exposure *duration*: seconds, minutes, years, etc.
- Exposure *frequency*: continuous, intermittent, cyclic, random

These can also be combined to obtain a new exposure index:
cumulative exposure = duration x concentration

- Exposure *variability*
  - Temporal
  - Spatial
  - Within-, between-subject variation

Quantitative vs. qualitative

- Quantitative measures:
  - Direct: Point-of-contact (e.g., personal air monitor) or biomarker
  - Indirect: Environmental monitoring (e.g., stationary air sampling, samples from water supply or food source)
- Qualitative measures:
  - Grouped: job title, residence in an area
  - Personal: questionnaire information (exposure history)

Exposure Assessment

The validity of environmental & occupational epidemiology studies depends on the quality of the exposure measure

- Ideally estimates should account for possible variations:
  - Within-individual
  - Between-individual
  - Over time
  - Across space
- Not always feasible in real life

Exposure Assessment

- Common sources of information:
  - Questionnaires
    (e.g. diet, residence in the area)
  - Job titles
  - Environmental measurements
    (area, personal).
- Individual differences of the internal dose?
  - Protective equipment, specific tasks
  - Non-occupational exposures
  - Toxicokinetic factors

Biomonitoring → to improve accuracy of exposure variables.

Environmental (Air) Measurements:

- Relatively easy methods
- Less expensive
- More acceptable to subjects
- Larger sample sizes
- Can be related to exposure limits and to control

Dose

- Once the agent is in the body it is described as a dose
- Level of contaminant in the body
- The amount of a substance that remains at a biological target during some specified time

Biomarkers of Exposure

- The contaminant of interest,
- It's metabolites,
- Any products of an interaction between the contaminant and a target molecule

  (e.g., DNA or protein adducts; these are also considered as **biomarkers of early effect**)
- These are measured in biological media (breath, urine, blood, or tissue samples).

Objective is to determine the internal dose, or the biologically effective dose to assess health risks related to the exposure

Biomarkers of exposure

Strengths:

- Reflect uptake through all routes & sources
- Reflect differences in absorption, distribution & elimination
- Reflect use of personal protective equipment
- Closer to the target organ, more relevant to outcomes

Limitations:

- More expensive, more labor intensive
- Only recent exposures
- Experimental and need validation in different settings, different time points

We are still in the early stages of biomarker research!

Mixtures

Simple mixtures:

Mixture of small number of chemicals (e.g., pesticide mixture) composition is qualitatively and quantitatively known

Complex Mixtures:

- 'Mixture of mixtures'
- Hundreds/thousands of components, inexact proportions
- Composition can vary over time, place, and conditions when the mixture is produced (welding fume, exhaust)

e.g.: Asphalt is a complex mixture (alkanes, aromatic hydrocarbons, and heterocyclic compounds containing sulfur/nitrogen/oxygen)

Health effects of the mixture?

- Overall direction of the combined effect is difficult to predict
- Can we anticipate the effects based on knowledge on individual components?
  - No interaction assumption (Interactions are rare)

How to assess human exposures to mixtures?

- Surrogates are used
- Biomarkers of surrogates

My overall research goals:

- Explore human exposure to chemical mixtures and health effects: PAHs, fuel, metals, PM, cigarette smoke
- Improve exposure measures by using cheaper, more sensitive and easy to use devices making them more feasible in large scale studies,
- Develop early markers of possible health risk,
- Develop a partnership with other researchers, government and industry to identify research needs, communicate research findings,
- Ultimately reduce work place exposures and prevent adverse outcomes

Past research exposure to mixtures: Biomarkers of exposure to JP-8 jet fuel

- Study with 323 Air Force Personnel
- Goal: Assess exposures to jet fuel
- Urinary benzene, naphthalene, and naphthols promising biomarkers of exposure
- A significant interaction between cigarette smoking and JP-8 exposure altering urinary naphthol levels

Past research exposure to mixtures: Biomarkers of exposure to PAHs among Chinese coke oven workers

- Simultaneous analysis of different PAH metabolites
- Highest levels of biomarkers in top-of-oven workers, followed by side-of-oven workers
- 72.5% of the variation of 1- and 2-naphthol and 82.8% of 1-pyrenol explained by
  - Parent PAH in urine
  - Work category
  - Smoking intensity

Polycyclic aromatic hydrocarbon (PAH) exposure and DNA damage in roofers

Why study roofers?

Many occupational risks (falls, accidents, back pain...)

Cancer in roofers?

Occupational exposures to polycyclic aromatic hydrocarbons, and respiratory and urinary tract cancers: a quantitative review to 2005

C. Bosetti[1]*, P. Boffetta[2] & C. La Vecchia[1,3]

[1]Istituto di Ricerche Farmacologiche 'Mario Negri', Milan, Italy; [2]International Agency for Research on Cancer, Lyon, France; [3]Istituto di Statistica Medica e Biometria, Univesità degli Studi di Milano, Milan, Italy

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Background: Exposure to polycyclic aromatic hydrocarbons (PAHs) has been reported in several industries, including those of the aluminum production, coal gasification, coke production, iron and steel foundries, coal tar and related products, carbon black and carbon electrodes production.

Patients and methods: This paper reviews the results from cohort studies conducted on workers exposed to PAHs in these industries, with a focus on cancers of the respiratory and urinary tract.

Results: An excess risk from lung/respiratory cancers was found in most industries, the pooled relative risk (RR) being 2.58 (95% CI 2.28–2.92) for coal gasification, 1.58 (95% CI 1.47–1.69) for coke production, 1.40 (95% CI 1.31–1.49) for iron and steel foundries, 1.51 (95% CI 1.28–1.78) for roofers and 1.30 (95% CI 1.06–1.59) for carbon black production. The evidence for cancers of the bladder and of the urinary system is less consistent, with a

Cancer Mortality Among European Asphalt Workers: An International Epidemiological Study. I. Results of the Analysis Based on Job Titles

Paolo Boffetta,[1*] Igor Burstyn,[1,2] Timo Partanen,[3] Hans Kromhout,[2] Ole Svane,[4] Sverre Langård,[5] Bengt Järvholm,[6] Rainer Frentzel-Beyme,[7] Timo Kauppinen,[3] Isabelle Stücker,[8] Judith Shaham,[9] Dick Heederik,[2] Wolfgang Ahrens,[7] Ingvar A. Bergdahl,[6] Sylvie Cenée,[8] Gilles Ferro,[1] Pirjo Heikkilä,[3] Mariëtte Hooiveld,[2] Christoffer Johansen,[10] Britt G. Randem,[5] and Walter Schill[7]

Roofers have higher rates of lung, bladder, stomach, skin and buccal cavity cancers, and leukemia

Research

A Case–Control Study of Lung Cancer Nested in a Cohort of European Asphalt Workers

Ann Olsson,[1,2] Hans Kromhout,[3] Michela Agostini,[3] Johnni Hansen,[4] Christina Funch Lassen,[4] Christoffer Johansen,[4,5] Kristina Kjaerheim,[6] Sverre Langård,[7] Isabelle Stücker,[8] Wolfgang Ahrens,[9] Thomas Behrens,[9] Marja-Liisa Lindbohm,[10] Pirjo Heikkilä,[10] Dick Heederik,[3] Lützen Portengen,[3] Judith Shaham,[11] Gilles Ferro,[1] Frank de Vocht,[12] Igor Burstyn,[13] and Paolo Boffetta[1,14,15]

Studies criticized for:

- Lack of specific personal exposure data (use of historical exposure scenarios, questionnaires, company records)
- Inadequate consideration of confounding factors: smoking

PAHs are the biggest concern.

Source: Asphalt, diesel exhaust, coal tar

Other sources?

ing rates among over 200 occupational groups using nationally representative data from the National Health Interview Survey (NHIS).[4] Pooled cigarette smoking rates in the period 1987 to 1994 varied from 4% in clergy and physicians to 58% in roofers, with consistently higher smoking rates among blue- versus white-collar work-

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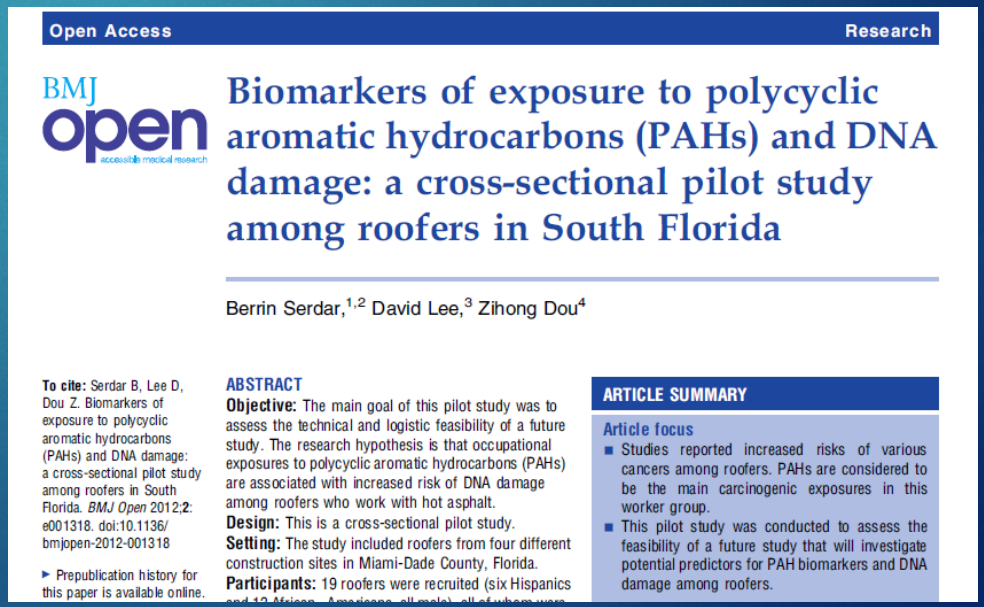
Asphalt

- Most is used for road paving & roofing
- About 50,000 on-roof workers are exposed to asphalt fumes during approximately 40% of their working hours
- Roofing asphalt a ‘probable human carcinogen’

  (Grp 2A, IARC)

Pilot study among roofers in Miami, FL

- To understand the feasibility of a larger study
- 19 roofers in Miami-Dade County
- All male, average age 38
- Hispanics (6), African-Americans (13)
- At 4 different roofing sites (12/2008, 1/2009, 6/2009)
- Blood & urine samples collected before- & after 6h work
- Questionnaires (before & after work)



Open Access Research

BMJ open accessible medical research

Biomarkers of exposure to polycyclic aromatic hydrocarbons (PAHs) and DNA damage: a cross-sectional pilot study among roofers in South Florida

Berrin Serdar,[1,2] David Lee,[3] Zihong Dou[4]

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► Prepublication history for this paper is available online.

ABSTRACT

Objective: The main goal of this pilot study was to assess the technical and logistic feasibility of a future study. The research hypothesis is that occupational exposures to polycyclic aromatic hydrocarbons (PAHs) are associated with increased risk of DNA damage among roofers who work with hot asphalt.

Design: This is a cross-sectional pilot study.

Setting: The study included roofers from four different construction sites in Miami-Dade County, Florida.

Participants: 19 roofers were recruited (six Hispanics

ARTICLE SUMMARY

Article focus

- Studies reported increased risks of various cancers among roofers. PAHs are considered to be the main carcinogenic exposures in this worker group.
- This pilot study was conducted to assess the feasibility of a future study that will investigate potential predictors for PAH biomarkers and DNA damage among roofers.

Biomarkers

Exposure

PAH metabolites (measured via LC/MS/MS)

- 1- & 2-OHNaphthalene
- 1-OHPyrene (gold standard)
- Other PAH metabolites

DNA damage (oxidative): 8-hydroxy-2'-deoxyguanosine in urine (ELISA):

- Oxidized derivative of deoxyguanosine
- Confounders: Age, gender, diet, smoking, alcohol consumption, physical activity, vitamin status
- DNA repair capacity, inflammation may alter levels
- Inter- & intra-individual variation?
- Lack of established basal levels

Findings

- PAH metabolites higher after work
- 8-OHdG levels higher after work
- No correlation between PAH & 8-OHdG before work
- Strong correlation between 8-OHdG and 1-OHPyr after work (Pearson $r = 0.8$, $p<0.0001$)
- Smoking was the single predictor of biomarkers before work
- Around 37% reported regular alcohol consumption (≥3d/wk) and 21% reported heavy consumption (≥12 drinks in one sitting)

Table 4 Linear regression models of urinary biomarkers

	Overall R^2	Predictor variables	Estimates	95% CI	p Value
Ln (8-OHdG)*					
Post-shift	0.868	Intercept	1.34	−1.11 to 3.78	0.261
		Ln (post-shift 1-OHPyr)	0.440	0.091 to 0.788	0.017
		Gloves	−1.09	−1.57 to −0.61	0.0002
Ln (1-OHPyr)					
Pre-shift	0.569	Intercept	4.91	4.30 to 5.52	<0.0001
		Ln (pre-shift creatinine)	1.10	0.333 to 1.87	0.008
		Smoker	1.09	0.309 to 1.87	0.009
Post-shift	0.920	Intercept	3.04	2.34 to 3.74	<0.0001
		Ln (pre-shift 1-OHPyr)	0.416	0.295 to 0.537	<0.0001
		Ln (post-shift creatinine)	0.712	0.459 to 0.964	<0.0001
		Skin burn history	0.528	0.262 to 0.794	0.001

- Highest levels of PAH metabolites and 8-OHdG among those who reported skin burn and did not wear gloves
- Lowest levels were among those who did not have skin burn and who reported wearing gloves
- Small sample size limits conclusions

Second exploratory study

Colorado Springs, CO

Study goals revised through several meetings with the industry members

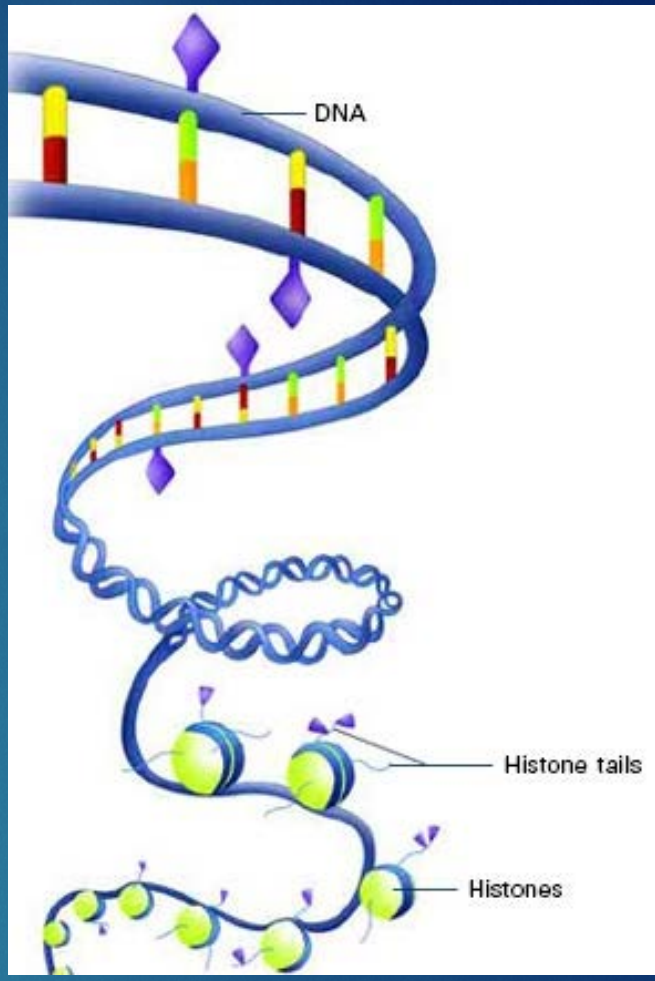
1) Investigate individual, environmental, work and task related factors that alter the levels of exposures, biomarkers and DNA damage
2) Explore the association between the composition of roof core (coal tar vs. asphalt) and levels of PAH exposures (biomarkers, dermal levels)

Study measures

- Goal: recruit 50 roofers
- Personal exposure:
  - Breathing zone air PAHs (GC/MS)
  - Dermal PAHs (GC/MS)
- Roof core samples: coal tar content?
- Biomarkers of exposure:
  - Plasma PAHs (GC/MS)
  - Urinary PAH metabolites (GC/MS)
- Early effect markers:
  - 8-OHdG (urine, ELISA)
  - New marker: γH2Ax (lymphocytes, Flow cytometry)

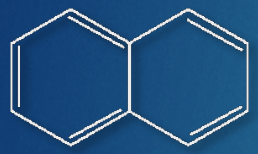
γH2Ax assay (lymphocytes)

- DNA is wrapped around proteins called Histones
- Early responder (within minutes) to double stranded DNA breaks
- Newly phosphorylated protein (γH2Ax) is the first step in recruiting and localizing DNA repair proteins
- Used in clinical studies, recently associated with exposure to radiation, cigarette some, particulate matter
- Flow cytometry more feasible
- Occupational studies?

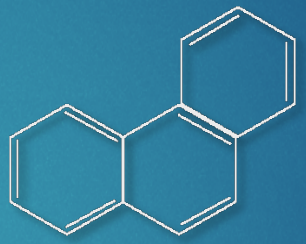


PAHs in Air

Gaseous phase (2-3 rings)

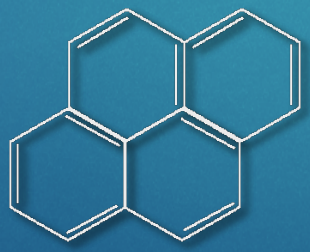


naphthalene



phenanthrene

Particulate phase (4+ rings)



pyrene

Personal breathing zone air

Particle-bound PAHs (FLT)

collected using personal sampling pumps (SKC XR-5000) fitted with $PM_{2.5}$ sampling inlets and 37 mm Teflon filters.

Gas-phase PAHs (XAD)

collected immediately downstream of the filters using standard adsorbent tubes (XAD-2, 2 section, 75/150 mg sorbent) with sample flow rate set at 2.7 L/min.

Air PAHs

Particle bound PAHs (FLT):

- Benzo(a)pyrene (65%)
- Naphthalene (57.5%)
- Chrysene (47.5%)
- Pyrene (35%)

Gas phase PAHs (XAD):

- Naphthalene (100%)
- Phenanthrene (97.5%)
- Pyrene (57.5%)

Pyrene 60-95-fold lower than previous studies in asphalt workers
Higher levels in smokers, especially on Thursday

Airborne PAHs. GM (GSD) in 8 smokers, 12 nonsmokers				
	Monday		Thursday	
	Nonsmokers	Smokers	Nonsmokers	Smokers
Naphthalene (ng/m³, XAD)	281.5 (2.0)	354.2 (3.0)	242.3 (3.0)	572.5 (3.5)
Pyrene (ng/m³, XAD)	1.7 (7.0)	1.7 (9.0)	1.3 (8.5)	5.2 (6.2)
Naphthalene (ng/m³, FLT)	0.534 (2.7)	1.2 (2.4)	0.839 (2.9)	0.622 (2.8)
Benzo(e)pyrene (ng/m³, FLT)	1.1 (7.1)	3.5 (9.3)	2.4 (8.7)	10.2 (8.5)

Dermal PAHs

- Hand wipe (Kriech et al 2011)
- Sunflower oil (3ml) into palm, rubbed, wiped
- Dichloromethane extracts
- GC with time of flight mass spectrometry (Cavallari et al 2012)

Dermal PAH analyses:

Naphthalene did not change significantly before/after work

Pyrene was higher after work (in smokers & nonsmokers)

Urinary biomarkers

Levels were similar to those observed in general population

- 1- and 2-OHNap:
  - Higher after work in nonsmokers ($p>0.05$)
  - Smokers had higher levels before work ($p>0.05$)!
- 1-OHPyr:
  - Overall, higher after work levels ($p>0.05$)
  - After work levels comparable to before work levels in observed in FL study
- 8-OHdG:
  - Higher after work ($p<0.05$ on Monday)
  - After work levels comparable to before work levels observed in FL

Correlations between exposure & biomarkers

- Positive correlations for air PAHs in same sampling medium (XAD or FLT), or in dermal wipes
- Inconsistent correlations between air/urine/dermal
  - Pyrene (XAD) & 1-OHNap on 2nd day, r = 0.47, p=0.04
- γH2ax and post-shift OHNap, 2nd day

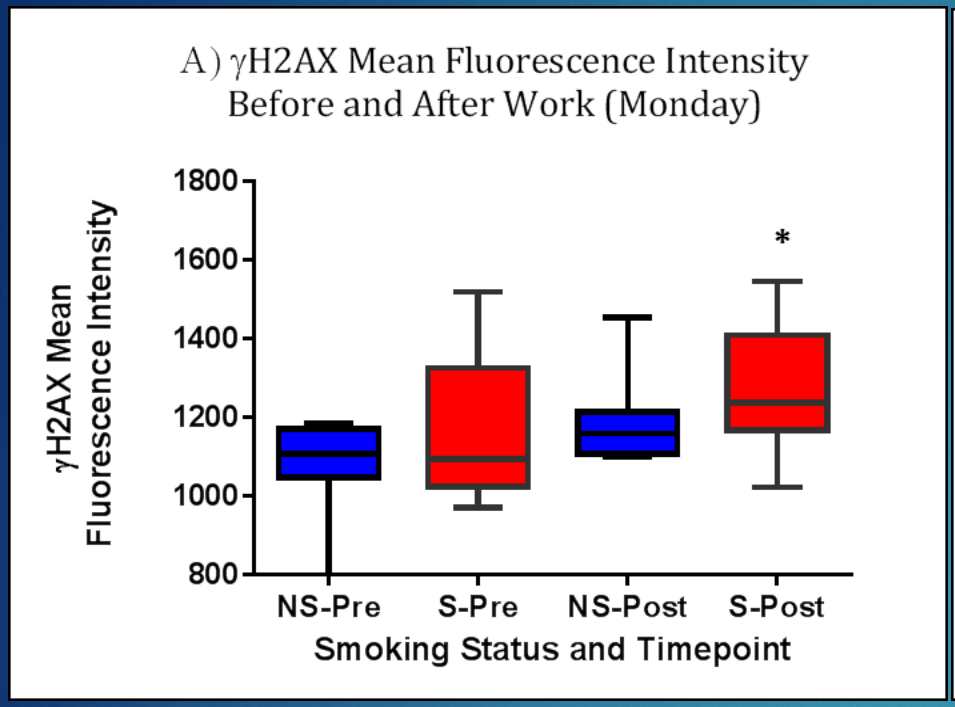
Smoking??

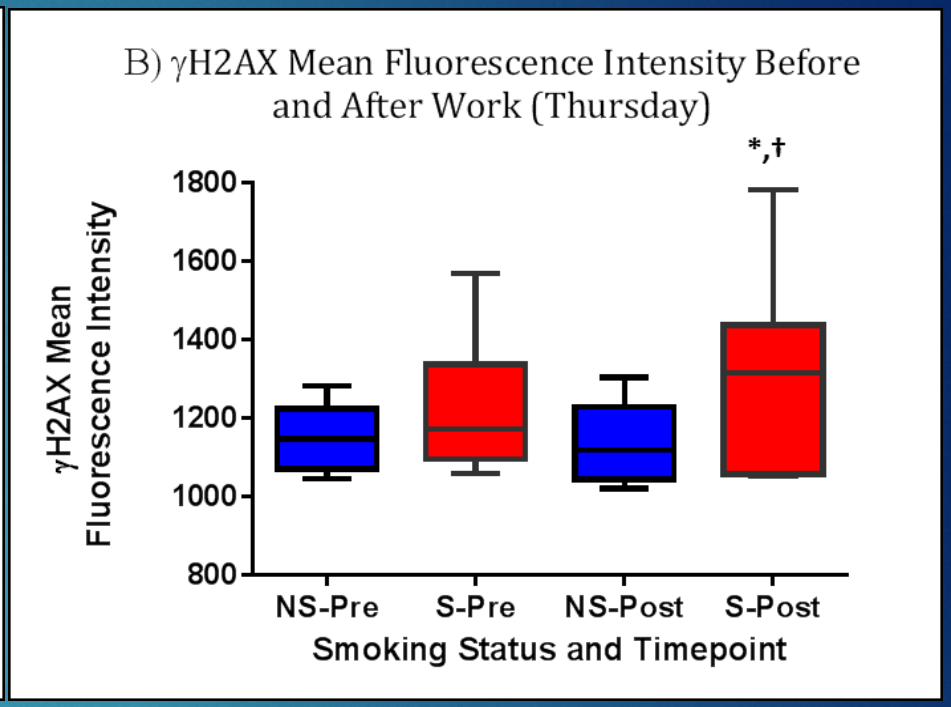
γH2ax & 1-OHNap, r = 0.58 (p=0.01)

γH2ax & 2-OHNap, r = 0.56 (p=0.01)

- No association with 8-OHdG

γ-H2AX (Mean fluorescence intensity)





NS=nonsmokers (n=8), S=smokers (n=12). Pre: pre-shift, Post: post-shift

*$p<0.05$ when compared to pre-shift nonsmokers,
†$p<0.05$ when compared to post-shift nonsmokers

Model for γH2ax (lymphocytes)		
	Estimate (SE)	***p*-value**
Fixed effects		
Intercept	6.97 (0.04)	<0.0001
Smoker	0.085 (0.04)	0.04
Time 2 (Monday, after work)	0.09 (0.03)	0.008
Time 3 (Thursday, before work)	0.06 (0.03)	0.06
Time 4 (Thursday, after work)	0.1 (0.03)	0.006
Time 1 (Monday, before work)	0 (ref.)	
Random effects		
Between-subject variance	0.006 (0.002)	0.02
Within-subject variance	0.011 (0.002)	<0.0001
Intraclass correlation coefficient %	35.3	

ICC= Between-subject variance / [between-s variance + within-s variance]
35.3% of unexplained variance is between-subjects

Model for 8-OHdG (urine)		
	Estimate (SE)	***p*-value**
Fixed effects		
Intercept	5.43 (0.09)	<0.0001
Urine creatinine	0.68 (0.08)	<0.0001
Time 2 (Monday, after work)	0.55 (0.12)	<0.0001
Time 3 (Thursday, before work)	0.13 (0.12)	0.27
Time 4 (Thursday, after work)	0.50 (0.12)	0.0002
Time 1 (Monday, before work)	0 (ref.)	
Random effects		
Between-subject variance	0.007 (0.02)	0.32
Within-subject variance	0.14 (0.03)	<0.0001
Intraclass correlation coefficient %	4.8	

Only 4.8% of unexplained variance between-subjects.

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Environmental Health

RESEARCH Open Access

Short-term markers of DNA damage among roofers who work with hot asphalt

Berrin Serdar[1,2,6*], Stephen Brindley[1], Greg Dooley[3], John Volckens[4], Elizabeth Juarez-colunga[5] and Ryan Gan[2]

Summary

- PAH exposure levels were low in this study
- Smoking has a major impact on biomarkers, especially on naphthalene metabolites
- γH2ax is a promising biomarker
  - Association with cigarette smoking can be problematic
  - Needs further testing in larger studies

Lung Deposition of Heavy Metals and Associated DNA Damage

Welding fume: possible human carcinogen (Group 2B, IARC)

- High hexavalent Cr (Cr VI) and Ni, both known human carcinogens (Group 1)
- Exposure associated with reduced lung function, bronchitis, pneumonia, neurological effects, and lung cancer

R21 exploratory study (funded by CDC/NIOSH)

Collaborator Dr Kirsten Koehler (Johns Hopkins)

Aims

- Usefulness of polyurethane foam lung deposition samplers for assessing Particulate Matter (PM) deposition?

Estimates of Ni and Cr in deposited PM will provide stronger correlations with urine biomarkers (compared to traditional measures of inhalable metals).

- The effect of heavy metals on markers of DNA damage?

Exposure to Ni and Cr during work (urine biomarkers, or estimates from deposited PM) will result in increased levels of oxidative DNA damage (urine 8-OHdG)

Currently finalizing study sites and preparing for the field study

Future directions: Biomarkers of the Exposome?

- Rappaport and Smith (*Science*, Vol.330, 2010) propose:

  To consider the 'environment' as the body's internal chemical environment and 'exposures' as the 'amounts of biologically active chemicals in this environment'

- Exposome (totality of environmental exposures from conception onwards) is critical for disease etiology
- Snapshots of critical portions of a person's exposome during different stages of life:
  - **Bottom-up approach:** all chemicals in each **external source** of a subject's exposome are measured at each time point
  - **Top-down approach:** This would measure all chemicals (or products of their downstream processing or effects) in a subject's **blood**
- Environmental equivalent of genome wide associations is possible when biomarkers of the exposome are characterized in humans with known health outcomes