Credit: Scott Stillborn

IARC Mechanistic Genetic Toxicity Evidence for Cancer in Firefighters

Alexandra Long, Ph.D

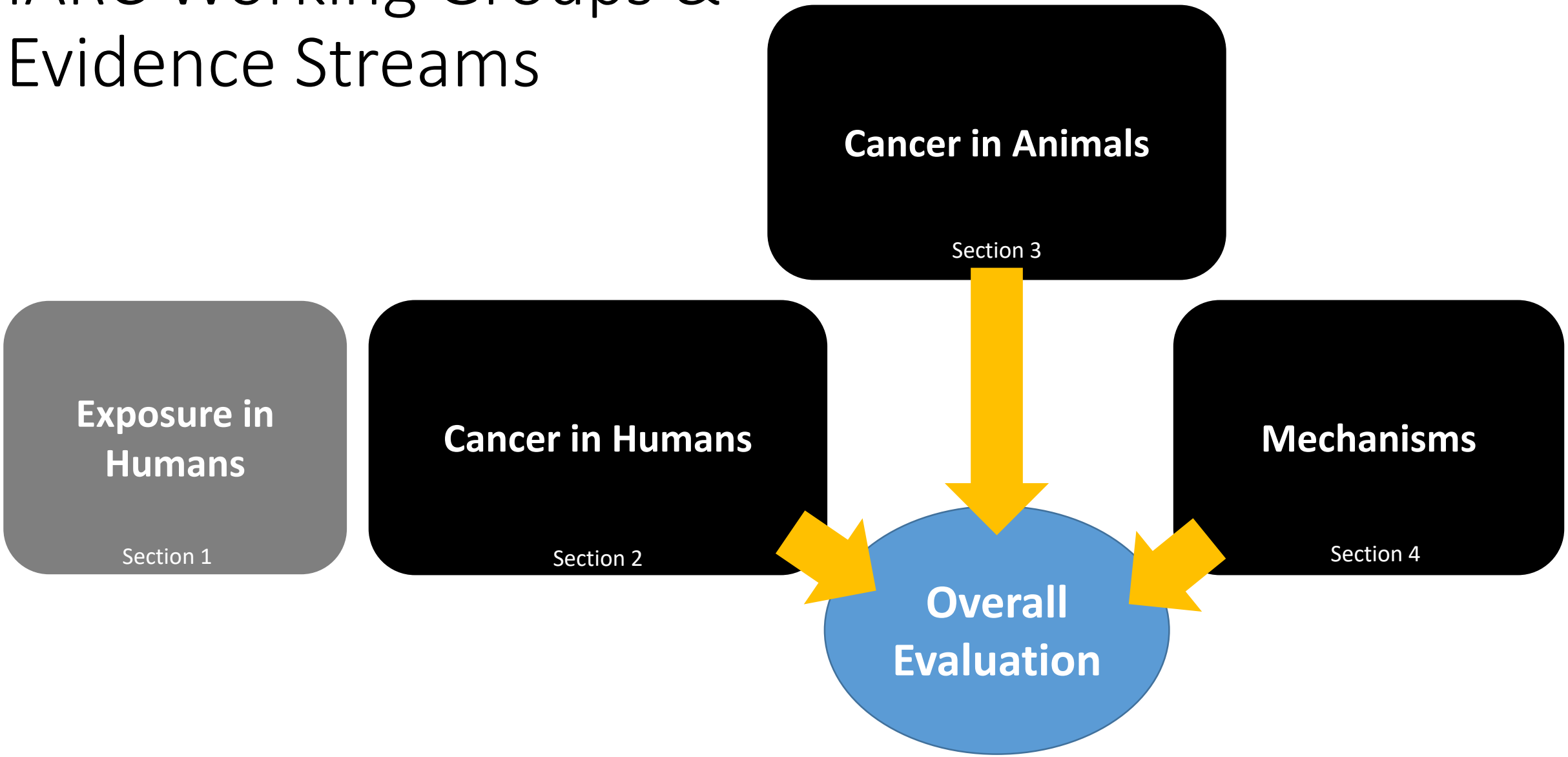
Emerging Approaches Unit

Health Canada Santé Canada

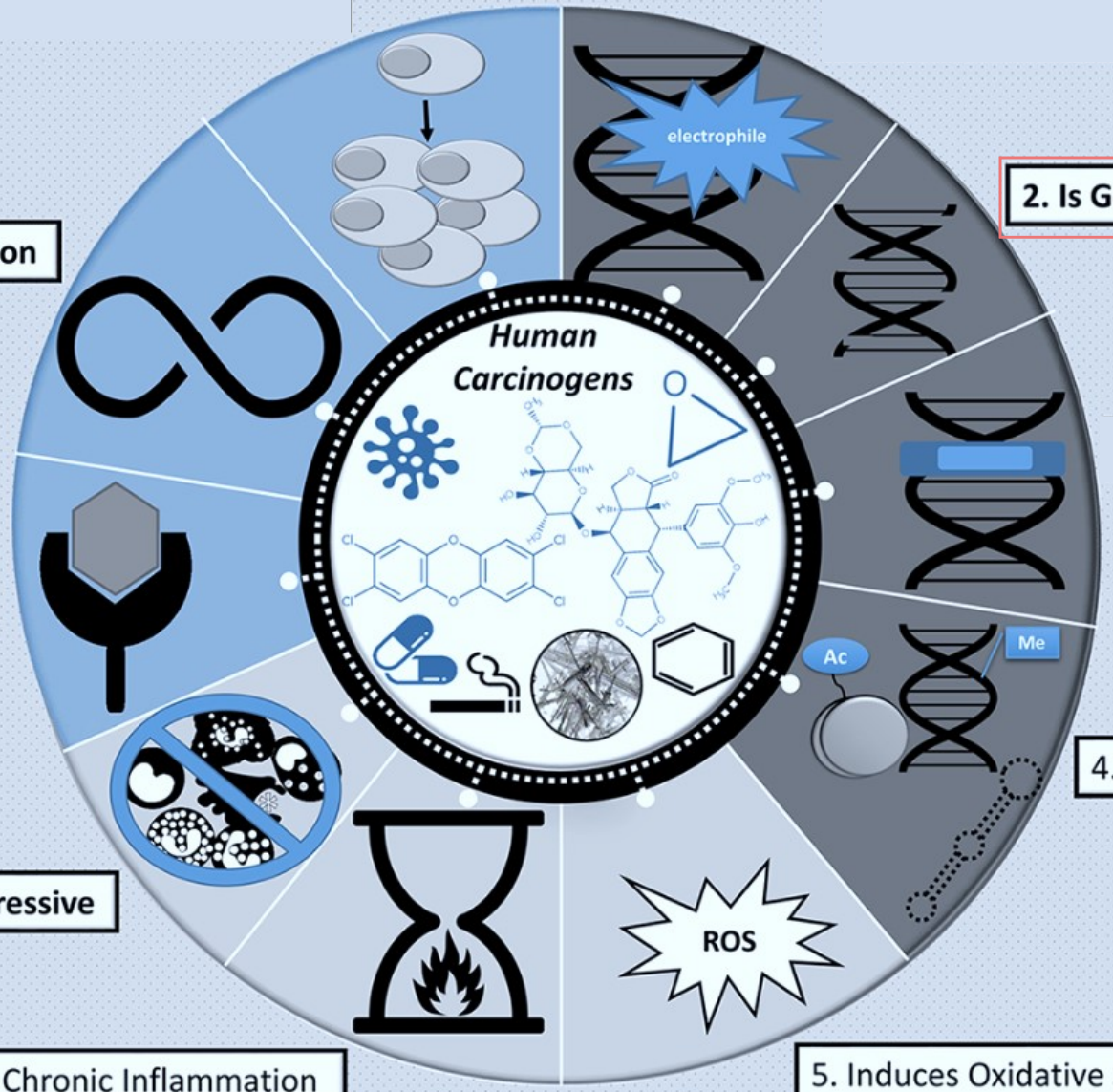
ESRAB Exchange

November 17, 2022

IARC Working Groups & Evidence Streams



THE KEY CHARACTERISTICS OF HUMAN CARCINOGENS



9. Causes Immortalization

2. Is Genotoxic

8. Modulates Receptor-mediated effects

4. Induces Epigenetic Alterations

7. Is Immunosuppressive

6. Induces Chronic Inflammation

5. Induces Oxidative Stress

Guyton et al. 2018. Chem. Res. Toxicol 31: 1290 – 1292.

Genetic Toxicity

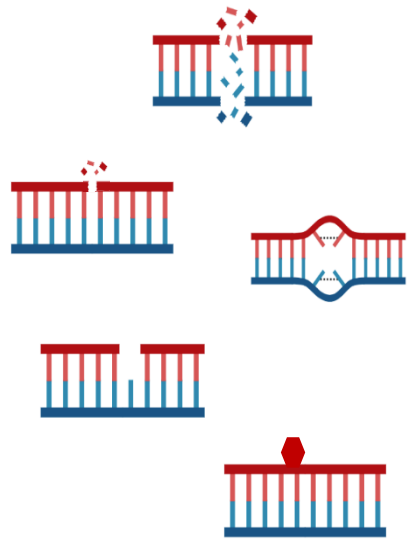
Different assays detect different stages of genetic toxicity

Genetox for human studies?

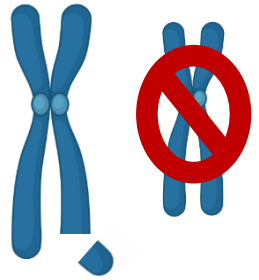
- Genetic damage assays
  - Comet assay
  - DNA adducts

Results transient – optimal sample collection 4 – 6 hours after exposure

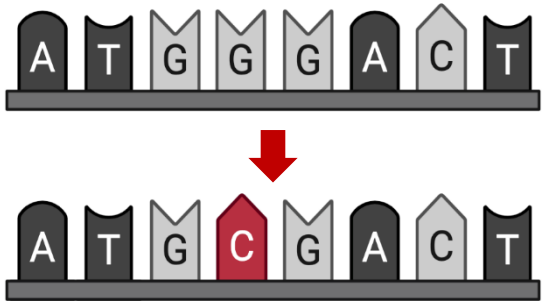
Results can be repaired but can be detectable days/weeks/months later



- Clastogenicity/aneugenicity
  - Micronucleus Assay



- Mutations
  - Ames/Salmonella assay



Urinary mutagenicity using Ames/Salmonella Assay

Urine sample collection timing dependent on excretion kinetics – i.e., the timing of when the chemicals come out in urine (usually sample within 24 hours). Depending on shift length may need to start collecting immediately following shift.

Mechanistic Data

Study Types (systems)

Most relevent

- Exposed humans
- Human cells
- Experimental systems
  - Animals
  - Non-human mammalian cells
  - Bacterial cells

Least relevent

<u>Pre/post sampling – firefighters served as own controls:</u>

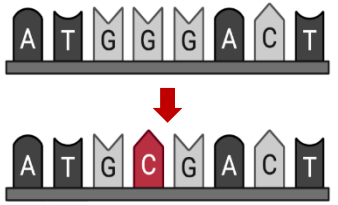
- On-shift studies involving fire event
- Training course

<u>Cross-sectional – firefighters vs. non-firefighter control:</u>

- Firefighters sampled following fire event vs control
- Firefighter (no specific exposure event) vs control

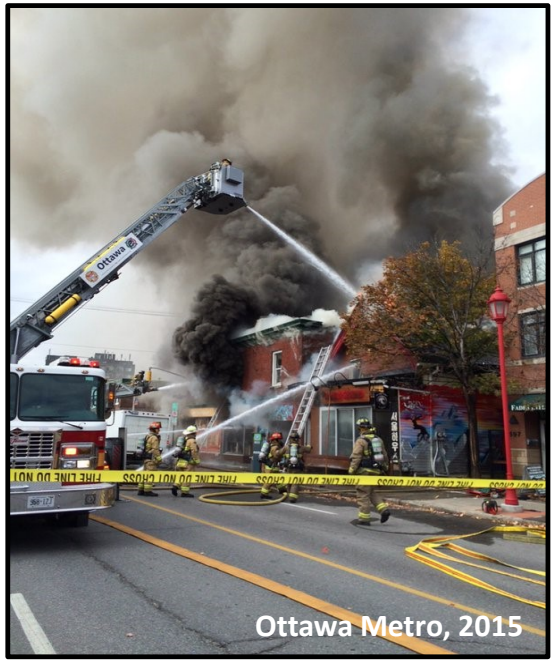
GENOTOXICITY

Structure Fire



Urinary Mutagenicity

- Canadian municipal firefighter study (Ottawa fire service)
- Samples collected pre & post on shift fire suppression events (31 samples from 16 non-smoking firefighters)
- Also included an unexposed control group (17 office workers)
- Did not consume charbroiled food & were not exposed to non-occupational combustion sources throughout the study
- Exposure assessment: personal air monitors, dermal wipes, urine metabolites



Environmental Science & Technology

Article

pubs.acs.org/est

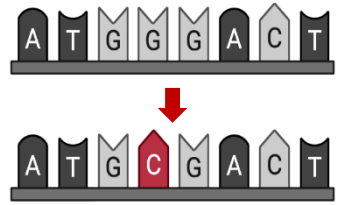
Elevated Exposures to Polycyclic Aromatic Hydrocarbons and Other Organic Mutagens in Ottawa Firefighters Participating in Emergency, On-Shift Fire Suppression

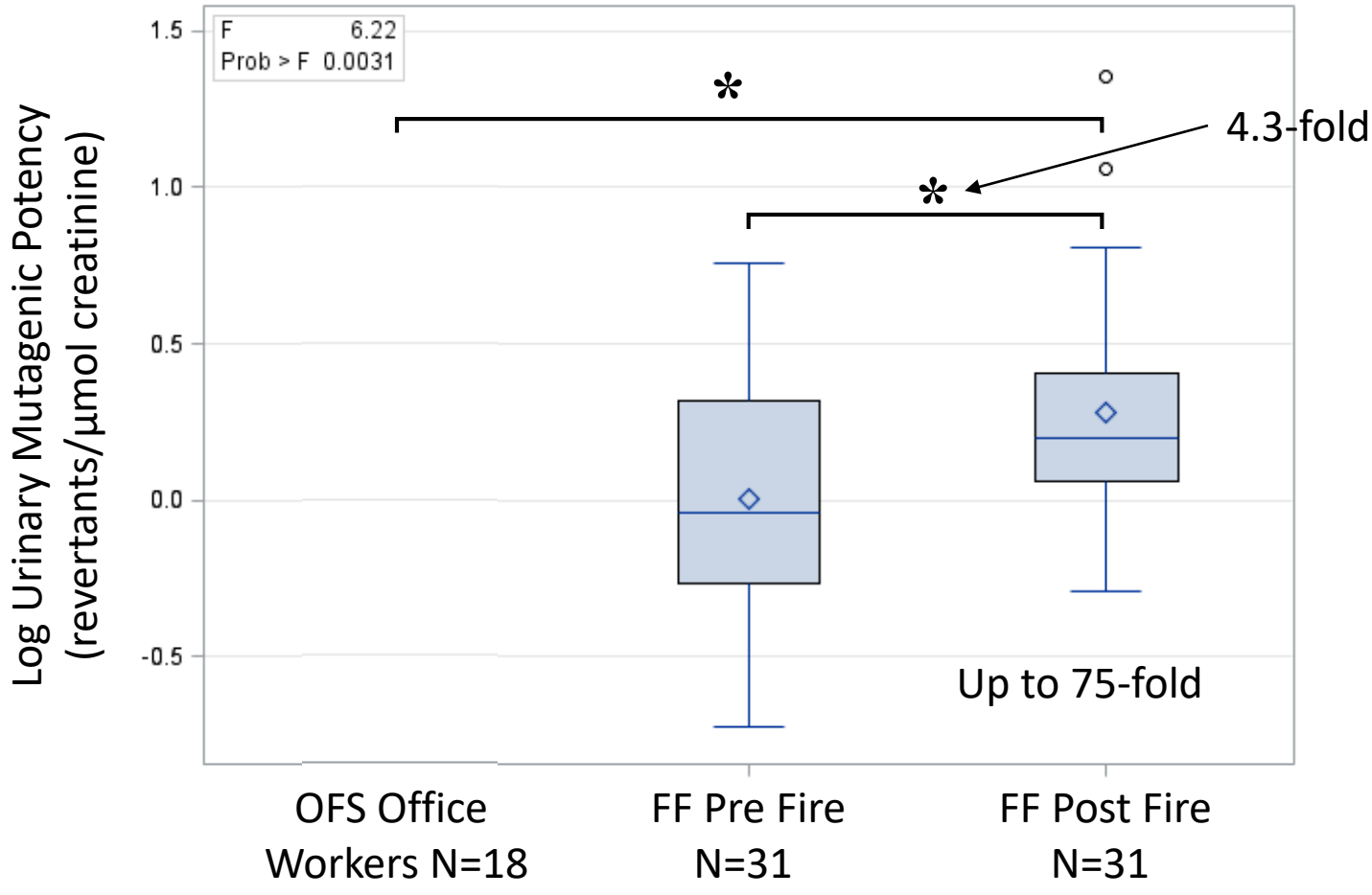
Jennifer L. A. Keir,[†] Umme S. Akhtar,[†] David M. J. Matschke,[‡] Tracy L. Kirkham,[§] Hing Man Chan,[†] Pierre Ayotte,[⊥] Paul A. White,[*,†,∥] and Jules M. Blais[*,†]

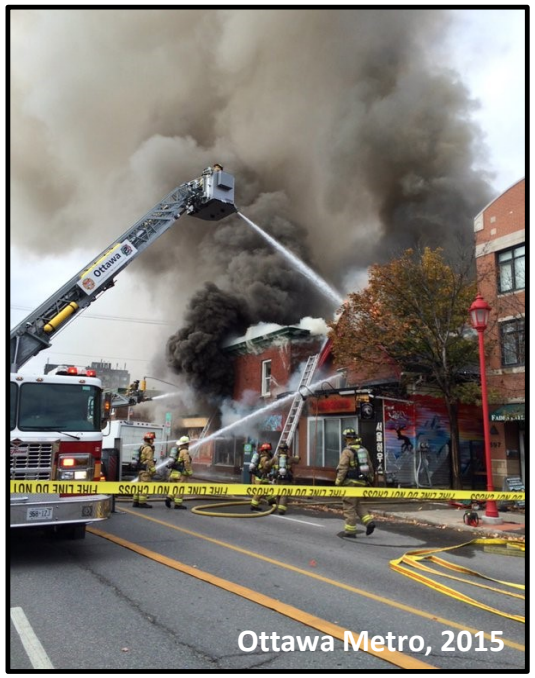
Keir et al. (2017) Environ Sci Technol 51(21): 12745-55

GENOTOXICITY

Structure Fire
Urinary Mutagenicity



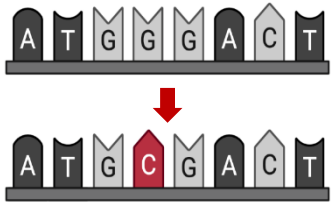




Keir et al. (2017) Environ Sci Technol 51(21): 12745-55

GENOTOXICITY

Wildland Fire (prescribed burns)



Urinary Mutagenicity

- American study, wildland firefighters
- Samples collected around both prescribed burn (burn day) and regular (non-burn day) work shifts:
  - Immediately before
  - Immediately after
  - Morning following
- 19 firefighters
- Exposure assessment: Air monitors for $PM_{2.5}$

Workplace

Original research

Urinary mutagenicity and oxidative status of wildland firefighters working at prescribed burns in a Midwestern US forest

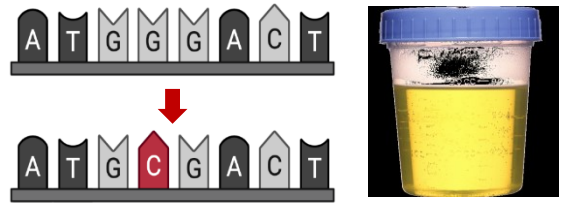
Chieh-Ming Wu,[1] Sarah H Warren,[2] David M DeMarini,[2] Chi (Chuck) Song,[3] Olorunfemi Adetona [1]

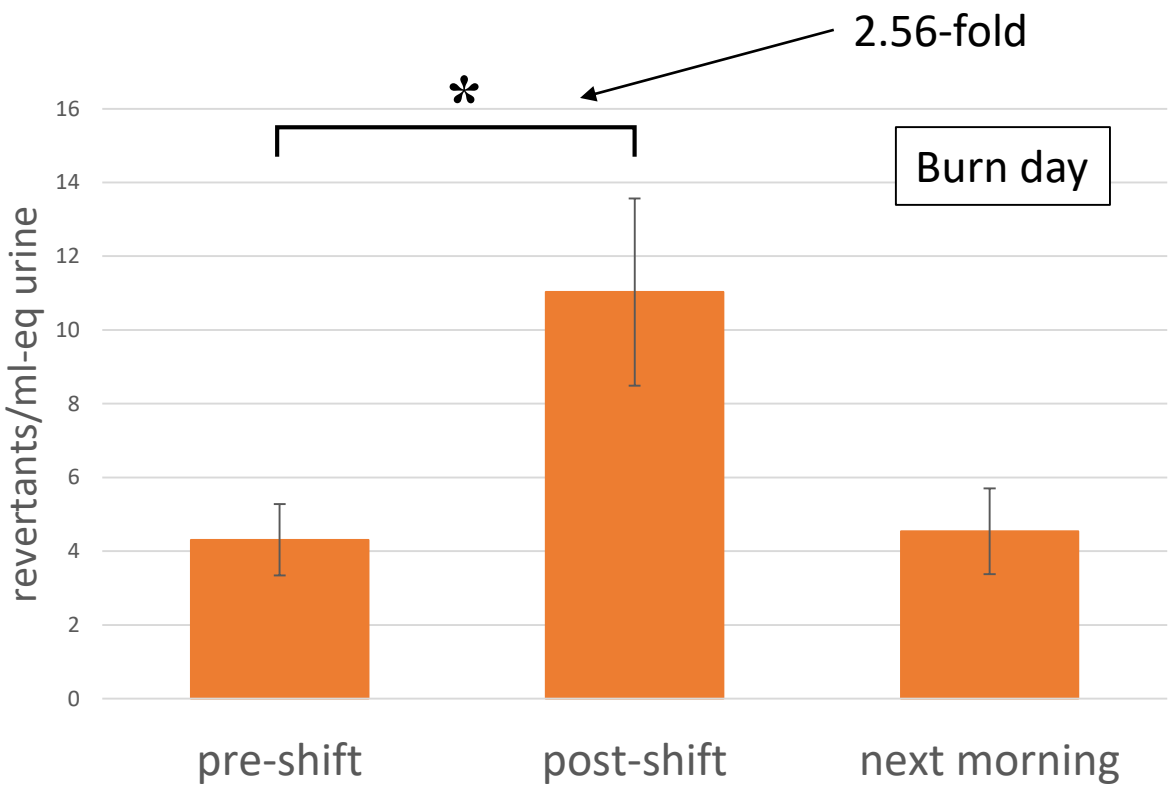
Wu et al. (2020) Occup Environ Med 78(5): 315-322

GENOTOXICITY

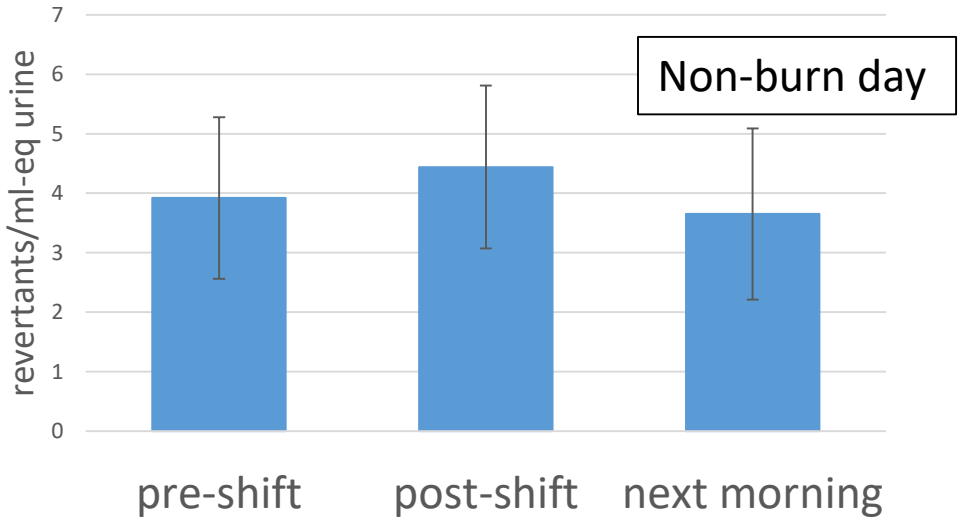
Wildland Fire (prescribed burns)

Urinary Mutagenicity





- Cross-shift changes in urinary mutagenicity significantly associated with length of smoke exposure (p = 0.01)



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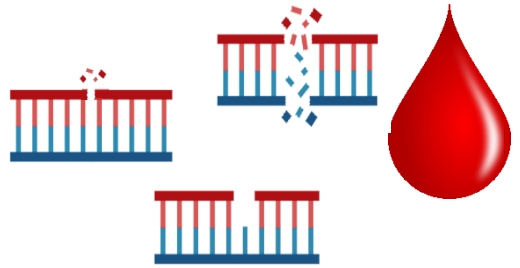
GENOTOXICITY

Structure Fire



Comet assay - blood

- Denmark, 9-month firefighter training course
- Samples collected around a 3-day course involving fire extinction exercises
  - 14-day before
  - immediately after
  - 14-days after
- 12 female & 41 male non-smoking firefighters
- Exposure assessment: dermal wipes, urine metabolites -> compounds in combustion emissions

Association between polycyclic aromatic hydrocarbon exposure and peripheral blood mononuclear cell DNA damage in human volunteers during fire extinction exercises

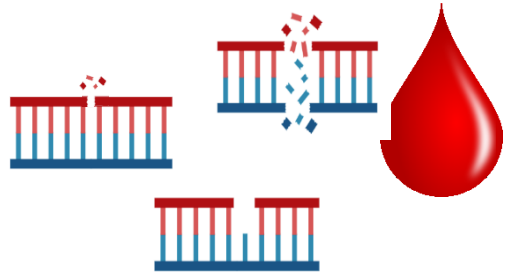
Maria Helena Guerra Andersen, Anne Thoustrup Saber,[1] Per Axel Clausen,[1] Julie Elbæk Pedersen,[1] Mille Løhr, Ali Kermanizadeh, Steffen Loft, Niels Ebbehøj,[2] Åse Marie Hansen,[1,3] Peter Bøgh Pedersen,[4] Ismo Kalevi Koponen,[1] Eva-Carina Nørskov,[4] Peter Møller* and Ulla Vogel[1,5,*]

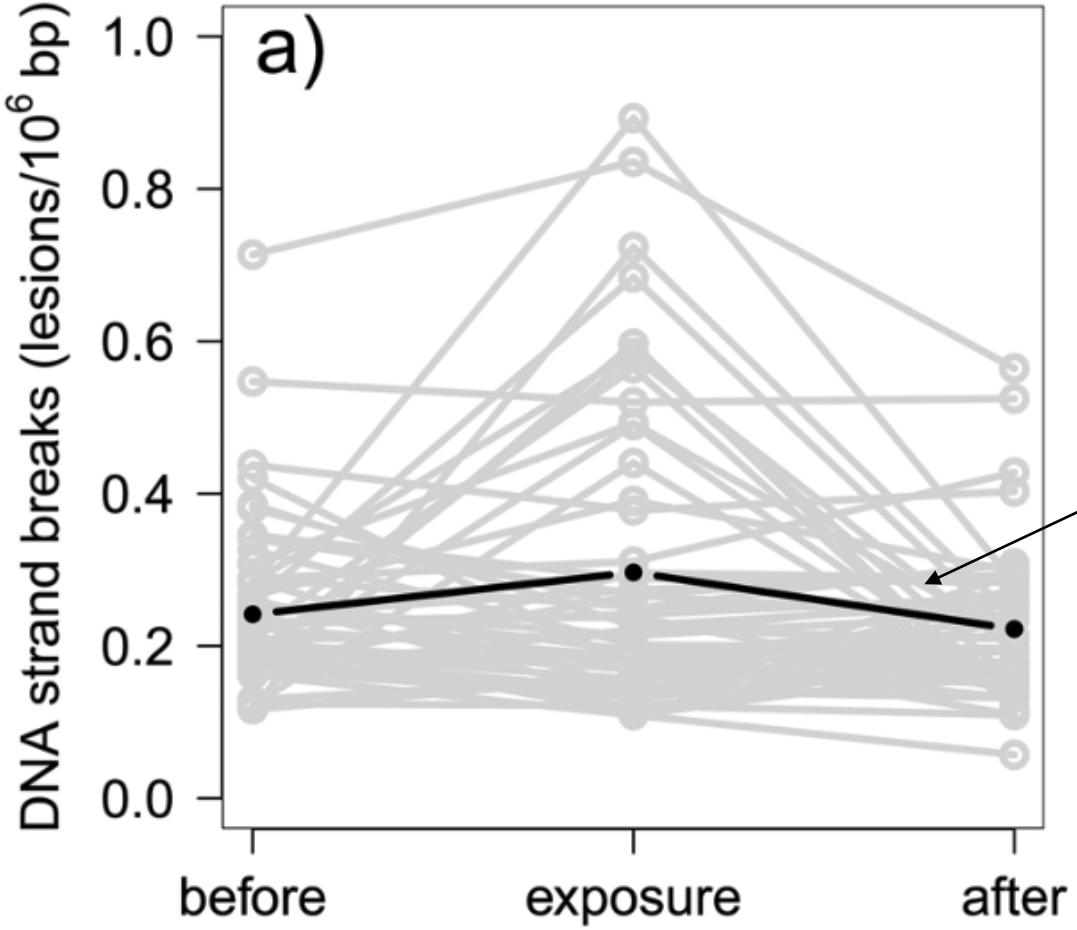
Andersen et al. (2018) Mutagenesis 33(1): 105-115

GENOTOXICITY

Structure Fire

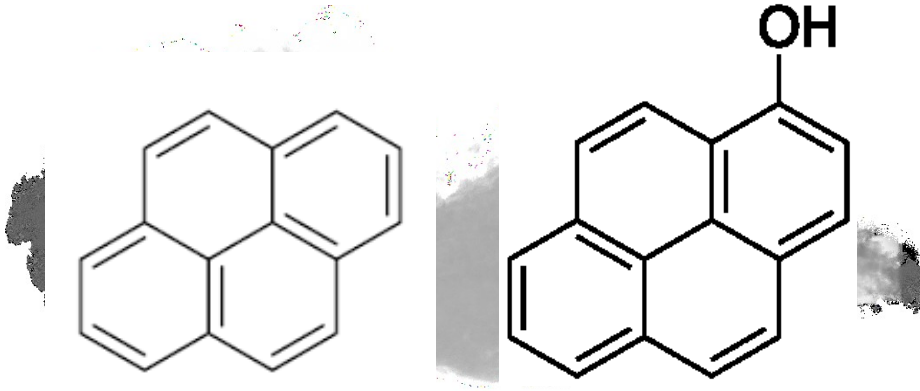
Comet assay - blood





*

- DNA damage frequency +ve correlated with:
  - Skin total polycyclic aromatic hydrocarbon concentration ($p<0.001$)
  - Skin pyrene concentration ($p<0.001$)
  - urinary 1-hydroxypyrene concentration ($p<0.001$)



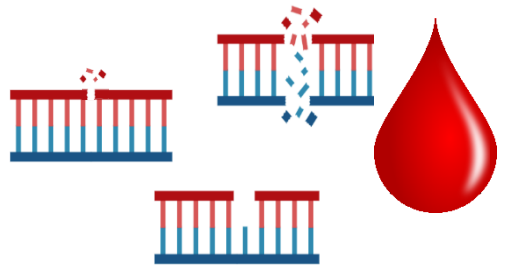
pyrene **1-hydroxypyrene**

(polycyclic aromatic hydrocarbons)

Andersen et al. (2018) Mutagenesis 33(1): 105-115

GENOTOXICITY

Employment as a firefighter (Wildland Fires)



Comet Assay - PBMC

- Portuguese study of wildland firefighters
- No specific exposure event - Cross-sectional study, samples collected from:
  - 60 volunteer wildland firefighter (>1 year experience)
  - 63 office-worker controls
- Samples matched by age, gender, smoking habits
- PPE use not recorded

ISSN: 1528-7394 (Print) 1087-2620 (Online) Journal homepage: http://www.tandfonline.com/loi/uteh20

Wood smoke exposure of Portuguese wildland firefighters: DNA and oxidative damage evaluation

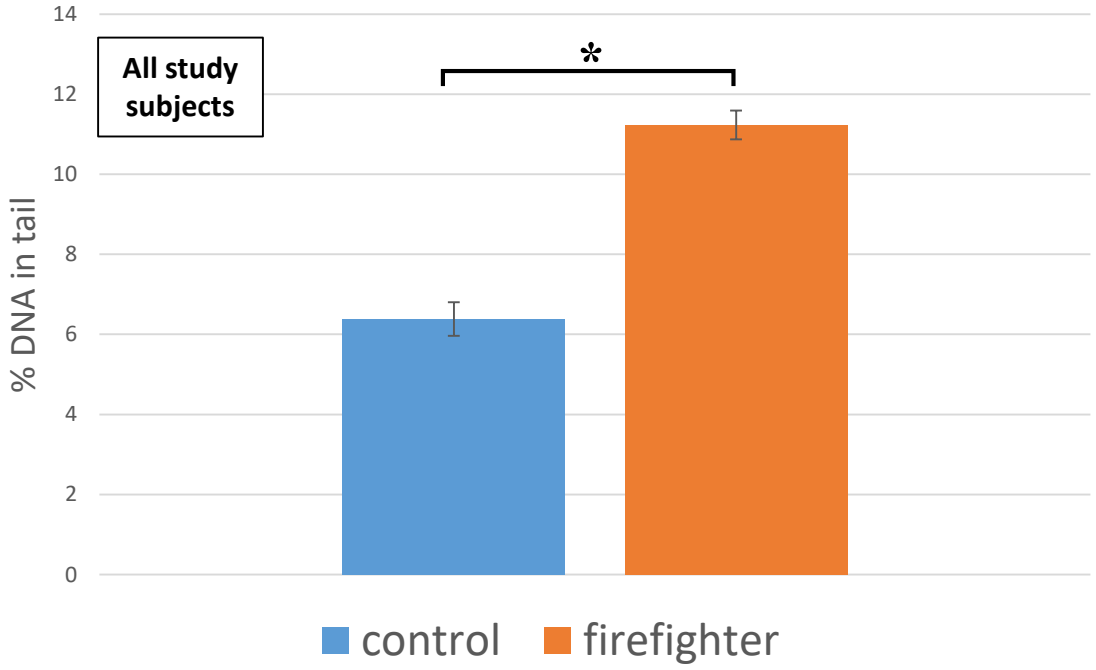
Ana Abreu, Carla Costa, Susana Pinho e Silva, Simone Morais, Maria do Carmo Pereira, Adília Fernandes, Vanessa Moraes de Andrade, João Paulo Teixeira & Solange Costa

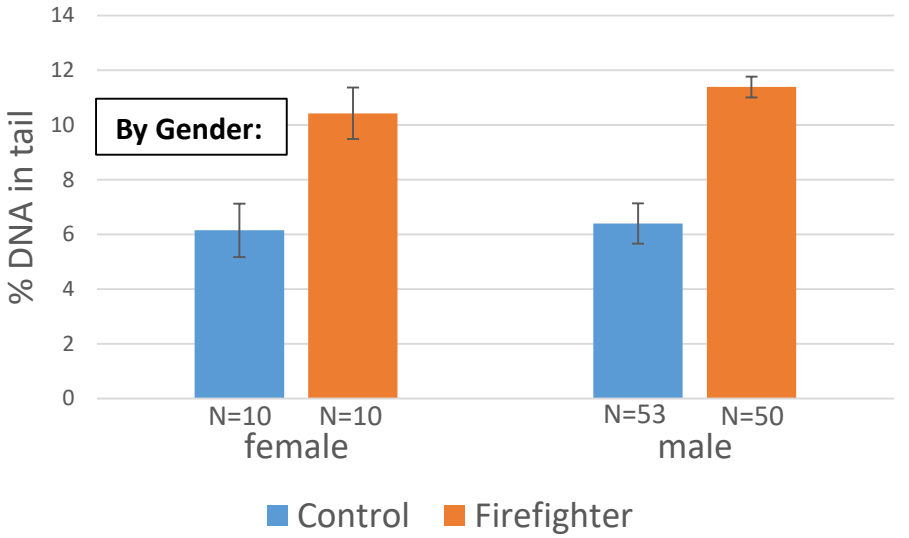
Abreu et al. (2017) J Toxicol and Env Health Pt A, 80: 13-15, 596-604.

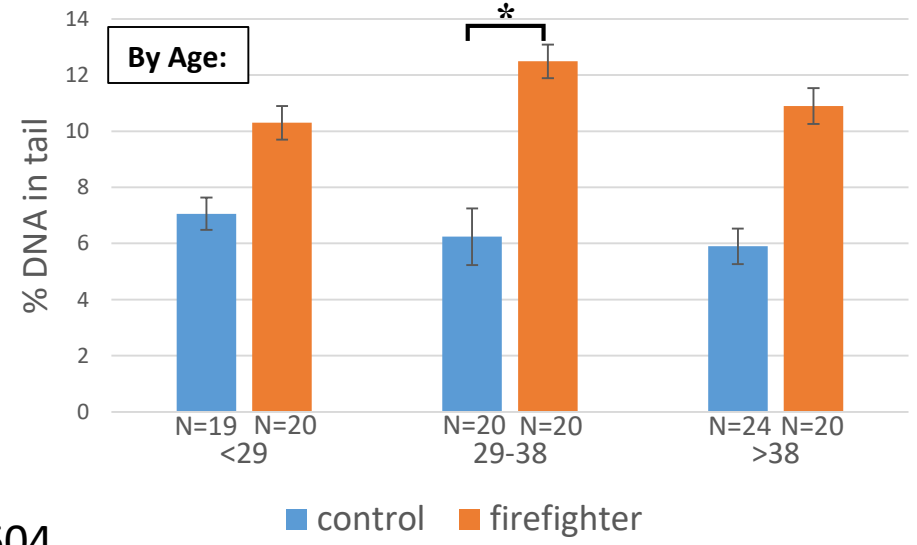
GENOTOXICITY

Employment as a firefighter (Wildland Fires)

Comet Assay - blood







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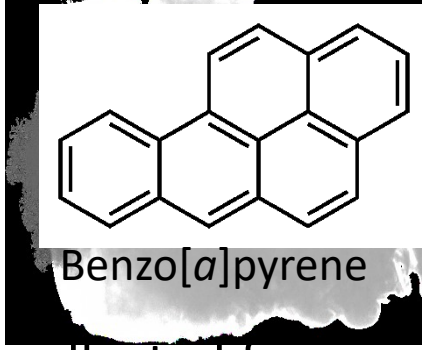
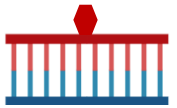
GENOTOXICITY

Employment as a firefighter (Municipal firefighters)





DNA adducts (polycyclic aromatic hydrocarbons) - blood

- American study of municipal firefighters
- No specific exposure event - Cross-sectional study, samples collected from:
  - 43 male municipal firefighters
  - 40 male controls
- Samples matched by age & smoking status

[CANCER RESEARCH 49, 4929–4935, September 1, 1989]

Biological Monitoring of Fire Fighters: Sister Chromatid Exchange and Polycyclic Aromatic Hydrocarbon-DNA Adducts in Peripheral Blood Cells[1]

Saou-Hsing Liou,[2] David Jacobson-Kram, Miriam C. Poirier, Dung Nguyen, Paul T. Strickland, and Melvyn S. Tockman

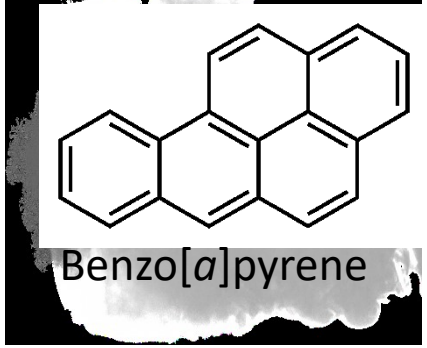
Division of Occupational Medicine, Department of Environmental Health Sciences, Johns Hopkins University School of Hygiene and Public Health [S-H. L., P. T. S., M. S. T.], and Radiobiology Laboratory, Johns Hopkins University Oncology Center [D. J-K.], Baltimore Maryland 21205, and Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Cancer Institute, NIH, Bethesda, Maryland 20892 [M. C. P., D. N.]

Liou 1989

GENOTOXICITY

Employment as a firefighter (Municipal firefighters)

DNA adducts (polycyclic aromatic hydrocarbons) - blood



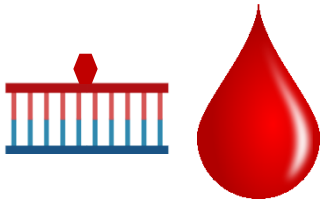


Table 7 *Odds ratio of fire fighting for BPDE-DNA antigenicity*[a]

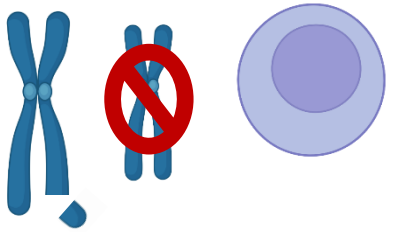
Adjustment parameter	Odds ratio (increased risk for detectable adducts)	Confidence interval (95%)
Crude data ($n = 43$)	1.03	0.41–2.58
Charcoal-broiled food (CBF) ($n = 29$)	1.73	0.60–4.99
Smoking ($n = 17$) + CBF	1.67	0.57–4.89
White race ($n = 37$) + CBF	3.36[b]	1.08–10.5
Nonwhite race ($n = 6$) + CBF	0.13	0.01–1.91
Daily alcohol ($n = 8$) + CBF	6.25	0.56–69.5

[a] Unadjusted and Mantel-Haenzel adjusted.
[b] $P = 0.04$.

Liou 1989

GENOTOXICITY

Employment as a firefighter (Municipal firefighters)



Micronucleus – exfoliated buccal epithelial cells (mouth)

- Indian study of municipal firefighters
- No specific exposure event - Cross-sectional study, samples collected from:
  - 47 male municipal firefighters with >10 years of service
  - 40 male office worker controls
- Samples matched for age, ethnicity, smoking status, alcohol consumption +

Micronucleus Frequencies and Nuclear Anomalies in Exfoliated Buccal Epithelial Cells of Firefighters

Manas Ranjan Ray[1], Chandreyi Basu[2], Senjuti Mukherjee[2], Sanghita Roychowdhury[2] and Twisha Lahiri[2]

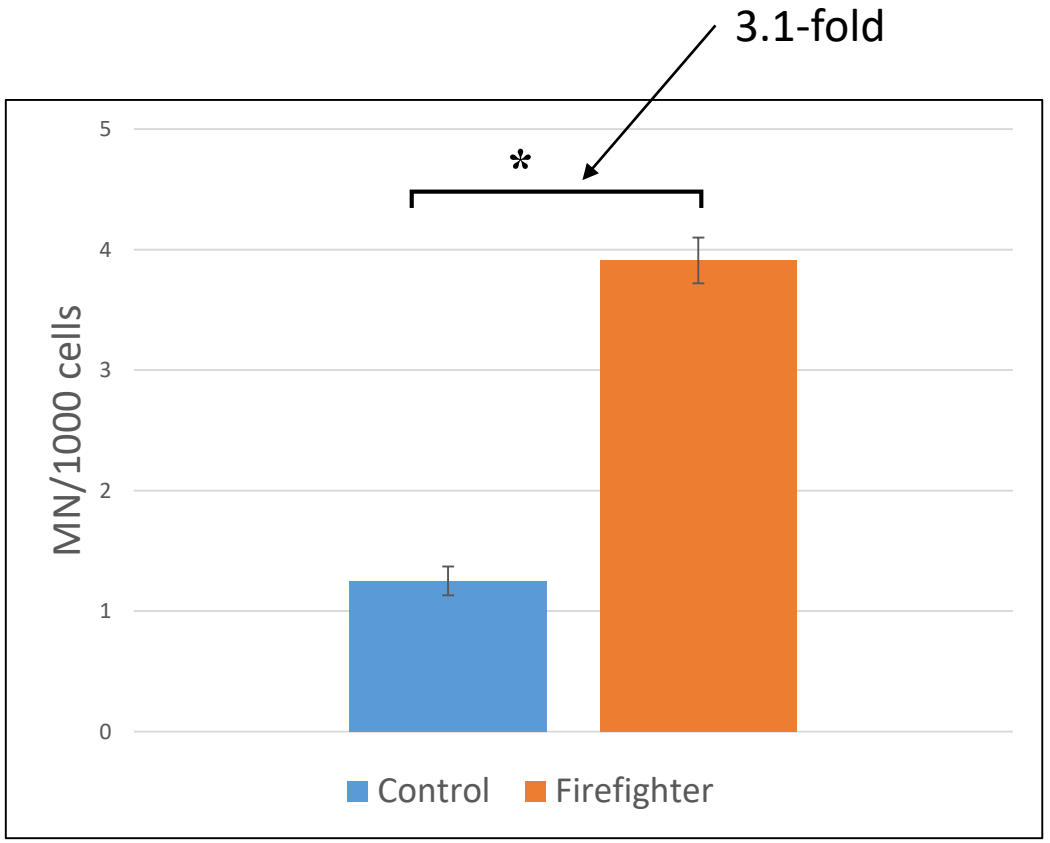
1. Experimental Hematology Unit and
2. Department of Neuroendocrinology, Chittaranjan National Cancer Institute, 37, S. P. Mukherjee Road, Kolkata 700 026, West Bengal, India

Ray et al. (2005) Int J Hum Genet 5(1):45-48.

GENOTOXICITY

Employment as a firefighter (Municipal firefighters)

Micronucleus – exfoliated buccal epithelial cells (mouth)



Ray et al. (2005) Int J Hum Genet 5(1):45-48.

IARC Monograph 132 Infographic

Impact of mechanistic data to final classification

Classification	Cancer in Humans	Cancer in experimental animals	Mechanistic Evidence
Group 1 (carcinogenic)	Sufficient		Strong

Need 1 in exposed humans

Thank you!

Carcinogenicity of occupational exposure as a firefighter

Lancet Oncol 2022

Published Online
June 30, 2022
https://doi.org/10.1016/
S1470-2045(22)00390-4