Pulmonary Pathogenicity of Ambient Particulate Dust from Iraqi Military Fields

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Research was conducted in compliance with the Animal Welfare Act and other Federal statutes and regulations relating to animals and experiments involving animals and adheres to principles stated in the Guide for the Care and Use of Laboratory Animals (NRC 2011) in facilities that are fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC).

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Agenda

- Background
- Animal studies of toxicity of particulate matter from Southwest Asia
  - "Sand and Smoke" Inhalational Study
  - Intratracheal Instillation Studies
    - Kuwait, Camp Buehring
    - Iraq, Camp Victory
- Wrap-up

Background

In Southwest Asia (SWA), dust/sand storms are a persistent problem.

- 300 µg/m^3 Total Suspended Particulates is the mean for Operation Iraqi Freedom locations (Iraq, Kuwait, Qatar).
  - *EPA hazardous cut point is 425 µg/m^3 TSP (24 hour value).*
- Aerosol partculate matter was sampled at 15 sites throughout SWA
  - *All sites exceeded the 1-year Military Exposure Guideline of 15 µg/m^3 for $PM_{2.5}$.*
  - (Engelbrecht et al. 2009, Inhalation Toxicology)

Reports of increases in respiratory disease and symptoms related to deployment

- Case cluster of Soldiers with acute eosinophilic pneumonia.
  - (Shorr et al. 2005 Mil Med)
- Cluster of Soldiers with constrictive bronchiolitis.
  - (King et al., 2011 N Eng J Med)
- Epidemiological analysis shows
  - Increased prevalence of upper respiratory complaints in theater.
  - Increased reporting of respiratory symptoms following deployment.
  - (See special edition of J Occup Env Medicine, June 2012)

Background

In 2005 Office of the Asst. Secretary of Defense for Health Affairs chartered a working group to assess state of knowledge of health effects of exposure to particulate matter in SWA.

Several *ad hoc* working groups have considered the same question since 2005 (Military Operational Medicine, National Jewish Health, VA/DoD Airborne Hazards Symposia).

Relevant reports issued by National Research Council (review of EPMS) and Institute of Medicine (burn pits).

All of this has led to

Ongoing clinical research on possible respiratory health effects of deployment to SWA at Brooke Army Medical Center.

Epidemiological studies through Millennium Cohort Study and US Army Public Health Command.

Animal studies of toxicity of SWA dusts

Smoke and Sand Study

Design and rationale

Project lead by NAMRU-Dayton (Naval Medical Research Unit)

Inspired by increased frequency of acute eosinophilic pneumonia reported early in Operation Iraqi Freedom.

May be associated with new-onset smoking.

Rats exposed to cigarette smoke and surface sand from Camp Victory (CV) or pure silica fractionated to respirable diameter.

Nose Only Exposure

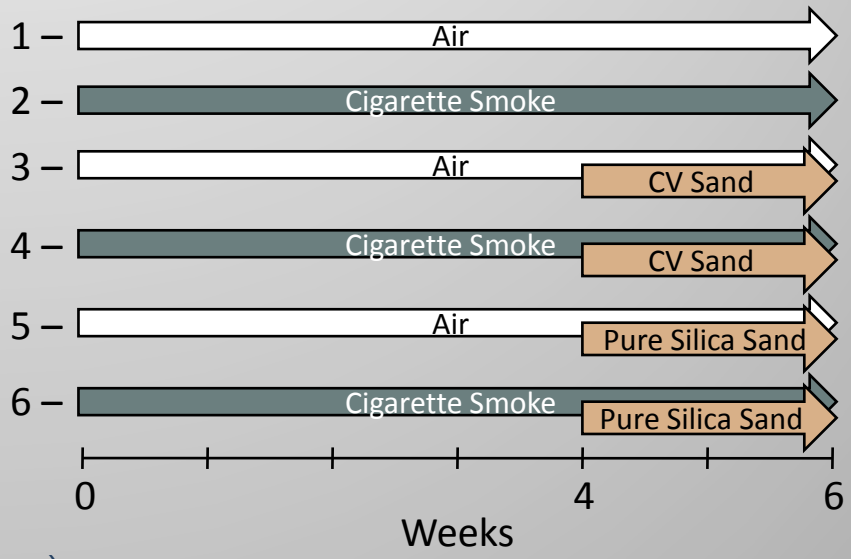
Air/Smoke [0.48 mg WTPM/L]

3 h/day, 5 d/week

Whole Body Exposure

Sand [1 mg/m³]

19 h/day, 7 d/week



(Dorman et al., 2012 Inhalation Toxicology)

Histology:
Mild air passage irritation from CV sand exposure but < silica.
Much stronger effect from smoke.
Some modest interactions between cigarette smoke and sands.

No statistically significant differences in pulmonary function due to silica/sand exposure.

Changes in gene/protein expression related to CV Sand exposure seem to be stress and/or inflammation –related

Endpoint	Air-Air	Smoke-Air	Smoke-CV Sand	Smoke-Silica
Body weight	421.6 ± 9.4	353.3 ± 5.6*	356.9 ± 12.3*	361.5 ± 11.7*
Baseline respiratory rate	154 ± 12	108 ± 9*	145 ± 16	144 ± 12
Tidal volume (ml) with MCh	2.01 ± 0.15	1.56 ± 0.07*	1.52 ± 0.08*	1.54 ± 0.10*
Baseline Penh	0.63 ± 0.04	1.16 ± 0.16*	1.23 ± 0.11*	1.10 ± 0.20
Penh with MCh	7.27 ± 1.03	3.75 ± 0.83*	2.15 ± 0.31*	3.11 ± 0.42*

(Dorman et al., 2012 Inhalation Toxicology)

Intratracheal instillation

Camp Buehring Kuwait

NAMRU-Dayton

Toxicity of settled, size-fractionated dust collected at Camp Buehring (N Kuwait)

Rats exposed with a single intratracheal instillation to 1, 5, 10 mg ≤10 µm dust; animals sacrificed 3, 7, 180 days post exposure

Histopathology, cytokines, markers of lung injury

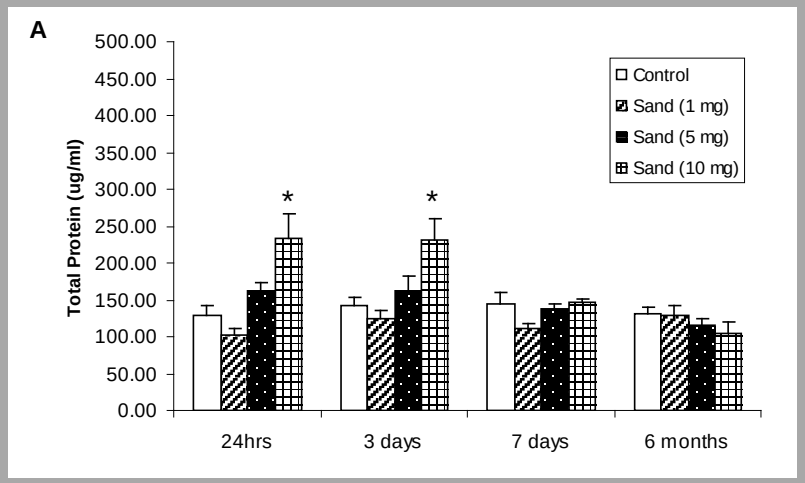
TiO_2 and silica controls

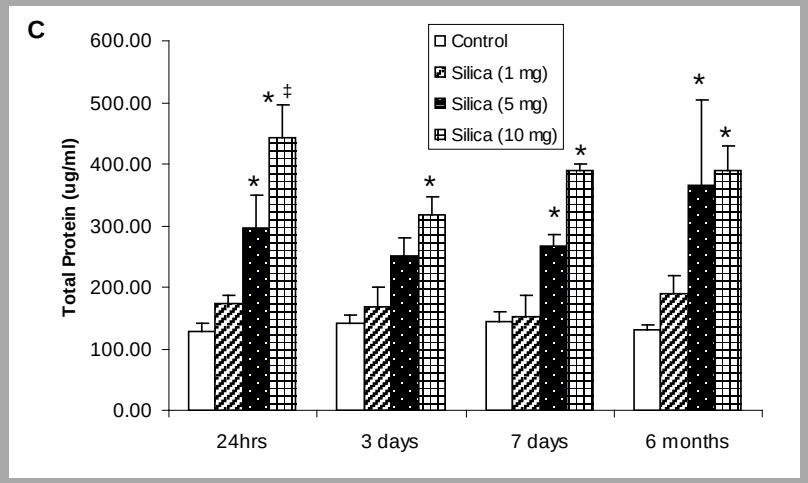
(Wilfong 2011, J Toxicol Env Health A)

Intratracheal Instillation

Camp Buehring Kuwait

Total Protein





Obvious inflammation in dust-exposed animals at short times—similar to TiO_2

Evidence of fibrosis and continuing inflammation in silica controls at 6 mo

However, at 6 months little evidence of disease in dust-exposed animals

(Wilfong 2011, J Toxicol Env Health A)

Intratracheal nstillation

Camp Victory, Iraq

Two rat intratracheal instillation studies

1. IR8: Camp Victory aerosol PM_{10} collected in 2008
   silica control
   3 doses (2.5, 5.0, 10.0 mg/kg)
   3, 7, 30, 60, 120, 150 days

2. PM_{10} from

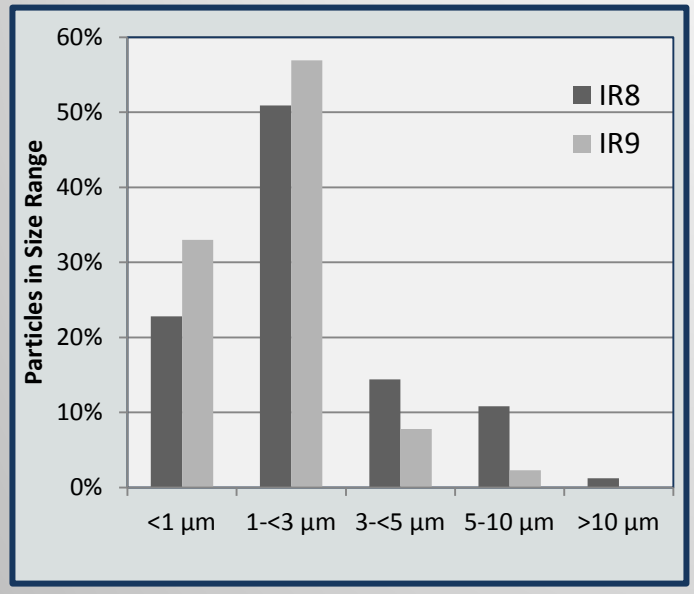
IR9	aerosol dust collected at Camp Victory in 2009
P15	Camp Buehring Dust
IR8	aerosol dust collected at Camp Victory in 2008
USUPM	US urban dust (NIST)
Si	silica control

3 doses (where possible)
60, 120, 150 days

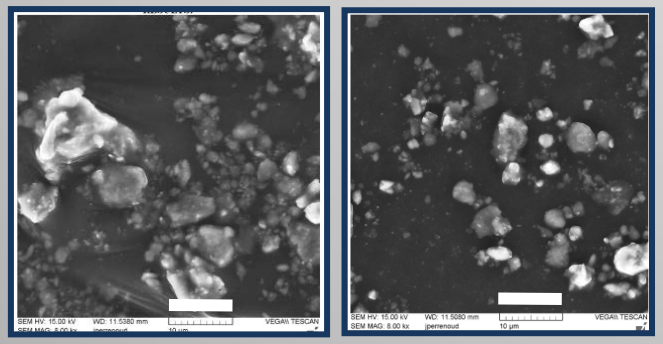
Characterization of dusts

Camp Victory, Iraq

Particle Sizes



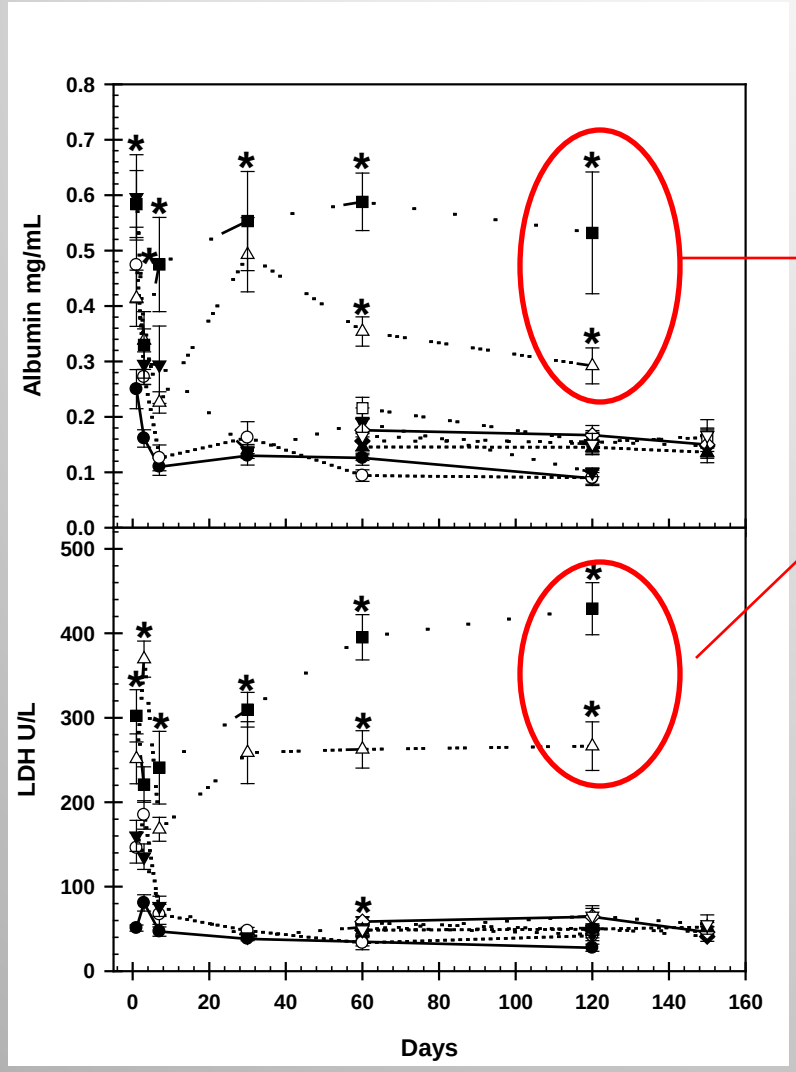
SEM



IR8 IR9

Silica NIOSH 7500 (wt %)		
	IR 8	IR 9
Cristabolite	ND	ND
Quartz	3.3	8.6
Tridymite	ND	ND
Silica	3.5	8.6

Elemental Composition (mg/kg)				
	IR8	IR9	P15	USUPM
Cu	99	120	660000	610
Ca	118000	110000	150000	58400
Fe	27700	26000	9900	39200
Al	19500	19000	6600	34300
Mg	23600	24000	19000	8100
K	5290	5900	1600	10600
Pb	52	74	42	6600



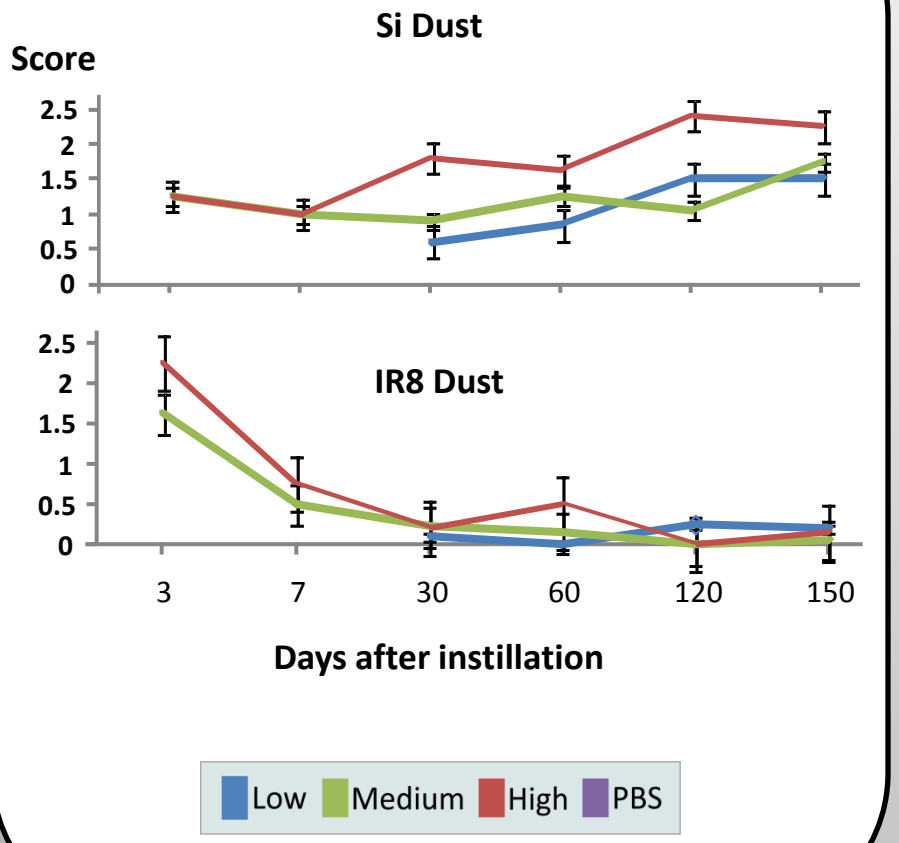
Protein in lung lavage fluid

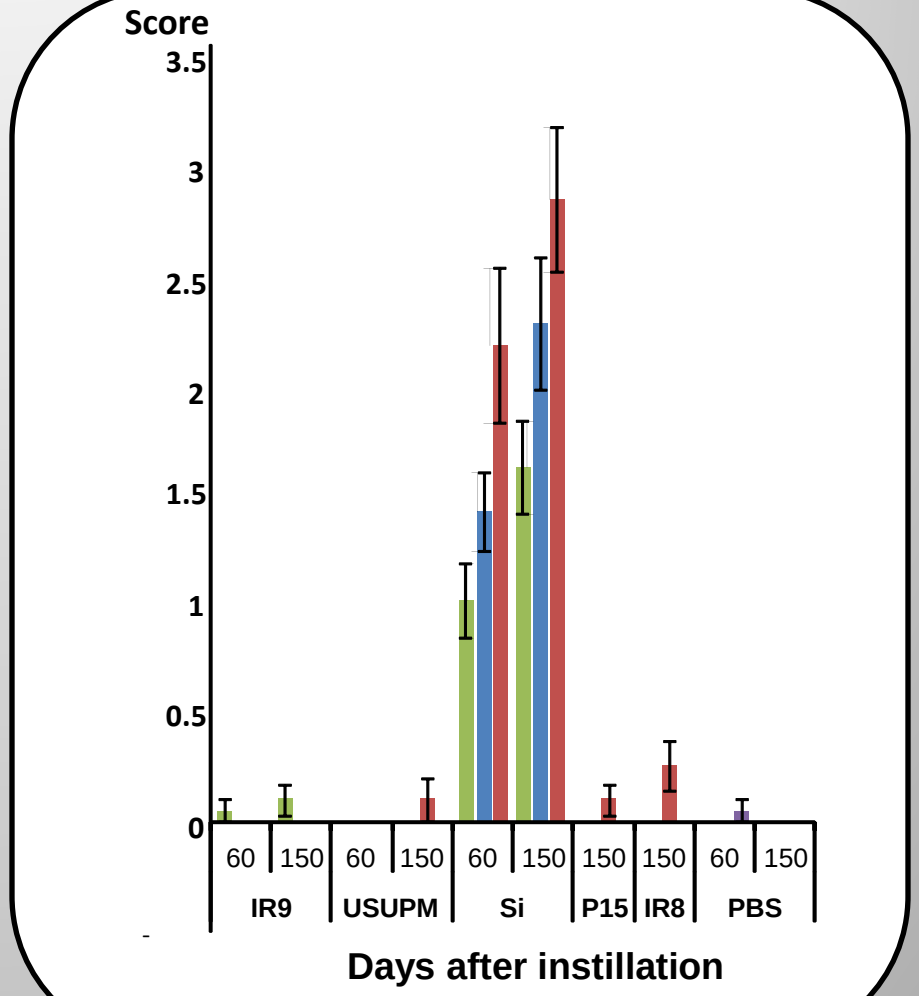
Silica

2008 Camp Victory (IR8)
2009 Camp Victory (IR9)
US Urban Dust (USUPM/NIST)
Camp Buehring Dust (P15)
PBS

All treatments result in some lung damage at early times; however, only silica produces a large persistent effect.

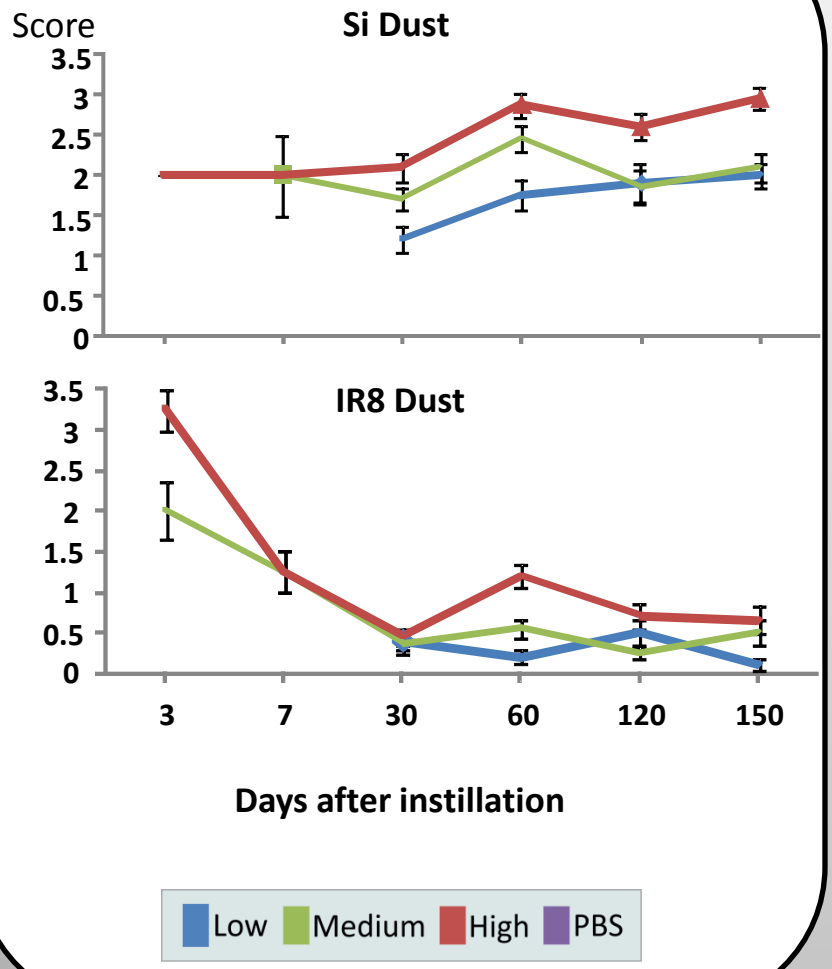
Histology—Semi-quantitative scoring

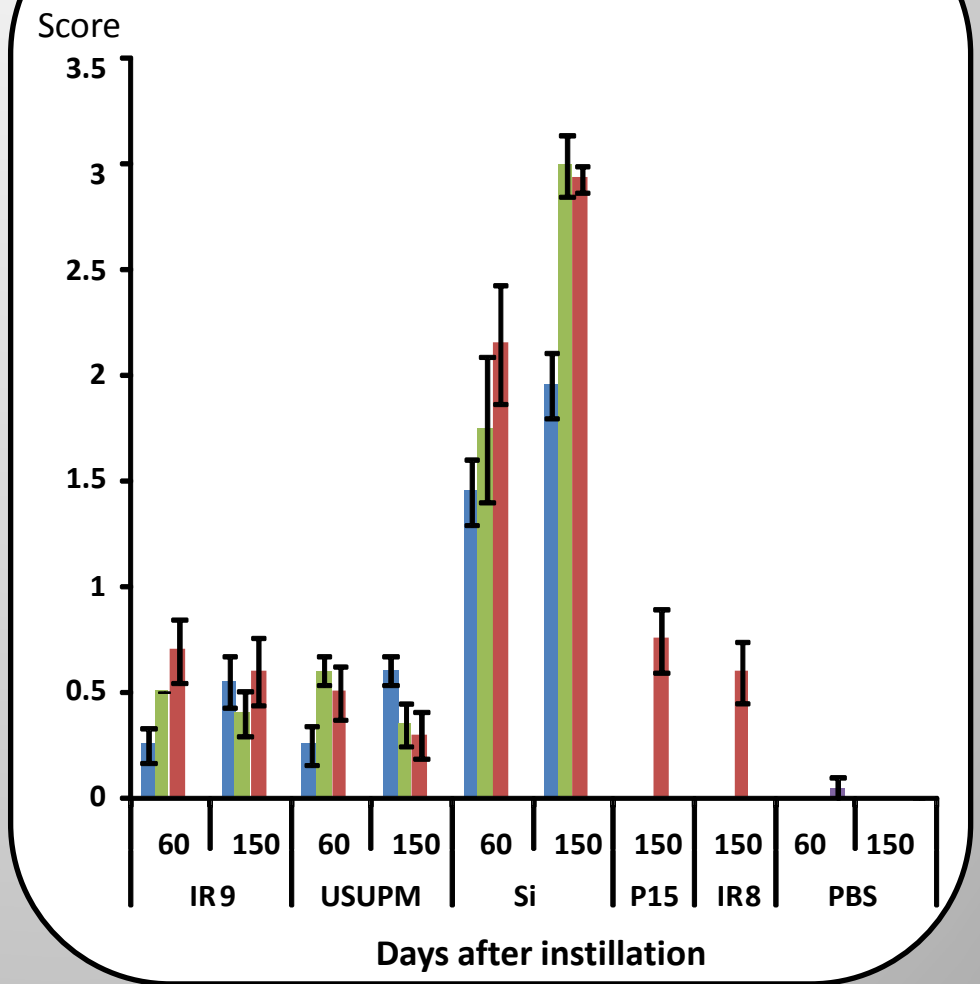




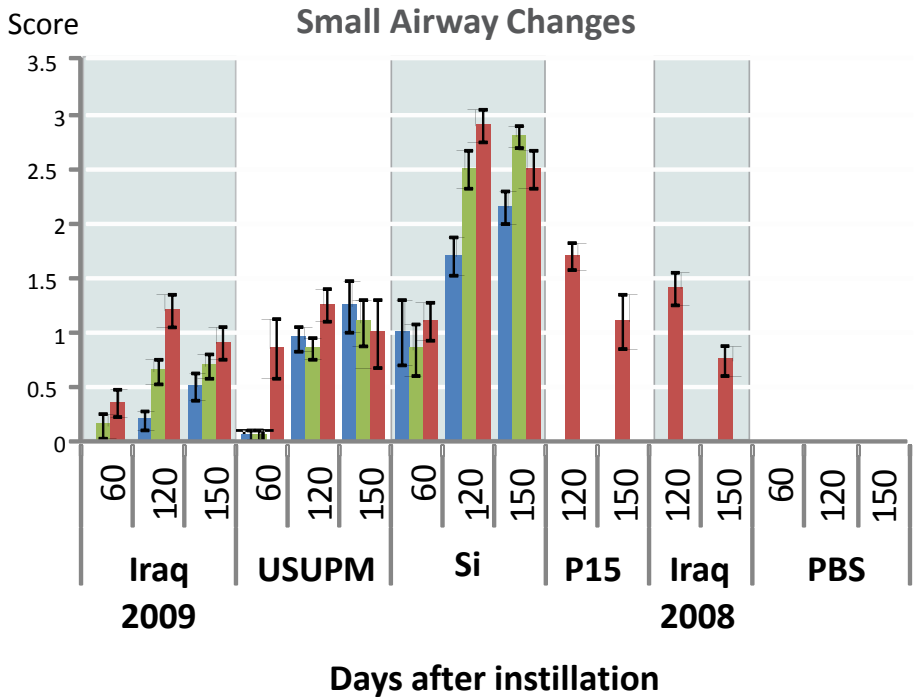
Alveolar epithelial hyperplasia

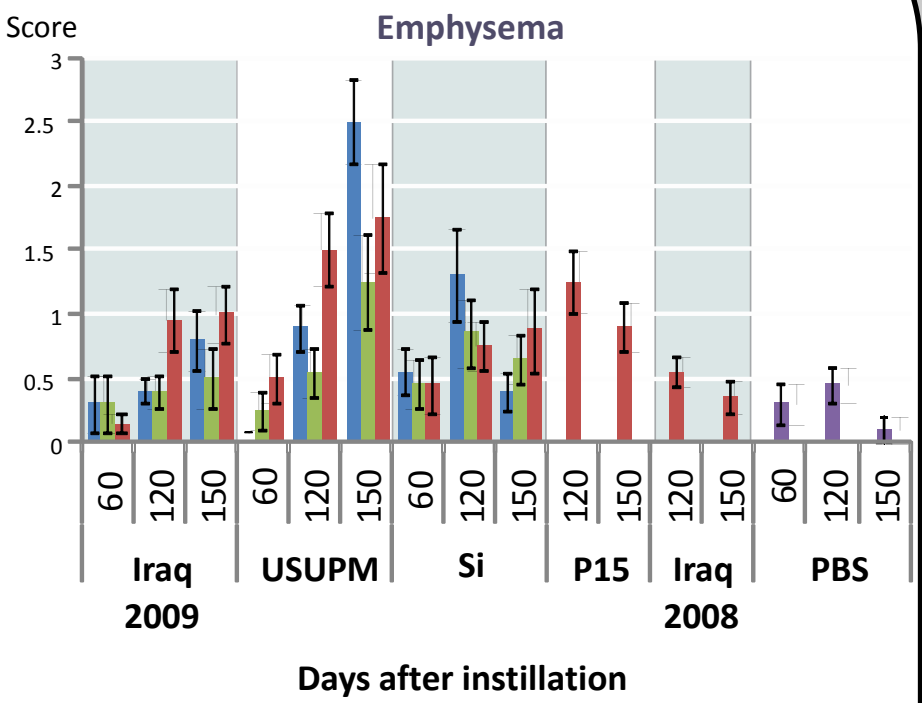
Pre-neoplastic changes





Small airways changes & emphysema





Low Medium High PBS

Intratracheal instillation

Camp Victory, Iraq

Silica: significant and persistent increases in inflammatory indicators
IR dusts: intense early inflammatory responses that fade but might lead to asthma or hypersensitivity pneumonitis on repeated exposure.

Silica: persistent increases in bronchiolar and alveolar hyperplasia.
IR dusts: early evidence of bronchiolar and alveolar hyperplasia which diminish.

All particles: inflammation, fibrotic, and destructive changes in the small airways , but they are most severe in the silica exposed animals.

IR dusts: mild emphysema at sites of dust deposition.
USUPM: more pronounced emphysematous changes than IR dusts.

No evidence of constrictive bronchiolitis in the medium-sized airways although some peribronchiolar inflammation and fibrosis was evident at high doses.

IR dusts are not intensely toxic but might cause asthma, hypersensitivity pneumonitis, and/or emphysematous changes with repeated exposures.

Wrap-up

Caveats:

PM from only two sites has been tested extensively.

Airborne materials were tested only in instillation experiments.

Data suggest that the toxicity of PM from different locations may differ.

Long term effects of continuous or repeated exposures have not been tested.

Future work:

Testing of aerosol PM from different sites.

Testing repeated exposures.

Long term effects of inhalational exposures.

Participants

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