How Do Inhaled Pollutants Exert Toxicity Outside the Lung?

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Learning Objectives

1) Brief history of inhalation toxicology.
2) Identify the critical moment in cardiopulmonary toxicology.
3) Learn what a successful research program looks like.
4) Risk and potential of engineered nanomaterials in human activities.
5) The significance of the microcirculation in all biological processes.
6) Developmental Origins of Health & Disease (DOHaD).
7) Why we do toxicological research.
### How Long Have Inhaled Pollutants Been a Health Hazard?

A) 80 years.
B) 153 years.
C) 1,000 years.
D) None of the above.

~1,000,000 YEARS!

### How Long Have We Been Aware of Such Health Hazards?

A) 80 years.
B) 153 years.
C) 1,000 years.
D) None of the above.

London, 1866

~153 YEARS

Donora, PA 1948
What Is the Major Health Hazard of Inhaling Pollutants?

A) Lung disease.
B) Brain disease.
C) Heart disease. \( \textcolor{red}{\text{Corrected}} \)
D) Kidney disease.

An Association between Air Pollution and Mortality in Six US Cities

1) Watertown, MA.
2) Harriman, TN.
3) St. Louis, MO.
4) Steubenville, OH.
5) Portage, WI.
6) Topeka, KS.

“Air pollution was positively associated with death from lung cancer and cardiopulmonary disease …”

How Do We Study Exposures to Inhalation Pollution?

Definitions

“As tedious as arguing about definitions is, it can’t hold a candle to arguing without definitions.”

David R. MacIver
(Mathematician)
**Xenobiotic Particles**

*XENOBOTIC: foreign to a living organism.*

*PARTICLE: piece or minute amount of something larger.*

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**Particulate Matter**

The US Environmental Protection Agency sets standards for six principal airborne pollutants:

1) Carbon Monoxide
2) Lead
3) Nitrogen Dioxide
4) Sulfur Dioxide
5) Ozone
6) *Particulate Matter (PM)*
Particle Size Distribution

Coarse Particles
PM_{10}

Fine Particles
PM_{2.5}

Ultrafine Particles
PM_{0.1}

HAIR
100 μm

POLLEN
50 μm

CELL
10 μm

RBC
5 μm

BACTERIA
1 μm

VIRUS
100 nm

MOLECULE
10 nm

“NANO”: 1,000,000,000 nm (10^{-9} nm) = 1 m

~8000 miles
**Engineered Nanomaterials (ENM) and Nanoparticles**

- Anthropogenic material with at least one dimension <100 nm.
- ENMs may be considered PM$_{0.1}$ … but PM is never considered an ENM.
- All Jacuzzis are hot tubs … but not all hot tubs are Jacuzzis!

**The Microcirculation**
All things are poison, and nothing is without poison; only the dose permits something not to be poisonous.

Paracelsus, 1567

Models of Cardiopulmonary Toxicity

Robertson & Miller. Particle & Fibre Toxicology 2018
Sprague Dawley Rats
1) 8‐12 weeks
2) virgin/pregnant/neonate/F1

Xenobiotic Particle Exposures
1) Nano: TiO2, CeO2, CNT, CB, QD
2) Pollutants: ROFA, 3DPE, MTM, combustion emissions, O3

Intravital Microscopy
1) Intraluminal Infusion
2) Microiontophoresis

Microvessel Isolation
1) Skeletal muscle
2) Heart, mesentery, uterus

Tissue Harvesting
1) Histology
2) "Omics" & Multiplex analyses

Methods & Techniques
Travis Goldsmith
Lung Burden = 38 μg

1) Focalized alveolitis
2) Nano-TiO₂ accumulation in macrophages
3) Macrophage interaction with alveolar wall
4) BAL—moderate responses in PMNLs, albumin, and macrophage activation

Nurkiewicz, et al. Particle & Fibre Toxicology 2008
Arteriolar Intraluminal Infusion—Dilation

Particle Size Influences the Intensity of Microvascular Dysfunction

Figure 5
Fine TiO₂ inhalation impairs systemic arteriolar dilation 24 hours after exposure in a dose-dependent manner. Sham/Control, n = 8; 90 μg, n = 8; 67 μg, n = 8; 36 μg, n = 8; 20 μg, n = 7; 8 μg, n = 12. Values are means ± SE. * P < 0.05 vs. all groups. † P < 0.05 vs. Sham/Control group. ‡ P < 0.05 vs. 8–36 μg groups. Adenosine (ADO).

Figure 6
Ultrafine TiO₂ inhalation impairs systemic arteriolar dilation 24 hours after exposure in a dose-dependent manner. Sham/Control, n = 8; 38 μg, n = 9; 19 μg, n = 11; 10 μg, n = 8; 6 μg, n = 7; 4 μg, n = 9. Values are means ± SE. * P < 0.05 vs. 19 μg group. † P < 0.05 vs. 10 μg group. ‡ P < 0.05 vs. 6 μg group. Adenosine (ADO).

Nurkiewicz, et al. Particle & Fibre Toxicology 2008
**Nano-TiO₂ Inhalation Elevates Plasma Inflammatory Markers**

*IL-1α*: activation, proliferation, inflammation, acute phase response

*ICAM-1*: leukocyte-endothelial cell interaction, transduction

*IL-13*: inhibits macrophage inflammatory cytokine production


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**Venular Leukocyte Adhesion and Rolling**

50.0 μm
Nano-TiO₂ Inhalation Increases Microvascular Reactive Species

LeBlanc, et al. Cardiovascular Toxicology 2010

What Is the Consequence of Gestational Uterine Under-Perfusion?

**Microvascular Effects of Gestational Nanomaterial Inhalation**

(40±2 μg/day; 8 days; cumulative lung burden=178±29 μg)

**Isolated Radial Arterioles**

**Intravital Microscopy**

* *, P<0.05 vs Sham/Control

**Fetal Consequence: Developmental Origins of Health and Disease**


Stapleton, et al. Reprod. Toxicol. 2018

Maternal Exposure

**Mechanism of Toxicity?**

*Kisspeptin Colocalization in the Placental Microcirculation*

Lizzie Bowdridge, PhD


**Maternal Nano-TiO₂ Inhalation Augments Uterine Artery Kisspeptin Reactivity**

10 mg/m³, 5 hr/d, 8 d, 30 mg/d lung burden, 240 mg cumulative burden

**Isolated Placenta: Vascular Function**

Alaeddin Abukabda, PhD


**Maternal Nano-TiO₂ Inhalation Impairs Placental Resistance and Structure**

10 mg/m³, 5 hr/d, 8 d, 30 μg/d lung burden, 240 μg cumulative burden

Summary of Nurk Lab Toxicological Research

**GOAL:** Identify xenobiotic particle characteristics, conditions of exposure, and mechanisms of interactions with host tissues that minimize risk of adverse health effects.

**BENEFITS:**
1) Toxicant identification
2) Exposure prevention, amelioration
3) Exposure limits
4) Safe nanomaterial identification
5) Drug discovery
6) Biomedical devices
7) *Improved Human Health and Safety*