Ultrafine Particles and Nervous System Effects: What can toxicological evidence tell us? Insights from the 2019 Integrated Science Assessment for Particulate Matter

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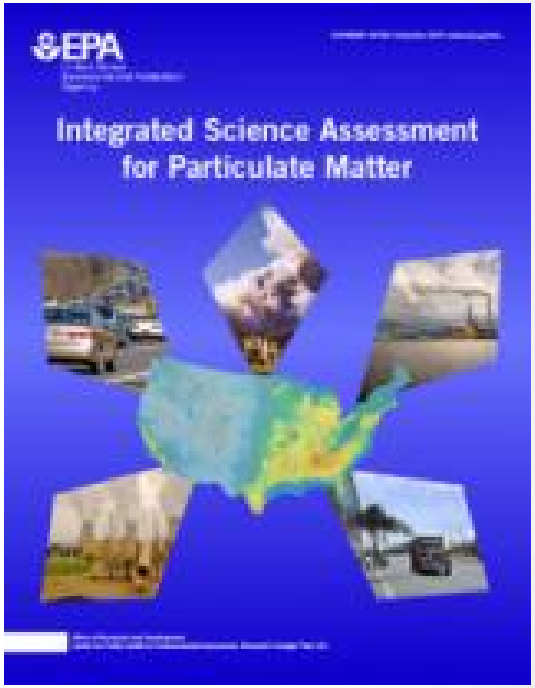
Disclaimer: *This presentation is based on information provided in the 2019 Integrated Science Assessment for Particulate Matter.*



Abbreviations:

Integrated Science Assessment: ISA

Particulate Matter: PM

Ultrafine Particles: UFPs

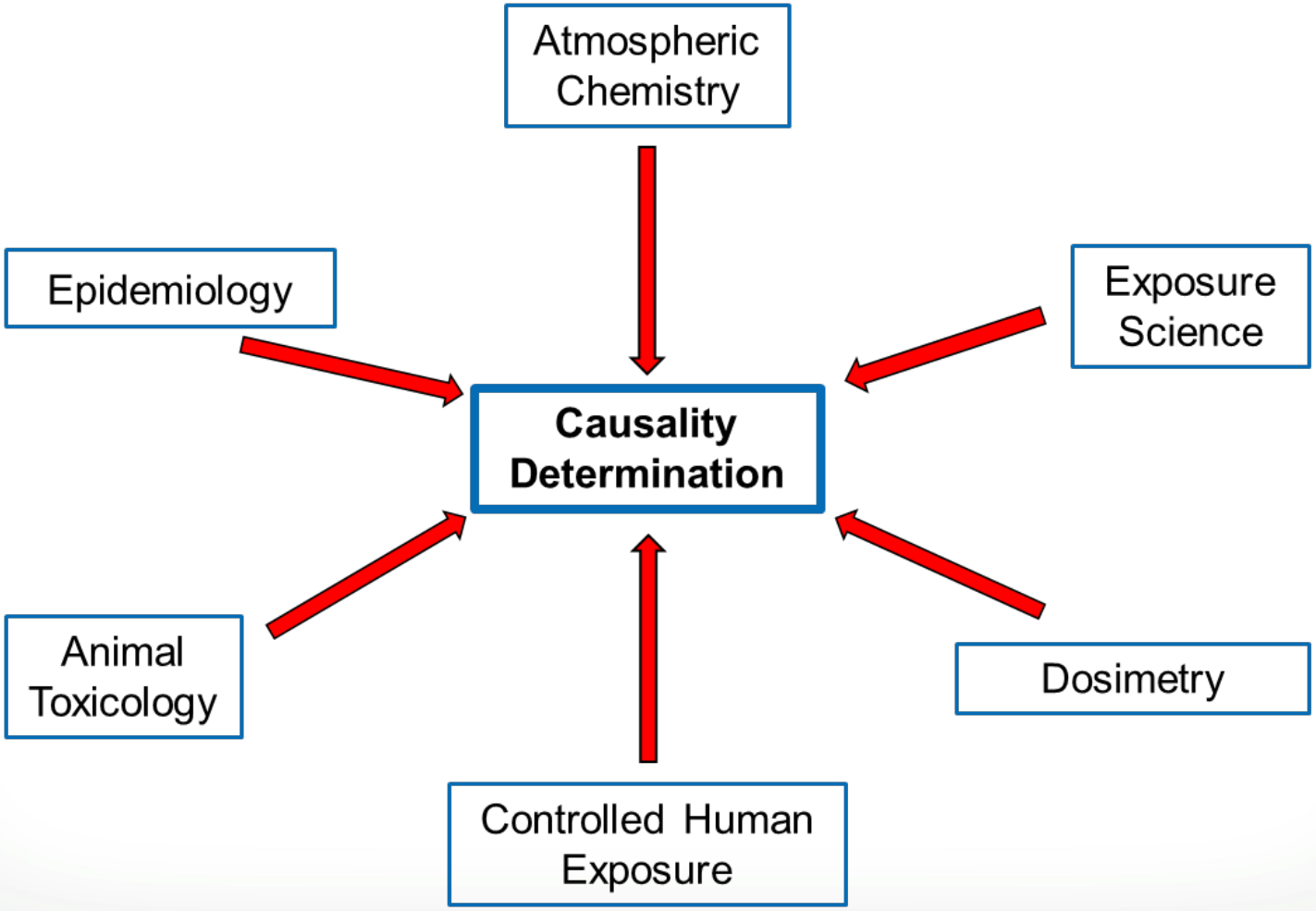
Outline

- Goals
  - Purpose and scope of 2019 PM ISA
  - UFP exposure and nervous system effects
    - Key findings
    - Limitations of evidence
  - Thoughts about advancing the field

2019 PM ISA

- **Purpose: Assess causality and inform hazard identification**
  - Organize relevant literature for broad health outcome categories
  - Evaluate studies, characterize results, extract relevant data
  - Integrate evidence across disciplines for health outcome categories
  - Develop causality determinations using established framework
  - Evaluate evidence for populations potentially at increased risk
- **Evidence spanning many scientific disciplines from source to effect is considered.**

2019 PM ISA


Atmospheric Chemistry
Epidemiology
Exposure Science
Causality Determination
Animal Toxicology
Dosimetry
Controlled Human Exposure

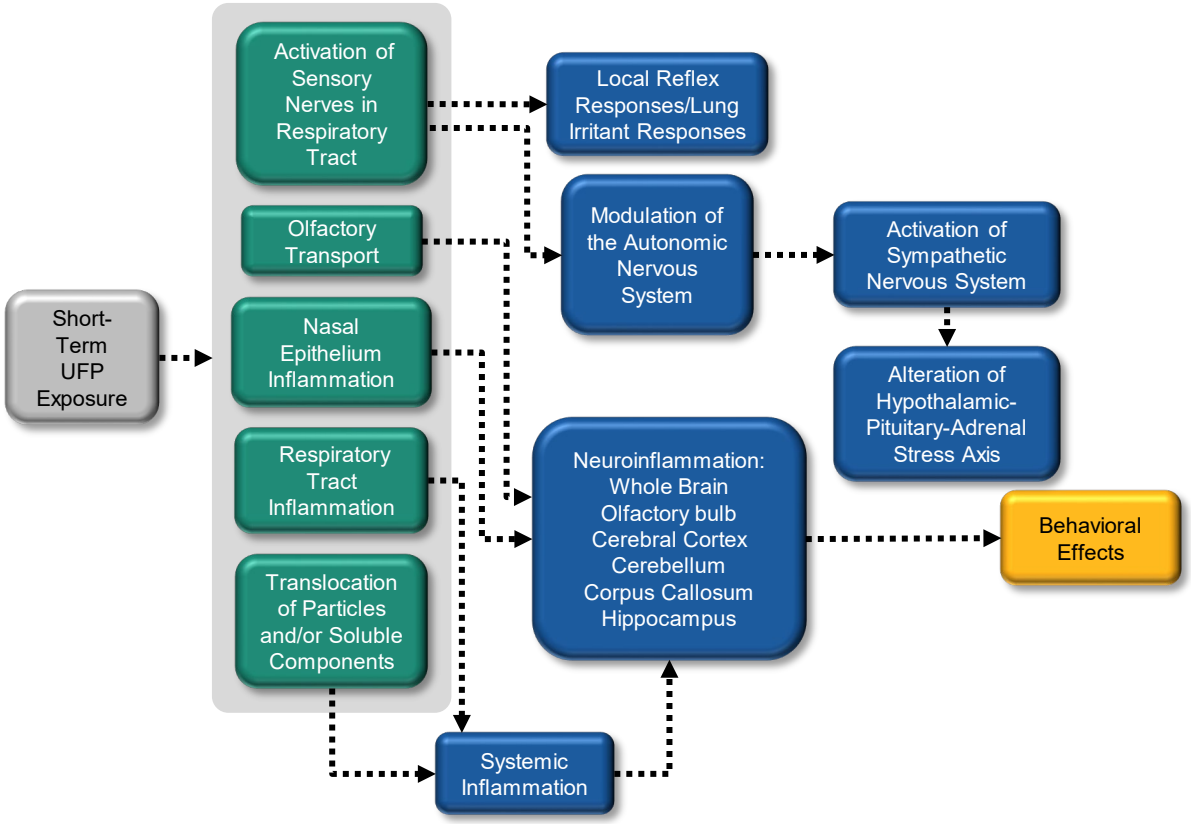
2019 PM ISA

- **Scope: Is there an independent effect of PM on health at relevant ambient concentrations?**
  - **Inclusion criteria for epidemiologic and experimental (i.e., controlled human exposure and animal toxicological) studies:**
    - PM exposures relevant to ambient concentrations (< 2 mg/m^3; ~1 to 2 orders of magnitude above ambient concentrations).
    - A composite measure of PM (e.g., $PM_{2.5}$ mass, $PM_{10-2.5}$ mass, UFP mass or number).
    - An approach to disentangle the effect of the particle from the mixture in the case of source-based exposures (e.g., use of a particle trap for diesel exhaust exposure).

Key Findings: Short Term Exposure

- **Epidemiologic Study**
  - Behavioral effects in older adults
- **Animal Toxicological Studies**
  - Brain inflammation and oxidative stress
  - Neuroendocrine stress response
  - Behavioral effects
- **Causality Determination**
  - **Suggestive** of, but not sufficient to infer, causality
  - Biological plausibility was part of weight of evidence approach

2019 PM ISA: Potential Biological Pathways – Short Term Exposure

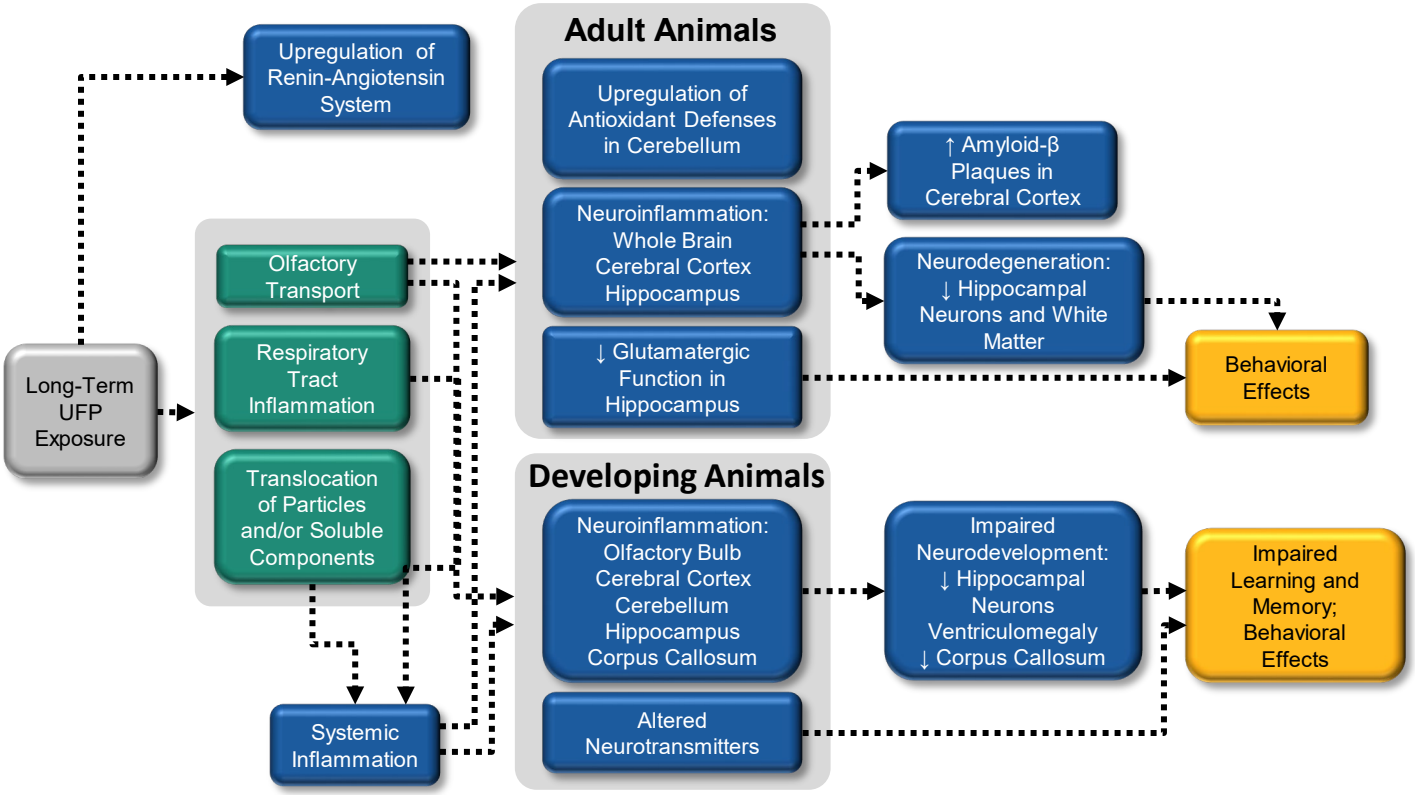


The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Key Findings: Long Term Exposure

- **Epidemiologic Study**
  - Neurodevelopmental effects in children
- **Animal Toxicological Studies**
  - Adult animals
    - Brain inflammation and oxidative stress
    - Changes in neurotransmitter function
    - Morphological changes including neurodegeneration
    - Behavioral effects
  - Young animals – perinatal exposure
    - Brain inflammation and oxidative stress
    - Changes in neurotransmitter levels
    - Morphological changes including ventriculomegaly
    - Cognitive and behavioral effects
- **Causality Determination**
    - **Suggestive** of, but not sufficient to infer, causality
    - Biological plausibility was part of weight of evidence approach

2019 PM ISA: Potential Biological Pathways – Long Term Exposure



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Limitations of Evidence

- **Epidemiology**
  - Small number of studies
  - Uncertainty with respect to the spatial and temporal variability in UFP concentrations
  - Possible exposure measurement error

- **Experimental**
  - Questions regarding the relevance of experimental UFP exposures to ambient exposures
  - Limited understanding of mechanisms by which inhaled UFPs affect the brain
  - Questions regarding the relevance of rodent models for human nervous system effects

Relevance of UFP Exposures

- **Are experimental UFP exposures relevant to ambient exposures?**
  - UFPs are often defined as <100 nm in diameter.
  - Different methods and particle sizes were used to assess the UFP-health effects relationship:
    - **Particle concentrators**:
      - Toronto group (< 300 nm)
      - Rochester group (≤ 100 nm)
    - **Re-aerosolized particles that were collected on filters**
      - Los Angeles group (< 200 nm)
    - **Motor vehicle exhaust passed through a denuder**
      - New Mexico group (< 150 nm)

Relevance of UFP Exposures

- **UFP or $PM_{2.5}$: Should experimental studies of the larger particles (200-300 nm) be evaluated as part of the $PM_{2.5}$ evidence rather than as part of the UFP evidence?**

- **Are the exposures in the experimental and epidemiological studies comparable?**
  - **Experimental**
    - Particle size distribution: 100-300 nm
    - Exposure metrics: mass and particle number concentration (PNC)
  - **Epidemiology**
    - Particle size distribution: 10-700 nm in one study, not specified in other
    - Exposure metric: PNC
    - PNC mainly represents particles with diameters ≤ 100 nm

Mechanisms

What are the mechanistic pathways by which inhaled UFPs impact the nervous system?

- **Direct**: Must solid particle UFPs or their soluble components reach the brain for neurotoxicity to occur?
  - Translocation of insoluble particles from the respiratory tract is dependent on particle size, with UFPs < 200 nm in diameter easily crossing barriers.
  - **Nose to Brain pathway-**
    - UFPs translocate from olfactory epithelium to the brain via the olfactory nerve or from the respiratory tract to the brain via other sensory nerves
  - **Lung to Brain pathway-**
    - Particle translocation from the respiratory tract to the circulation
    - Trafficking of phagocytized particles to the brain via immune cells
  - **Gut to Brain Pathway-**
    - Clearance of UFP from the respiratory tract to the gut followed by translocation to the circulation

Mechanisms

- **Indirect**: Do UFPs that deposit in the respiratory tract exert neurotoxic effects by other mechanisms?
  - Respiratory tract inflammation leading to systemic inflammation
  - Paracrine effects due to nasal or olfactory epithelial inflammation
  - A neuroendocrine stress response

Mechanisms

- **2019 PM ISA points to several potential biological pathways**
  - **Direct Pathways**
    - Olfactory transport – neuroinflammation **(Nose to Brain)**
    - Translocation of particles or soluble components from respiratory tract to systemic circulation **(Lung to Brain)**
  - **Indirect Pathways**
    - Respiratory tract inflammation – systemic inflammation – neuroinflammation
    - Nasal epithelial inflammation – neuroinflammation (paracrine effect)
    - Activation of sensory nerves – activation of the hypothalamic-pituitary-adrenal stress axis (neuroendocrine stress response)

Relevance of Rodent Models

- **How relevant are the rodent models for understanding human nervous system effects?**
  - **Adult rodent models**
    - Young and middle aged adult mice and rats
    - Allergic mice
    - ApoE deficient mice
    - Alzheimer disease mouse model (EFAD mice carrying transgenes for human APOE and five familial AD mutations)
  - **Neonatal mouse model**
    - Pups exposed by inhalation
    - Developmentally equivalent to a third trimester human fetus – rapid neuro- and gliogenesis
  - **Gestational exposures in mice**
    - Dams exposed by inhalation

Relevance of Rodent Models

- **Rodent models provide consistent evidence of nervous system effects in response to UFP exposure, but:**
  - **Are there sufficient similarities between the nervous systems of rodents and humans to warrant concordance?**
    - Alzheimer's disease pathogenesis - older animals
    - Neurodevelopment - young animals
  - **Does postnatal exposure in neonatal mouse pups sufficiently mimic gestational exposure of humans**
    - Pups, rather than the dam, are exposed by inhalation in this model.
  - **Are there differences in respiratory tract anatomy between rodents and humans in terms of the amount and proportion of olfactory epithelium?**
    - The amount of UFP depositing on olfactory epithelium and thus available for olfactory transport could be dramatically different between the species.

Summary – What can the toxicological evidence tell us?

- **How relevant are the experimental UFP exposures to ambient exposures?**
  - The exposures are relevant to ambient exposures.
  - But differences in UFP particle size distributions and exposure metrics between experimental and epidemiologic studies complicate the interpretation of evidence across disciplines.

- **How do inhaled particles affect the brain?**
  - Animal toxicological studies provide evidence of biologically plausible pathways that underlie the nervous system effects resulting from UFP exposure.
  - But there is uncertainty about whether UFPs translocate to the brain to exert their effects or whether they exert their effects indirectly.

Summary – What can the toxicological evidence tell us?

- **How relevant are the rodent models for understanding human nervous system effects?**
  - Rodent models need to be evaluated for concordance with humans in terms of neurodegeneration and neurodevelopment.
  - Studies of neurodevelopment should take into account that UFP exposures may result in effects on both the dam and the developing animal and that these effects may occur through direct and/or indirect mechanisms.

Further Considerations

- **What may help to advance the evaluation of health effects due to UFP exposure?**
  - Consistency in exposure metrics and UFP particle sizes both within and between epidemiologic and toxicological studies
  - Reconsidering the definition of UFP to take into account the ability of <200 nm particles to translocate across biological barriers
  - Better characterization of population exposure to UFP

Supplemental Slides

- **Mechanistic Evidence**

Mechanisms

- **Direct Pathways**
  - Translocation of < 200 nm inhaled nanoparticles from olfactory epithelium to olfactory bulb occurs in rodents (Elder 2006, Oberdoerster 2004), but it is not known whether the nanoparticles diffuse throughout the brain or result in neurotoxicity.
  - Combustion-derived nanoparticles are found human in brain tissue (Maher 2016) and in human heart tissue (Calderon-Garciduenas, 2019). This suggests that translocation of ambient UFPs may occur via the circulation to reach distal organs.
  - Inhaled gold nanoparticles translocate from the respiratory tract into the circulation of humans and some particles localize in atherosclerotic vascular tissue (Miller 2017).
    - *For this study, it was estimated that 0.05% of the 3.8 nm particles that deposited in the alveolar region were excreted in the urine. This is consistent with what has been observed in rats. Total translocation from the human lung is unknown.*

Mechanisms

- **Indirect Pathways:**
  - Evidence from studies relevant to air pollution exposures, but outside the scope of the 2019 PM ISA, suggests that circulating factors may transmit a signal from the respiratory tract to the brain, leading to blood brain barrier disruption and neuroinflammation.
    - Blood brain barrier disruption, neuroinflammation, and a possible role for serum thrombospondin-1 was shown in mice exposed acutely to multiwalled carbon nanotubes by oropharyngeal aspiration (Aragon 2017).
    - Prolonged microglial activation was shown a study of rats acutely exposed to ozone, suggesting a role for microglial priming in neurodegeneration (Mumaw 2016).
    - Exposure to fine particle pollution was associated with increased circulating endothelial-derived microparticles in humans (Pope 2016).

References

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- **Oberdoerster et al.,** Inhal Toxicol 16: 437-445, 2004
- **Pope et al.,** Circ Res. 119: 1204-1214, 2016