"Diesel Exhaust Research: What Has It Told Us About Ambient Organic PM Toxicity"

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Rationale for studying diesel emissions

1) PM source and linkage to PM-associated health effects

2) Diesel health effects- uncertainties lung cancer, cardiopulmonary, allergy/ asthma, other effects (in utero, reproductive)

3) Susceptible/sensitive populations (eg, school bus issues, genetic polymorphisms)

4) Changes in diesel emissions (PM and gases) and types: Does this affect human health & how (better, worse, no change)?

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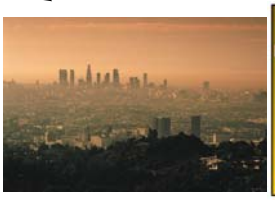
Rationale: PM source and linkage to PM-associated health effects

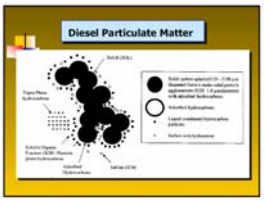
Off road

On road

Diesel exhaust from buses, trucks, and trains is a sensitive concern in East L.A.

Fine PM
How Close?





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Diesel Fuel Consumption Trends

United States

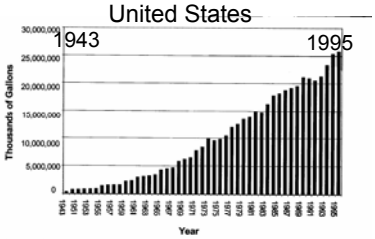
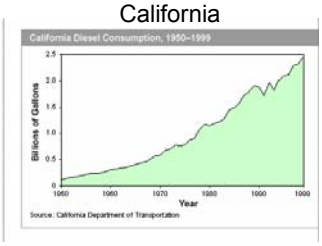
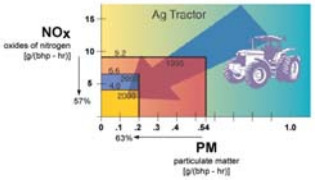


Figure 2-17. On-highway diesel fuel consumption since 1943, values in thousands of gallons.

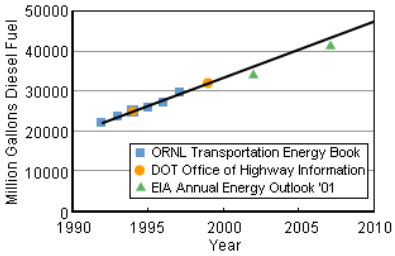
Source: Federal Highway Administration, 1995.

California





Future Predictions



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Rationale: **Diesel exhaust Associated Health Effects**

- Diesel & lung cancer:
  "likely" (EPA), "probable" (IARC)

  [Fine PM & lung cancer association; ACS Cancer Prevention StudyII (Pope et al, 2002)]
- Pulmonary :
  Inflammation [Similar to PM]
  Airways Resistance [? With PM]
- Cardiac:
  ? with Diesel; [PM: HRV, Repolarization]

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Rationale: Diesel Exhaust Associated Health Effects, cont'd

- Vascular:
  - ↓response to vasodilators [? PM]
  - ?clotting factors
- Allergy/ asthma:
  - ↑IgE responses with some diesel PM [similar with ETS]
- Lung Infections:
  - in vitro and rodent models show increased viral & bacterial infections (via multiple mechansims)
  - [PM epi ↑ hospitalizations for lung infections]
- Other effects (in utero, reproductive)
  [PM epi association atrial septal defects]
- Symptoms (unpleasant odor, headache, nausea, dizziness, eye/nose/throat irritation)

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Tale of 2 particles: IgE response:

Particle 1 ("High" methylene chloride extractable organic content):

-Increased IgE in asthmatics & nonasthmatics with nasal instillation

-[monocytic increase in rodent lung]

Particle 2 ("Low" methylene chloride extractable organic content):

-IgE levels not altered in asthmatics & nonasthmatics

-[neutrophilia in rodent lung]

Diaz-Sanchez et al, 1994; Kongerud et al, 2006; Singh et al, 2004

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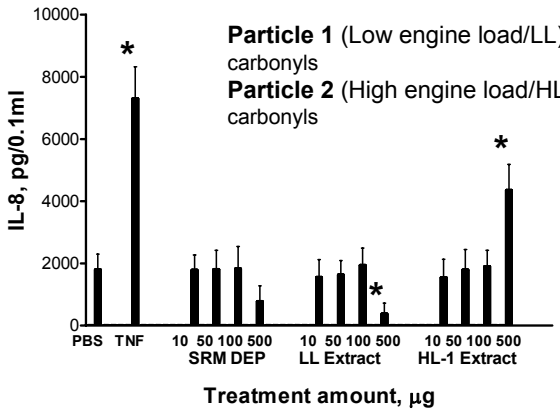
Tale of 2 particles: Cytokine responses

[In vitro airway epithelial cells]



Particle 1 (Low engine load/LL): 1º C2-C4 carbonyls

Particle 2 (High engine load/HL): 1º C6-C9 carbonyls

LL= ~0% engine load
HL=~75% engine load
Madden et al 2003

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Rationale: Susceptible/sensitive populations

- Certain human polymorphisms associated with response to diesel exhaust particles
  GST P1 wildtype & M null → greater induction of IgE and allergy mediators (DEP & ragweed allergen challenge)
- Other polymorphisms, ages, behaviors, diets

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Susceptible Populations

Polymorphisms:

Allergic (ragweed) subjects

Nasally challenged with allergen, or DEP & allergen

GSTM1 null GSTP1 wild genotype- ↑responses to DEP+allergen vs allergen

DEP+allergen/allergen ratio

	GSTM1 null	GSTM1
IgE	15.4	5.6
histamine	5.8	3.5

Gilliland et al, 2003

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Susceptible Populations, cont'd

- Diesel exposures: Asthmatics?
  - No Δ from nonasthmatics, but high variability (lung endpoints) (Salvi et al, 1999; Stenfors et al, 2004)
- PM: Elderly

  Asthmatics

  Metabolic syndrome/diabetics

  Obeseity (BMI)

  COPD

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Rationale: Changes in diesel emissions

Traps, filters, oxidative catalysts, low S fuels, fuel additives, etc

Particle Traps with Emission Differences:

decreased PM, some gases (eg, acrolein, benzene)
increased 1,3-butadiene, di-n-butylphthalate

- Ullman et al, 2003

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Biodiesel Mutagenicity

Table 6. Mutagenic potency values for test fuels - cold start conditions.

Test Fuel	UC Davis Sample ID	CSM Run #	TA98 Mutagenic Potency (Rev/µg Eq)* (+S9)	(-S9)
Petroleum D 2	CbioD.5	4517	0.84**	1.32**
Soy S M E	CbioD.9	4524	1.23	1.28
Canola C M E	CbioD.13	4532	2.53**	2.82**
Pork Lard P L M E	CbioD.17	4539	2.23	1.69
Beef Tallow B T M E (edible)	CbioD.21	4569	2.17	2.01
Yellow Grease Y G M E (LFFA)	CbioD.25	4585	2.69	2.04

* Data for each fuel represents TA98 revertants per microgram equivalent from a single cold start; +S9 = bioassay with metabolic enzymes, -S9 = bioassay without metabolic enzymes.
**Data is the average result from two independent bioassay experiments.

Kado et al 2003

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What are the responsible components?

PAHs and PAH-like compounds:

-Phenanthrene induced increase in IgE formation in vitro B-lymphocyte cell line (Tsien et al., 1997)

-Association of PAHs with cancer risk

Carbonyls:

-Modulate prostaglandin production (immune effects, inflammation)

-Effects on DNA structure (cross links) & repair (inhibit enzyme activitiy)

-Odor, irritants

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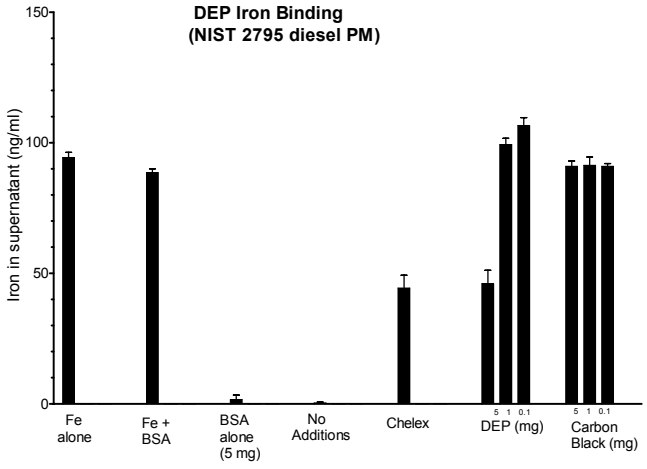
What are the responsible components? Cont'd

Interaction of transition metals with diesel particles (cell free system)



Madden & Ghio, unpub.

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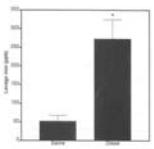
What are the responsible components?

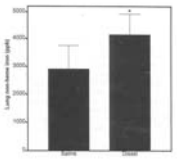
Interaction of transition metals with diesel particles

Lavage Iron, ppb

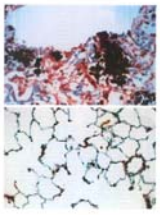


Saline DEP

Lung non-heme iron, ppb



Saline DEP



Ferritin in rat lung tissue

Ghio et al, 2000

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Components- human exposures filtered diesel exhaust

Particle Trap (~50% ↓PM): No Δ lung endpoints (lavage)

Combinations of PM filters and activated charcoal filters:

- PM+charcoal filters tended to better alleviate symptoms (irritation, odor, headache) than PM filter alone
- PM filters alone tended to decrease mutagenicity (Ames/4 tester strains) as well as, or better, than the combo PM+charcoal [gas phase inhibitor mutagenesis?]

Further studies using this PM vs Gas components approach warranted with newer technologies, newer biological responses

Rudell et al, 1999a & 1999b

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Needs & approaches

1. Availability of Material for Biological Testing
2. How do we test: PM, PM extracts, impingers, freshly generated only?
3. Exposure biomarkers with susceptible biomarkers
4. With & Without approach:
   -controlled exposures with scrubbing selected components
   -field studies where changes will occur (eg, Utah Valley, Dublin Ireland, mines)

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Approaches: Boldly go…

vs

where no one else has

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