An Update on the
HEALTH EFFECTS OF DIESEL EMISSIONS

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Because you never breathe only one Pollutant!!

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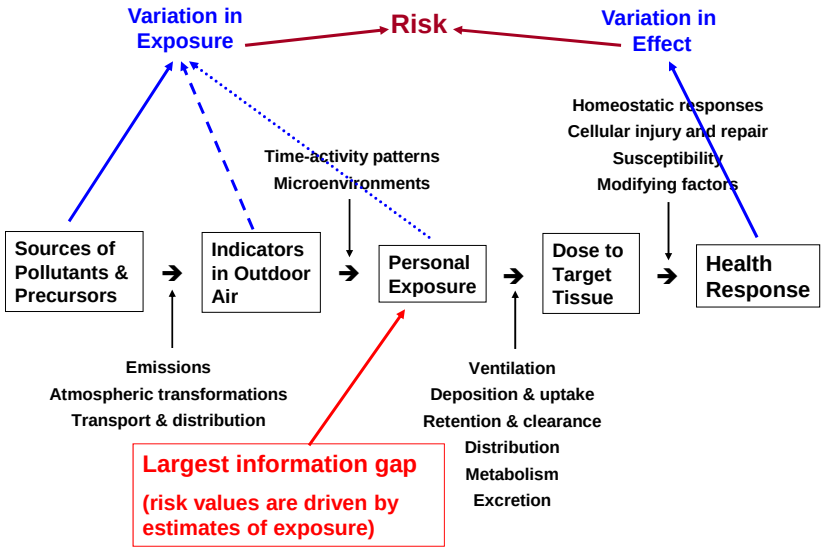
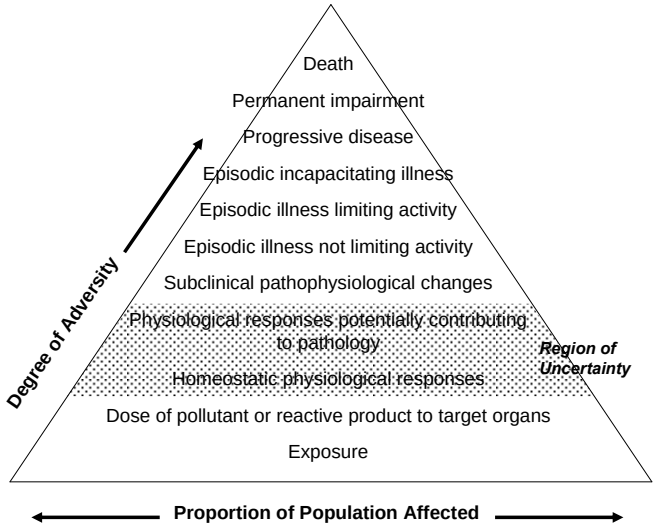
LONGSTANDING INTEREST IN THE HEALTH EFFECTS OF DIESEL EMISSIONS

- **Potential cancer hazard demonstrated in 1950s**
- **Occupational epidemiology from 1980s to present suggest cancer and non-cancer risks**
- **Animal studies from 1980s to present demonstrate effects of extreme exposures**
- **Experimental exposures cause a diverse range of non-cancer effects in humans and animals**
- **Very little information on impacts of mine-specific exposures**

EPIDEMIOLOGICAL EVIDENCE OF RISK



DEFINING AN "ADVERSE" EFFECT IS NOT ALWAYS EASY

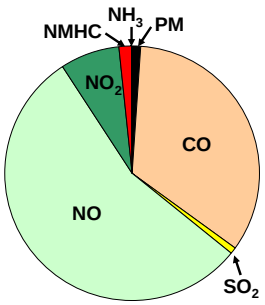


In health chapter of NARSTO review of multipollutant air quality management – in review

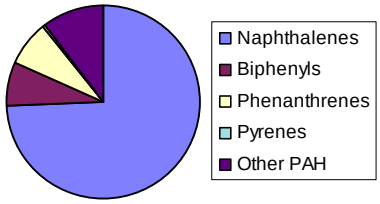
PERSPECTIVES ON DIESEL EXHAUST COMPOSITION

Fresh exhaust from 2000 Cummins 5.9L ISB turbo on HD FTP burning pre-2007 U.S. certification fuel (300 ppm S, 30% aromatics)

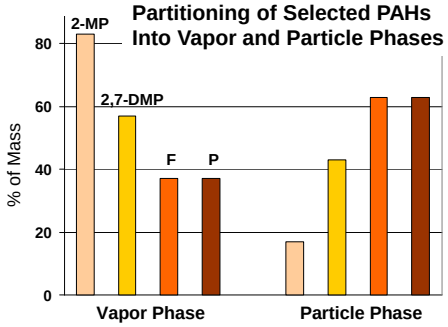
Distribution of Mass (less CO_2, CH_4, and H_2O)



Distribution of Polycyclic Aromatic Hydrocarbons (PAHs)



Partitioning of Selected PAHs Into Vapor and Particle Phases



McDonald et al. *Environ. Sci. Technol.* 38: 2513-2522, 2004

EFFECTS HAVE BEEN ASSOCIATED STATISTICALLY WITH OCCUPATIONS HAVING PRESUMED HIGH EXPOSURES TO ENGINE EMISSIONS

Populations

- Railroad workers
- Truck drivers
- Miners

Outcomes

- Lung cancer
- Bladder cancer
- Cardiovascular mortality
- Respiratory mortality

None of the studies:

- Measured actual exposure
- Could confirm that engine exhaust caused the effects

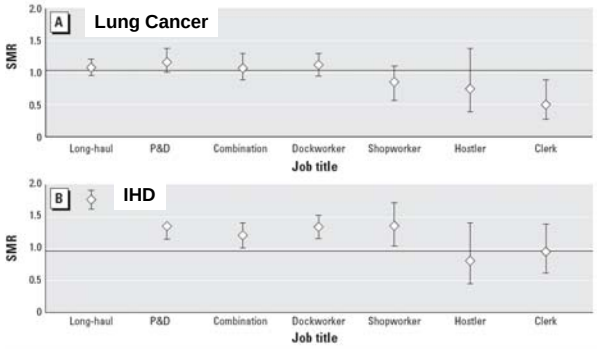
MOST RECENT STUDY OF TRUCK DRIVERS

Laden et al., *Environ. Health Perspect.* 115:1192-1196, 2007

- 54,319 male union drivers, 1 or more years on job during 1985-2000
  - Long-haul, pickup & delivery, and dock workers
- Standardized mortality ratio (SMR) for lung cancer and ischemic heart disease (IHD) mortality compared to U.S. general population

Results:

Significantly increased risk for IHD, but only slight increase for lung cancer



FOLLOW-UP ANALYSIS OF TRUCK DRIVER STUDY

Garshick et al. *Environ. Health Perspect.* 116: 1327-1332, 2008

- 31,135 male drivers <u>over 40 yr old</u>, 1985-2000
- Cumulative years worked in job vs. lung cancer
- Hazard ratio standardized to <u>20 yrs</u> on job
- Adjusted for industry data on smoking & region

Results:

- Hazard Ratio for 20 yrs on job *(95% CI)*

Long-haul	1.40 (0.88-2.04)
Pickup & delivery	2.21 (1.38-3.52)
Dock workers	2.02 (1.23-3.33)
Combination	2.34 (1.42-3.83)

- Interpreted as association with "vehicle exhaust" *(not just diesel)*

ONGOING STUDY OF DIESEL-EXPOSED MINERS

www.dceg.cancer.gov/oeeb/research/industrialchemicals
www.cdc.gov/niosh/nas/mining/researchproject68

- **NCI - NIOSH retrospective cohort mortality study with nested case-control study of lung cancer *(also non-cancer mortality)***
- **12,000 miners employed at least 1 yr in 8 dieselized non-metal mines**
  Limestone, potash, salt, trona
- **Measured EC, PM, gases, & PAHs in representative locations**
- **Data through 1997**

Results have not been released

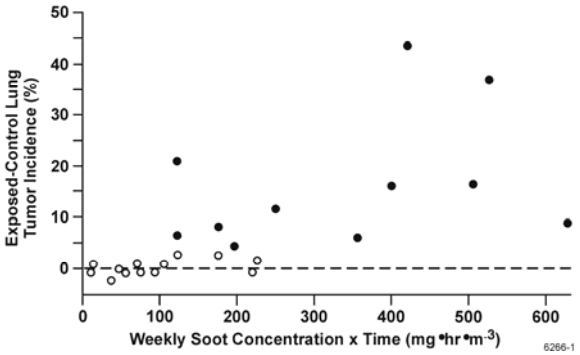
- **Legal challenge of experimental design**
- **Court order for review of pre-publication results**
  - **U.S. congressional committee**
  - **United Steel Workers Union**
  - **Methane Awareness Research Group**

LUNG TUMORS IN DIESEL-EXPOSED RATS

Mauderly, in: *Environmental Toxicants*, M. Lippmann, Ed., Wiley, New York, 2000, pp. 193-241.

- **Rats exposed 6+ hr/day, 5-7 days/wk for 24-30 mo**
- **Exhaust from medium & light-duty engines on simulated urban cycles**
- **Papers published 1986-2005**

Results from 9 studies in 5 countries:



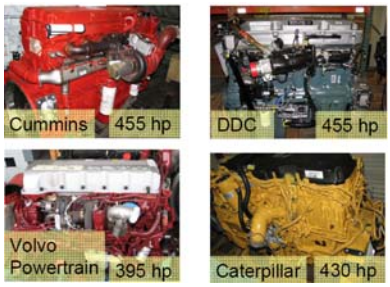
- **Threshold at ~2,500 μg DPM/m³ equivalent 40 hr/week exposure***
- **Exposures were not carcinogenic in mice or hamsters**
- **Rat response to particle loading differs from that of humans**

***Threshold demonstrated by meta-analysis**
Valberg & Crouch *Environ. Health Perspect.* 107: 693-699, 1999

NEW STUDY OF EXHAUST FROM HD ON-ROAD DIESEL ENGINES MEETING 2007 STANDARDS

Advanced Collaborative Emissions Study (ACES)

- **Tested exhaust from 4 engines**
- **Selected 1 engine for study**
- **Expose rats for 30 mo**
  - **16 hr/day, 5 days/wk *(3 dilutions TBD)***
  - **Engines on road use duty cycle**
- **Evaluate lung tumors and other effects**
  - **Lifetime cancer study in rats**
  - **Interim evaluations of non-cancer effects**



- **The engines all met standards and had very similar emissions**
- **The test engine is now operating at LRRI *(identity confidential)***
- **Animal study will begin in February**

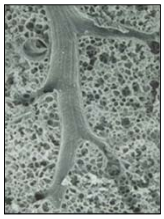
Health Effects Institute (www.healtheffects.org)

EVIDENCE FOR NON-CANCER EFFECTS IN HUMANS

- **Work-shift changes in lung function and respiratory symptoms**
- **Epidemiological evidence of increased risk for cardiovascular mortality and respiratory disease**
- **Experimental short-term exposures to emissions**
- **Experimental exposures to diesel PM**
- **Associations with proximity to traffic**

LUNG INFLAMMATION IN NORMALS AND ASTHMATICS

Sandström et al., Sweden, several papers



- Whole or filtered exhaust from idling vehicles
  - Exposed 1-2 hr – some with exercise
- Measured:
  - Inflammation by bronchoalveolar lavage and biopsy
  - Lung function
  - Airway reactivity

Results:

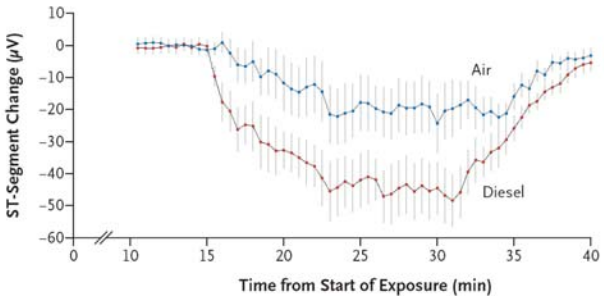
- 1 hr exposure of normals at 300 μg PM/m^3 ↑ inflammation
  - Removal of particles by filtration did not reduce the effect
- 1 hr exposure of asthmatics at 300 μg PM/m^3 ↑ airway reactivity
- 2 hr exposure at 100 μg PM/m^3 ↑ airway resistance and inflammation in normals and asthmatics
  - The increase in inflammation was less in asthmatics

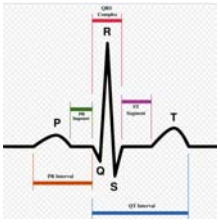
ISCHEMIC CHANGES IN ECG OF MEN WITH PRIOR MYOCARDIAL INFARCTIONS

Mills et al., *N. Engl. J. Med* 357:1075-1082, 2007

- Exposed 20, 60 yr old men for 1 hr to exhaust at 300 μg PM/m^3
  - Idling 4.5L Volvo TD45B 6 cyl. turbo engine on 500 ppm sulfur fuel
  - Intermittent moderate bicycle exercise
- Monitored ECG during exposure

Result: Exercise-related depression of ST segment was greater during exhaust exposure





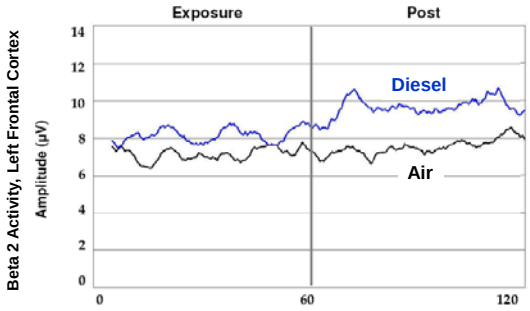
CHANGES IN BRAIN ACTIVITY

Crüts et al. *Part. Fibre Toxicol.* 5:4, 2008

- Exposed 10 subjects for 1 hr to exhaust at 300 μg PM/m^3
  - Idling 4.5L Volvo TD45B 6 cyl. turbo engine on 500 ppm sulfur fuel
- Monitored brain activity (EEG) during and 1 hr after exposure

Result: ↑ median power frequency of EEG in frontal cortex

- **Significant by 30 min, increased through 1 hr after exposure**
- **Interpreted as a "cortical stress" response**



Increased beta2 activity has been associated with several neurological and psychopathological disorders (e.g., headache, post-traumatic stress, burnout).

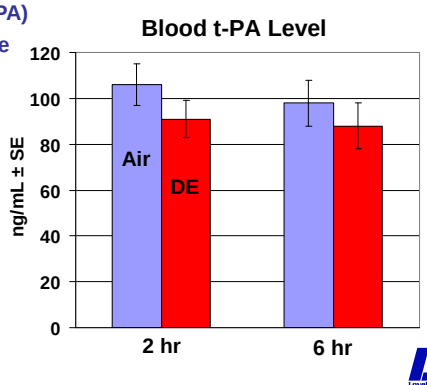
IMPAIRED "ENDOGENOUS FIBRINOLYSIS"

Mills et al., *Circulation* 112: 3930-3936, 2005

- Exposed 15 healthy men for 1 hr to exhaust at 300 μg PM/m^3
  - Idling 4.5L Volvo TD45B 6 cyl. turbo engine on 500 ppm sulfur fuel
  - Moderate exercise
- Measured 2-6 hr after exposure
  - Tissue plasminogen activator (t-PA)
  - Forearm blood flow and response to vasodilators

Results:

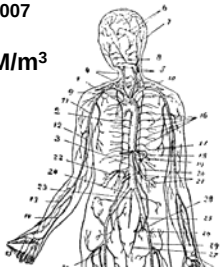
- **Reduced t-PA**
- **Reduced response to 3 of 4 vasodilators**



REDUCED RESPONSE TO VASODILATORS AT 24 HR

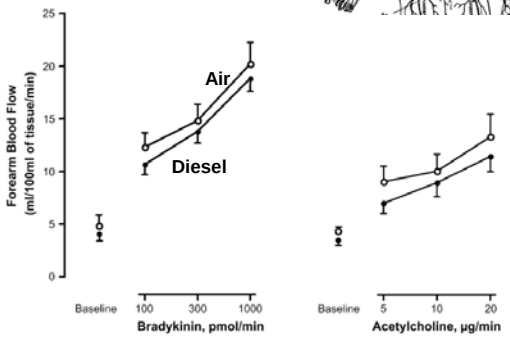
Törnqvist et al., *Am. J. Resp. Crit. Care Med.* 176:395-400, 2007

- Exposed 15 healthy men for 1 hr to exhaust at 300 μg PM/m^3
  - Idling 4.5L Volvo TD45B 6 cyl. turbo engine on 500 ppm sulfur fuel
- Measured blood and peripheral vascular variables
  - Blood markers of inflammation
  - Forearm blood flow and response to vasodilators



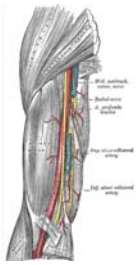
Results:

- Increased blood levels of inflammatory markers *(TNFα, IL-6)*
- Decreased response to vasodilators *(bradykinin, acetylcholine)*



REDUCED BLOOD VESSEL DIAMETER

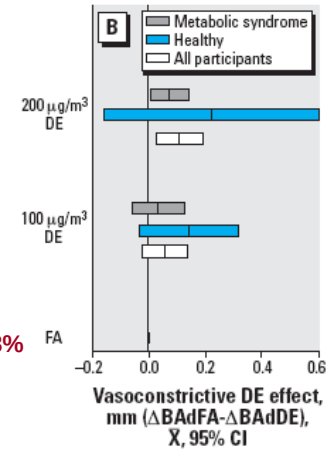
Peretz et al. *Environ. Health Perspect.* 116: 937-942, 2008



- Exposed 27 adults for 2 hr to exhaust at 100 or 200 μg PM/m^3
  - 17 with metabolic syndrome (MS) predisposing to atherosclerosis
- 2002 Cummins 5.9L ISB turbo in generator set at 75% load
- Measured:
  - Brachial artery diameter
  - Plasma levels of endothelin-1

Results:

- Slightly reduced brachial artery diameter
  - Not significant at 100 μg PM/m^3
  - Not significant in normals at 200 μg PM/m^3
- ET-1 level increased 24% in MS, 88% in normals



NOT ALL STUDIES FIND SIGNIFICANT EFFECTS OF EXPERIMENTAL EXPOSURES OF HUMANS

The University of Washington group* found no consistent significant effects on:

1. **Blood coagulation factors**
   - 2 hr exposure of healthy adults at 100 or 200 μg PM/m^3
   - Carlsten et al., *Thromb. Res.* 120: 849-855, 2007
2. **Pro-thrombotic markers**
   - 2 hr exposure of adults with metabolic syndrome at 100 or 200 μg PM/m^3
   - Carlsten et al., *Inhal. Toxicol.* 20: 917-921, 2008
3. **Heart Rate Variability**
   - 2 hr exposure of healthy adults at 100 or 200 μg PM/m^3
   - Peretz et al., *Environ. Res.* 107: 178-184, 2008

*All studies using exhaust from 2002 Cummins 5.9L at 75% load on genset

DIESEL PARTICULATE MATERIAL (DPM) AMPLIFIES NASAL ALLERGIC RESPONSES

Diaz-Sanchez et al., UCLA, (several papers)

- **Normal, atopic, & allergic subjects**
- **Instilled 0.3 mg DPM into nose with or without antigen**
  - Japanese "chilled" DPM
- **Measured inflammation and antibodies in nose**

Results:

- **DPM induced local inflammation**
- **Instillation of DPM before antigen increased:**
  - Antibody production in KLH-sensitized atopics
  - Symptoms and histamine release in dust mite-sensitive subjects
- **Similar responses to pyrene and solvent extracts of DPM**

MANY NON-CANCER EFFECTS HAVE BEEN CAUSED BY EXPOSURE OF ANIMALS TO DIESEL EXHAUST

Reviewed in:

Mauderly, Diesel Exhaust, in: ***Environmental Toxicants***, 2nd Ed., M. Lippmann, Ed., Wiley, New York, 2000, pp. 193-241 (3rd Ed. In press)

Hesterberg et al., ***Crit. Rev. Toxicol.*** 35:379-411,2005

Lloyd and Cackette, ***J. Air Waste Man. Assoc.*** 51:809-847, 2001

Lung inflammation and fibrosis	Altered *in utero* development
Altered maternal hormone balance	Amplification of allergic responses
Reduced clearance of bacteria	Reduced clearance of virus
Altered respiratory allergic response	Altered systemic immune function
Altered heart function (ECG)	Altered serum chemistry
Pro-atherosclerotic vascular injury	Altered blood clotting factors
Reduced lung function	Altered gene expression in lung

Nearly all significant effects occurred at extreme exposure levels

ENHANCED DEVELOPMENT OF ALLERGY

Maejima et al., ***Inhal. Toxicol*** 13:1047-1063, 2001

- **Exposed 5 wk old mice 16 hr/d, 5 d/wk x 24 wk**
  - 6.9 L engine in steady-state at medium load

Whole diesel exhaust at 3,200 µg PM/m^3	+ JC pollen
Filtered diesel exhaust	+ pollen
Air	+ pollen
Air	- pollen

- **Measured allergic antibody (IgE) in blood at end of exposure**

Results:

- **Exposure increased portion of mice developing allergy**

Percentage of mice developing antigen-specific circulating IgE:

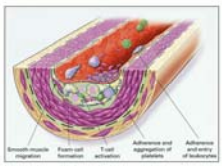
Whole exhaust + pollen	72%
Filtered exhaust + pollen	67%
Air + Pollen	33%

- **Non-PM components caused most of the effect**

PRO-ATHEROSCLEROTIC EFFECTS ON VESSELS OUTSIDE THE LUNG

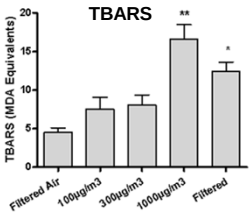
Campen et al., *The Toxicologist* 102: 150, 2008

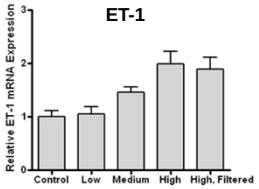
- Exposed ApoE$^{-/-}$ mice 6 hr/d, 7 d/wk x 7 wk *(on high-fat diet)*
  - Cummins 5.9L ISB 6 cyl turbo engine on HD FTP cycle burning pre-2007 cert. fuel
  - Exposed at 0, 100, 300, & 1,000 µg PM/m^3 and ± PM at highest level
- Measured in aorta near heart:
  - TBARS (oxidative stress)
  - ET-1 (vascular endothelial activation)
  - MMP-9 (vascular remodeling)

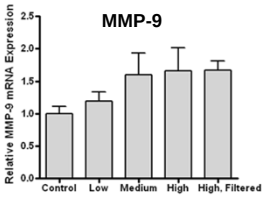


Results:

- Exposure increased all three indicators
- PM influenced TBARS response, but not others







EFFECTS OF PROXIMITY TO TRAFFIC SUGGEST RANGE OF ADVERSE OUTCOMES

Total Mortality (Laden et al., *EHP* 108:941, 2000; Hoek et al., *Lancet* 360:1203, 2002; Finkelstein et al., *Am. J. Epidemiol.* 160:173, 2004)

Cardiovascular mortality (Marr et al., *EHP* 108:347, 2000)

Myocardial infarction (Peters et al., *NEJM* 351:1721, 2004)

Heart rate and HR variability (Riediker et al. *AJRCCM* 169:934, 2004)

Respiratory illness (Duhme et al., *Epidemiol.* 7:578, 1996)

Respiratory infection (Brauer et al., *AJRCCM* 166:1092, 2002)

Lung function of adults and children (Battigelli et al., *Arch. Environ. Health* 10:165, 1965; Brunekreef et al., *Epidemiol.* 8:298, 1997)

Wheeze in adults (Garshick et al., *Epidemiol.* 14:728, 2003)

These effects are not unique to either traffic or air pollution

No studies could isolate causality to diesel exhaust

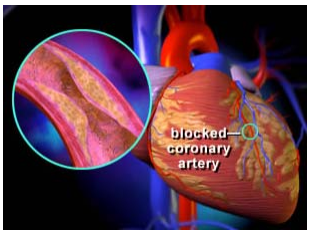
EXAMPLE: MYOCARDIAL INFARCTION vs. TIME IN TRAFFIC

Peters et al., *N. Engl. J. Med.* 351: 1721, 2004

- Case-crossover study of myocardial infarction (MI) in Augsburg, Germany
  - Compared exposure before MI to exposure on other days
- 691 cases surviving to compete questionnaire
  - 80% male, mean 61 yrs old, 80% 1st MI, 30% smokers

Results: 1. Time in traffic was higher than average on the day of MI

2. Risk was highest for exposure 1-2 hrs before MI



Odds Ratio (p<) for MI After Exposure to Traffic

Time of exposure – in any transportation

Concurrent	1.50	(p<.02)
1 hr prior	2.92	(p<.001)
2 hrs prior	2.01	(p<.001)
3 hrs prior	1.15	(p<.47)

1 hr prior - by transportation type

Bicycle	3.94
Public	3.09
Car	2.92

DOES REDUCING EMISSIONS BY RETROFITS REDUCE HEALTH RISKS?

- "Less is better", but there is little way to judge benefits quantitatively
- Epidemiology links reductions of environmental air pollution to reduced population health impacts
- Only one animal study has simulated a diesel retrofit

DIESEL "RETROFIT" REDUCES HAZARDS

McDonald et al. *Aerosol Sci. Technol.* 38: 62-78, 2004
McDonald et al., *Environ. Health Perspect.* 112: 1307, 2004

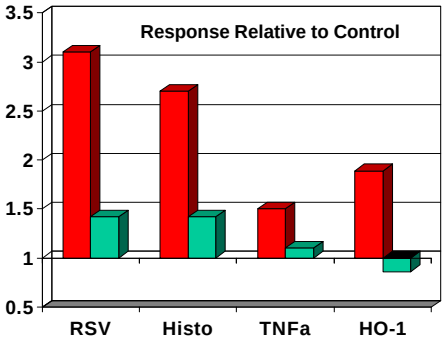
Compared at same operating condition and dilution:

Pre-2007 certification fuel, 350 ppm S
No after-treatment

15 ppm S fuel (BP-15)
Catalyzed DPF

- Yanmar YDG5500E diesel generator at SS full load
- Exposed mice 6 hr/day x 7 days
- Measured:
  - Clearance of Respiratory Syncytial Virus (RSV)
  - Histopathology (HISTO)
  - Pro-inflammatory cytokine (TNFα)
  - Indicator of oxidative tissue stress (heme-oxygenase-1 [HO-1])

Result: Health effects were eliminated or reduced to non-significant levels



ARE ALTERNATE FUELS AND OTHER NEW TECHNOLOGIES SAFER?

Alternative fuels?
- New feedstocks
- Biodiesel
- Other biofuels
- Water emulsions
- Gas-to-liquid
- Coal-to-liquid

New lubricants?
- Synthetics
- Ionic fluids

Advanced combustion technologies?
- Cold exhaust gas recirculation (EGR)
- Homogenous charge compression ignition (HCCI)

Fuel additives?
- Cerium

HAZARDS OF BIODIESEL EMISSIONS?

Information largely from cultured cells

- **127 citations 1994-2007**
- **Most used Ames bacterial mutagenicity assay**
- **Relative toxicity of PD and BD varied with fuel and test conditions**

Literature reviews predict that BD emissions are not more toxic than PD

- **Mauderly, In: *Plant Oils as Fuels*, Springer, Berlin, p. 92-103, 1992**
- **McCormick et al., *Inhal. Toxicol.* 19(12): 1033-1039, 2007**
- **Swanson et al., *Environ. Health Perspect.* 115(4): 496-499, 2007**

The only inhalation study was conducted at LRRI to meet U.S. EPA Tier 2 test requirements

MUTAGENICITY OF DIESEL PM FROM RAPESEED OIL, RAPESEED METHYL ESTER, AND FOSSIL FUELS

Bünger et al., *Arch Toxicol.* 81:599-603, 2007

- **Generation of PM**
  - **Mercedes OM 906 LA 6.4L 6 cyl. turbo meeting Euro 3**
  - **13-mode European stationary cycle**

- **Fuels:**

	Revertants per L exhaust	
	Mean	SD
Rapeseed oil (cold pressed)	494	62
Low-viscosity RSO (heated to 70°C)	1,3784	74
Rapeseed methyl ester	57	13
Coal gas-to-liquid	46	10
Petroleum diesel	51	7

~ same

- **Bacterial mutagenicity of condensates + particle extracts**

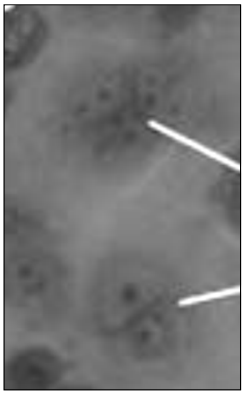
Results:

- **Exhausts from raw oils were most mutagenic**
- **No difference between PD and BD**

MAMMALIAN CELL TOXICITY OF DIESEL PM

Ackland et al., *Immunol. Cell Biol* 85:617-622, 2007

- Treated cultured A549 cells with 25 µg/mL PM extract
  1979 VW 1.6L on Euro 2 urban cycle
- Blends of petroleum diesel (PD) and biodiesel (BD)
  Canola BD
- Incubated 5 days, then counted multinucleated cells



Results: BD less toxic than PD

%BD	%PD	% Multinucleated Cells
0	0 (control)	7
100	0	12
80	20	16
60	40	47
40	60	48
20	80	52

U.S. EPA TIER 2 PROTOCOL (new fuels & additives)

U.S. Code of Federal Regulations, 40 CFR 79, subpart F (CAA Part 211)

- Expose rats 6 hr/day, 5 days/wk for 3 mo
  - 3 dilutions of whole emissions + clean air control
  - Highest concentration should cause measurable effects
  - No detailed characterization of exposure atmosphere
- Measure:
  - Body weight, food consumption, clinical signs
  - Histology of all major organs at end of exposure + 28-day recovery
  - Serum chemistry & hematology (29 variables)
  - Ophthalmology (pre- & post-exposure)
  - Fertility/reproductive toxicity (mated wk 10, examined at 20 d of gestation)
  - Micronucleus (bone marrow, with DMBA pos. control)
  - Sister chromatid exchanges (with DMBA pos. control)
  - Neurotoxicity (histology of CNS, GFAP, with acrylamide pos. control)
  - Ames bacterial mutagenicity test (5 strains)
- Does not include some outcomes of current interest
- No directly comparable "baseline" data for petroleum diesel

EFFECTS OF INHALED BIODIESEL EXHAUST

Finch et al. *Inhal. Toxicol.* 14:101-132, 2002

- 100% soybean oil methyl ester
- 1998 model Cummins 5.9L ISB 6 cyl. turbo
  - No after-treatment other than standard muffler
  - EPA heavy-duty certification cycle
  - 125 hrs on cycle for break-in before study
  - Cold start excluded
  - Shell Rotella-T™ 15W-40 crankcase oil
- Whole emissions diluted to 500, 200, 40 & 0 µg PM/m^3

Results: mild effects – most significant only at highest level

- Increased lung macrophages containing PM
- Reduced serum cholesterol
- Decreased liver weight in males & females
- Increased testicle weight

SOYGOLD

WHAT ABOUT OTHER ALTERNATIVE FUELS?

Petroleum diesel-water emulsions (Tier 2 studies at LRRI):

- PD-water emulsion (Reed, et al. *Inhal. Toxicol.* 17:851-870, 2005)
  - 2002 model Cummins ISB 5.9L turbo on FTP
  - 77% CARB diesel, 20% water, 3% emulsifiers
  - Whole emissions diluted to 400, 200, 100 & 0 µg PM/m^3
- PD-methanol-water emulsion (Reed et al. *Toxicol. Ind. Health* 22:65-85, 2006)
  - 2002 model Cummins ISB 5.9L turbo on FTP
  - 74% CARB diesel, 17% water, 6% methanol, and 3% emulsifiers
  - Whole emissions diluted to 500, 250, 125 & 0 µg PM/m^3

Results: like biodiesel, both emulsions caused few significant effects

Compressed natural gas:

- No inhalation study
- Samples from new, normal emitter, & high-emitter transit buses
  (Seagrave et al., *Toxicol. Sci* 87:232-241, 2005)

Results: PM extracts mutagenic
Lung toxicity generally less than diesel or gasoline
Lube oil components appeared to drive toxicity

Alcohols: No health studies – potential concern for aldehydes

BOTTOM LINES

1. **Diesel emissions merit continued attention – and reduction**
   - Wide range of potential cancer and non-cancer effects
   - Magnitude of risks from mine exposures are uncertain

2. **The health effects of diesel emissions are not unique**
   - Other exposures and personal factors contribute
   - We will never precisely know the portion of miner health burdens attributable to diesel exhaust

3. **Laboratory studies have demonstrated hazards at exposure concentrations overlapping with occupational levels:**
   - Human studies: ~ 100 μg PM/m^3 for 1-2 hr exposures
   - Animal studies: ~ 100 μg PM/m^3 for 7 day exposures

4. **Both PM and non-PM components are important**

5. **Emission reductions by retrofit and alternative fuels should reduce hazards and risks**

6. **No laboratory studies during past 20 yrs have used mine diesel engines**