DIESEL EXHAUST EMISSIONS, HEALTH EFFECTS AND REGULATIONS

Roger O. McClellan
Advisor, Toxicology and Human Health Risk Analysis
Albuquerque, NM 87111
Email: roger.o.mcclellan@att.net

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Internal Combustion Engine

- **One of the most significant inventions of the industrial revolution influencing the modern world**
- **Converting hydrocarbon fuels to power for multiple uses**
- **Two paths of development**
  - **Spark ignition engines with multiple inventors**
  - **Compression ignition engines traceable to Rudolph Diesel (1892)**

Historical Perspective

- "This machine is destined to completely revolutionize engine engineering and replace everything that exists" (1892)
- "So much has been written and said about the diesel engine in recent months that it is hardly possible to say anything new." (1910)

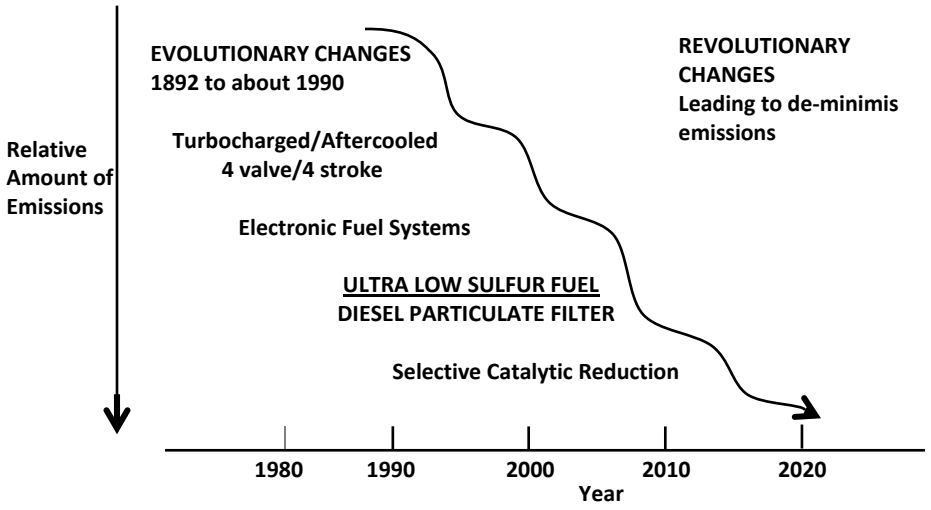
Rudolf Diesel

Technologies are Constantly Changing

In Response to:

- Wider application
- Desire to increase efficiency
- Concern for potential health and environmental impacts
- Regulations
  - Workplace
  - Ambient
  - Global
- Economic considerations

Evolutionary Followed by Revolutionary Changes in Diesel Technology

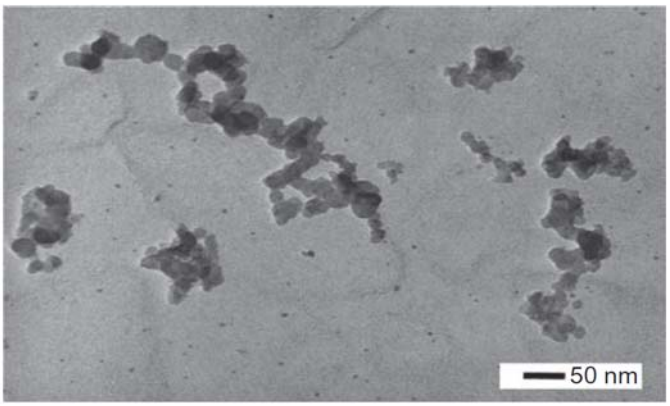


Terminology

- **TDE – "Traditional Diesel Exhaust"**
- **NTDE – "New Technology Diesel Exhaust"**

Hallmark Traditional Diesel Exhaust Emissions

Aggregated Carbonaceous Nanoparticles with Associated Hydrocarbons



Early Concern for Environmental and Health Impacts

- **Earliest concerns were for odor and visibility**
- **Early indications of potential for diesel exhaust to be carcinogenic**
  - **Extracts of combustion particles from both gasoline and diesel engines contained polycyclic aromatic carcinogens known to be carcinogenic**
  - **Positive results in mouse skin painting cancer assay (Kotin et al, 1955)**
  - **With beginning of molecular biology revolution, extracts of diesel exhaust particles shown to be mutagenic in bacterial assays (Huisingh et al, 1978)**

Mutagenicity Studies

- **Some mutagens generated by reactions with NO_x during PM collection**
- **Mutagenic compounds associated with particles not readily bioavailable**
- **Mutagens extracted from particles using hot organic solvents**
- **Typically use very high concentrations in *in vitro* assays**
- **Lung clearance, metabolism, DNA repair not present or overwhelmed in vitro**

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Chronic Inhalation Studies of Traditional Diesel Exhaust

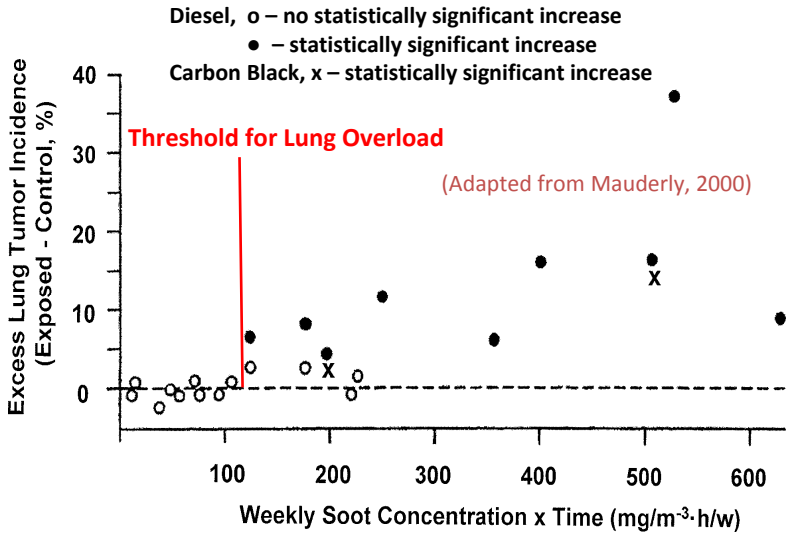
- **Conduct stimulated by positive mutagenicity findings**
- **Twenty two chronic studies of TDE over last 30 years**
- **Exposed rats, mice, or hamsters by inhalation**
- **100-12,000 µg/m^3 of diesel exhaust particles**
- **Reviewed in Hesterberg et al., *Critical Reviews in Toxicology* Vol. 35, 2005**

Chronic Animal Inhalation Studies of TDE

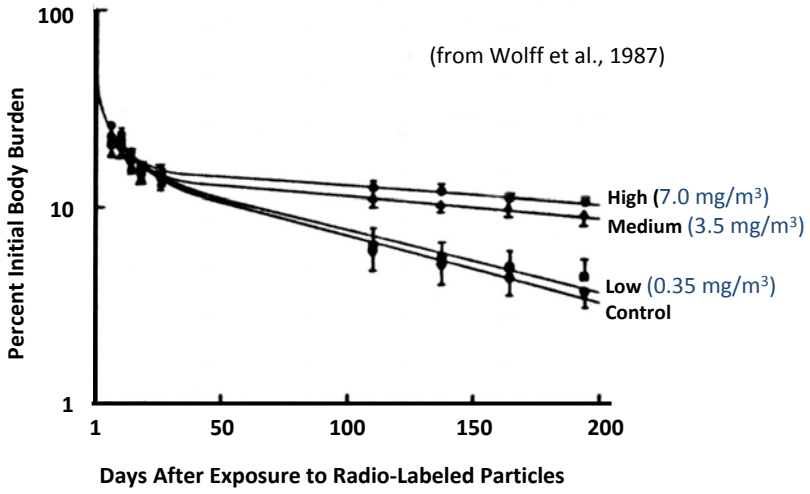
- Positive results in nine rat studies
- Lung tumors in rats only after:
  - Very high "overload" levels (> 1,000 µg/m^3)
  - Other "inert dusts" produce overload-related tumors in rats—e.g. TiO_2, carbon black
- No excess lung tumors observed in mice or hamsters

Lung Tumor Excess in Rats

Only Above Lung Overload Exposures



Impaired Lung Clearance with Chronic High Concentration Exposure to TDE



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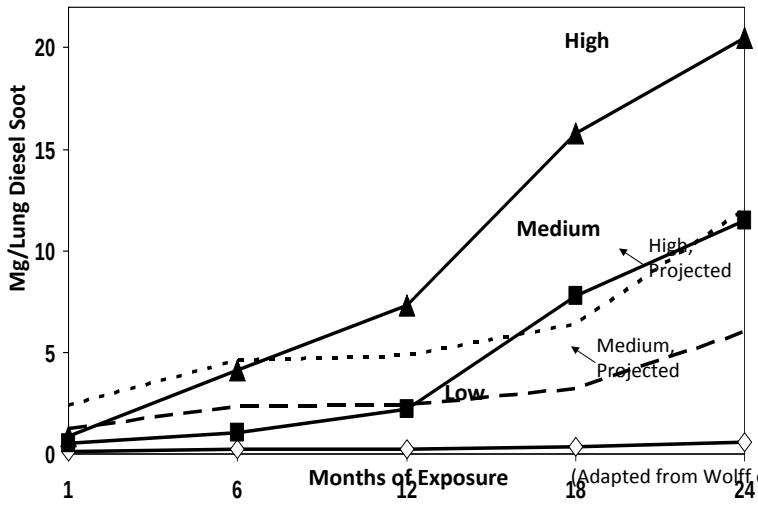
Particle Overload with High Concentration Exposure to TDE Leads to Increased Lung Burden



(Adapted from Wolff et al. 1987).

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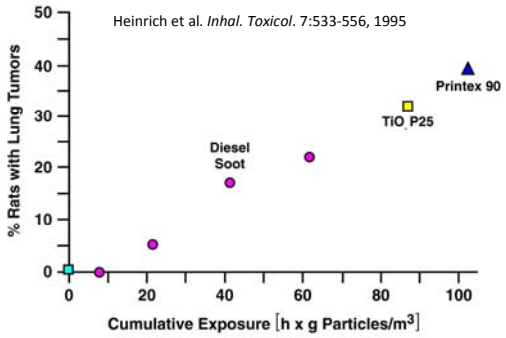
LUNG "OVERLOADING" CONCEPT EVOLVED



Other poorly-soluble, respirable PM fell on the same exposure-response line in rats

Mutagen-free carbon blacks gave same result in two studies (LRRI & Fraunhofer)

The same exposures were not tumorigenic in normal test strains of mice

Patterns of particle retention in the lung differ between rats and humans

Consensus evolved that results from "overloaded" rats should not be used to estimate risks to humans

- Threshold
- Nonspecific
- Species-specific

} Not reliable for estimating human risk

Risk Assessment Paradigm

- Hazard Identification or Characterization
  Does exposure to this agent or occupational setting have the potential to cause human cancer?
- Exposure (dose)-response assessment:
  What is the relationship between exposure and excess cancer? (Potency)
- Exposure Assessment:
  What exposures have occurred or are likely to occur in the future?
- Risk Characterization:
  What is the estimated excess cancer risk for a specific exposure scenario? Requires knowledge of both exposure and potency

Hazard does not equal risk!

Key Cancer Hazard Evaluations (1988-2003)

NIOSH (1988)	**DE classified as "potential occupational carcinogen"**
IARC (1989)	**DE classified as "probable human carcinogen" (Group 2A)**
WHO (1996)	**DE is "probable human carcinogen"**
California EPA (1998)	**DE designated as a "toxic air contaminant"** **DE and lung cancer association is "reasonable and likely"** **DE quantitative cancer risk coefficient**
NTP (2000)	**DE Particulates classified as "reasonably anticipated to be a human carcinogen"**
USEPA (2002)	**DE "likely to be carcinogenic to humans"**

CONCERN FOR HEALTH HAZARDS LEAD TO STRINGENT STANDARDS

1988 IARC Carcinogenic Hazard Evaluation of Diesel and Gasoline Engine Exhaust

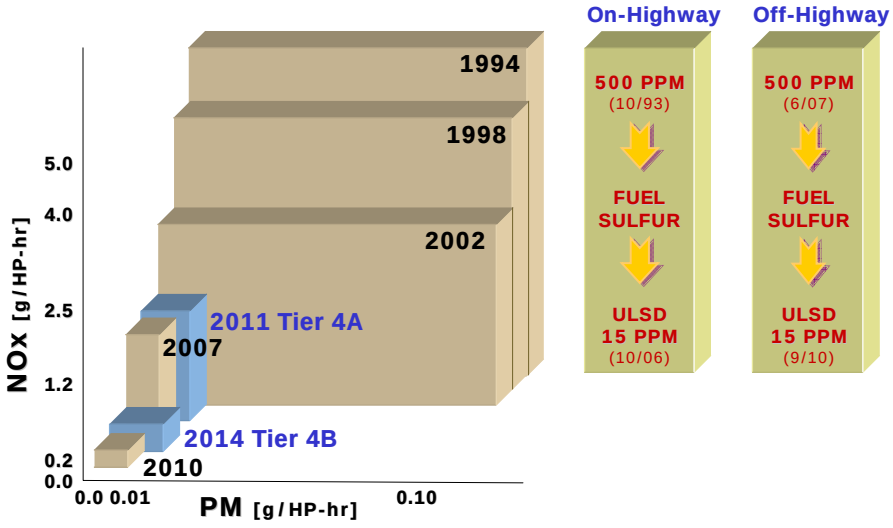
Diesel

- **"limited evidence" in humans**
- **"sufficient evidence" in laboratory animals**
- **"strong evidence" based on mutagenicity**
- **Overall evaluation – "probably carcinogenic to humans," Group 2A**

Gasoline

- **"inadequate evidence" in humans**
- **"inadequate evidence" in laboratory animals**
- **"evidence" of mutagenicity**
- **Overall evaluation – "possibly carcinogenic to humans," Group 2B**

Increasingly Stringent US Heavy Duty Diesel Emission Standards



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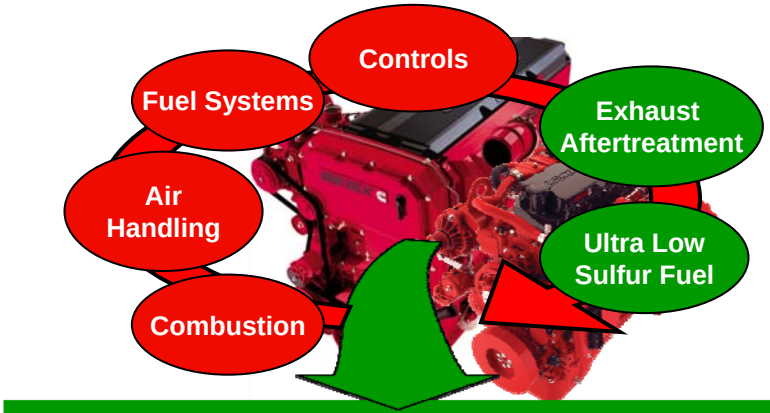
Transition to Clean "New Technology" Diesel Requires Integrated System



New Technology Diesel

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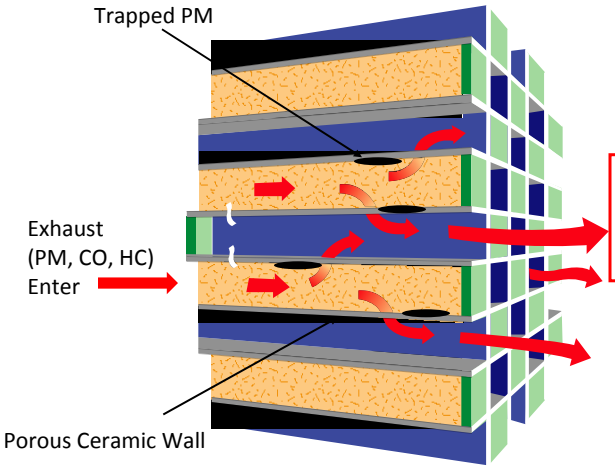
Emissions Reductions in NTDE REQUIRES

Ultra-low Sulfur Fuel and Wall-flow Diesel Particulate Filter



Reductions:
99+% PM
80 to 100% HC, CO
80 to 99+% PAH, toxins

Adapted from MECA May 2000

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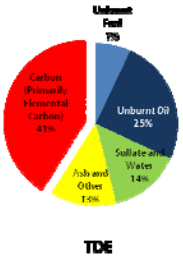
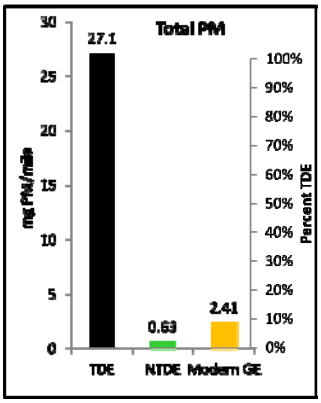
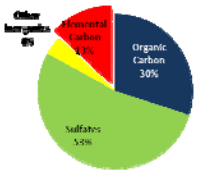
PM Composition and Mass

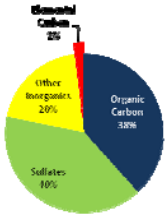
Comparison with Modern Gasoline Exhaust





(Not to scale)





Traditional Diesel Exhaust (TDE) (Kittleson, 1998), New Technology Diesel Exhaust (NTDE) (Khalek et al. 2011) and Modern Gasoline Exhaust (GE) (Cheung et al. 2009).

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NTDE Reduces Emissions Across a Broad Spectrum of Compounds

Category	Reduction Relative to TDE
Single Ring Aromatics	82%
PAH	79%
Alkanes	85%
Hopanes/Steranes	99%
Alcohols & Organic Acids	81%
Nitro-PAHs	81%
Carbonyls	98%
Inorganic Ions	71%
Metals & Elements	98%
Organic Carbon	96%
Elemental Carbon	99%
Dioxins/Furans	99%

Khalek et al., JAWMA 2011.

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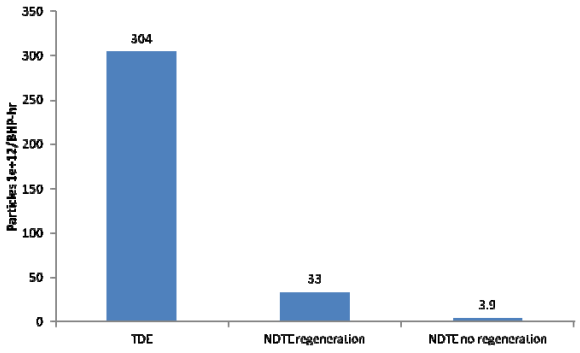
NTDE Has Lower Particulate Number Concentrations



ACES Study: Khalek et al., CRC, 2009.

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New Technology Diesel Exhaust (NTDE) is Markedly Different than Traditional Diesel Exhaust (TDE)

- **PM concentration in New Diesel Technology Exhaust (NTDE) are more than 100-fold lower than pre-regulation DE**
- **NTDE PM is chemically different from TDE PM**
- **NTDE PM is much closer in composition to PM found in CNG and gasoline exhausts**

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Health Effects Studies: Post -1990

- **Additional lifespan studies in rats confirmed earlier results of "overload" concentration-duration exposures causing excess of lung cancer in rats**
- **Over 6,000 papers published on wide range of health responses to diesel exhaust, almost all with TDE. TDE became a favorite material for use as a "representative" particulate material ($PM_{2.5}$)**
- **Three major epidemiological studies completed**
  - **Diesel Exhaust Miners Study Cohort (Attfield et al, 2012) Case-Control (Silverman et al, 2012)**
  - **Truck Drivers Cohort (Garschick et al, 2012)**

Studies with New Technology Diesel Exhaust (NTDE) Conducted under Sponsorship of Health Effects Institute (HEI)

(Advanced Collaborative Emissions Study (ACES)

- **Extensive emissions characterization studies conducted on four EPA-2007 compliant engines (Khalek et al, 2011)**
- **One of the above engines used to generate exhaust used for inhalation exposure studies with rats and mice conducted at the Lovelace Respiratory Research Institute (McDonald et al, 2012)**
- **Extensive emissions characterization studies with three EPA-2010 compliant engines now under way**

ACES Health Effects Studies

Primary (Null) Hypothesis: "Emissions ….. will have very low pollutant levels and not cause an increase in tumor formation or substantial toxic effects in rats or mice at the highest concentration of exhaust that can be used …. compared to animals exposed to clean air, although some biological effects may occur."

Exposures: 16 hours/day for 5 days/week for 24-30 months

Gases (ppm)	High	Mid	Low
NO_2	4.2	0.9	0.1
NO	5.8	1.4	0.3
NO_x	9.9	2.3	0.4
CO	6.8	-	-
PM ($\mu g/m^3$)			
Chamber Inlet	9	3	2
Chamber	27	31	21

Findings:
Rodent 1, 3 and 12 Month Sacrifices

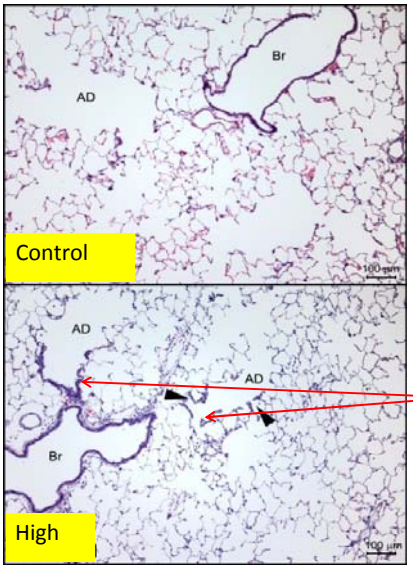
The majority of the analyses showed no difference between diesel exhaust exposure and clean air control.

Histopathology analysis revealed mild/minimal lung epithelial hyperplasia in high exposure rats after 3 months of exposure, but not in mice. Hyperplasia increased at 12 months, but was still considered mild/minimal severity.

Statistically significant findings were noted for several indicators of pulmonary stress and inflammation in rats and mice (fewer findings in mice).

Pulmonary function assessments in rats showed slight differences in high exposure rats compared with control after 3 months of exposure.

HISTOPATHOLOGY IN RATS AT 3 MONTHS



Hallmark lesion of oxidant gases

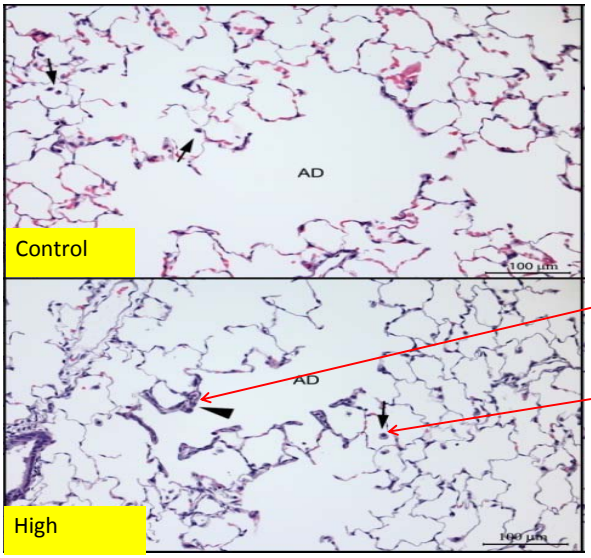
Epithelial hyperplasia observed at high exposure level (associated with alveolar ducts)

Findings generally mild

Thickening of alveolar duct septae

AD = Alveolar Duct; Br = Bronchiole

Histopathology in Rats at 3 Months: Higher Power View of Previous Slide

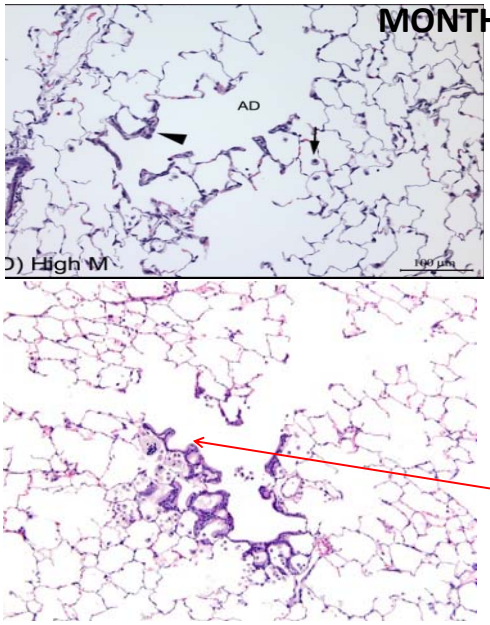


Hallmark lesion of oxidant gas

Thickening of alveolar duct septae

Macrophage

HISTOPATHOLOGY IN RATS AT 3 AND 12 MONTHS:



Hallmark lesion of oxidant gas

3 months

12 months

Enhanced epithelial hyperplasia at 12 months. Only observed at high level, but in both sexes.

Role of NO_2 in Observed Effects?

When HEI designed the study, it was expected that at the high concentration (16 hr/day 4.2 ppm NO_2) some NO_2-related effects might be observed based on previous studies

HEI Study (Mauderly et al., 1989) F344 rats exposed (7hr/day, 5 days/week) to 9.5 ppm NO_2

Pulmonary function, histopathology, and, immune response assessed after 12, 18, 24 mo (1820, 2730, 3640 hr) of exposure

Findings: **NO_2 caused epithelial hyperplasia, thickening of walls of terminal bronchioles, inflammation, and oxidative stress. There was little effect on respiratory function.**

Effects at 12 mo not significantly different than at 24 months

Similar NO_2 exposure-time concentrations at 12 mo

Mauderly et al:	**17,290 ppm-hr.**
ACES:	**17,472 ppm-hr**

2012 IARC Carcinogenic Hazard Evaluation of Diesel and Gasoline Engine Exhaust

- **Multiple parties asked IARC to delay the evaluation until the ACES study was concluded. IARC decided to not delay the evaluation**
- **IARC evaluation of Diesel**
  - **"Sufficient evidence" in humans**
  - **"Sufficient evidence" of whole engine exhaust, diesel exhaust particles and extracts of DEP**
  - **"Strong evidence" based on mechanistic considerations**
  - **Overall evaluation – "Carcinogenic to Humans," Group 1**
- **IARC overall evaluation of gasoline engine exhaust – "possibly carcinogenic to humans," Group 2B**

Major Epidemiological Evidence

Diesel Exhaust Miners Study (DEMS)

- **Cohort study (Attfield et al, 2012) – 12,315 workers in 8 non-metal mines**
  Mortality ratio for lung cancer – 1.26 (CI-1.09-1.44)
- **Nested Case Control Study (Silverman et al, 2012) – 198 lung cancer deaths and 562 matched controls**
  Among heavily exposed workers (REC - ≥ 1005 μg/m^3-yr) OR – 3.20 (CI-1.33-7.69)
  Among never smokers
  OR – REC - < 8 μg/m^3 – yr – 1.00
  REC - 8 to ≤ 304 μg/m^3 – yr – 1.47 (CI-0.29-7.50)
  REC - > 304 μg/m^3 – yr – 7.30 (CI-1.46-36.57)

Trucking Industry Study

- **Cohort Study (Garshick et al, 2012)**
  31,135 workers – 1985-2000
  Hazard Ratio (per 1000 μg/m^3 – mo of Elemental Carbon)
  5 yr exposure lag – 1.07 (CI-0.99-1.15)
  10 yr exposure lag – 1.09 (CI-0.99-1.20)

Major Issues with all Three Studies

- **DEMS studies released on-line in March 2012. Data sets still not released for independent evaluations**
- **Major issues with reconstruction of REC index**
- **All cohort analyses conducted in accord with original protocol were negative, only post-hoc analyses yielded positive results**
- **Teamsters Study released on-line week before IARC meeting, limited opportunity for critical review**

Exposure Measurements in Diesel Exhaust Miners Study (DEMS)

	1954-1997		1998-2001		
Agent	Area	Personal	Area	Personal	Total
CO	10,916	46	208	0	11,170
NO_2	4,658	764	387	1,031	6,848
REC	12	73	216	1,156	1,457

- Mortality follow-up through 1997
- Exposures started as early as 1967
- Used 15 year lag, thus, relevant exposures were pre-1983
- Essentially all Respirable Elemental Carbon (REC) values based on extrapolation from CO or HP and ventilation extrapolated to CO and then to REC

IARC Decided to Not Provide Separate Evaluation for NTDE

There was an option

- **Category 3: The agent is not classifiable as to carcinogenicity to humans. This category is used most commonly for agents for which the evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals.**
- **It will be of interest to see the extent the final published Monograph released in 2013 makes reference to NTDE.**

Need to Consider Diesel Health Issues in Context of Other Regulatory Actions

Particulate Matter

- **Shift from TSP (1971) to PM_{10} (1987) to $PM_{2.5}$ (1997)**
- **2006, $PM_{2.5}$ Annual – 15 µg/m^3**
  24-hr – 35 µg/m^3, 98th percentile over 3 years
- **Current consideration being given to further reductions**
  Grounded in linear, no threshold exposure-response relationship

NO_2

- **1971, annual standard – 53 ppb**
- **2010, annual standard of 53 ppb retained and augmented by 1-hour standard -100 ppb, 98th percentile of yearly values**

Ozone

- **1971, Total photochemical oxidants, 1 hr-0.08 ppm**
- **1979, O_3, 1 hr – 0.12 ppm**
- **1997, O_3, 8-hr – 0.08 ppm, 4th highest averaged over 3 years**
- **2008, O_3, 8-hr – 0.075 ppm, 4th highest averaged over 3 years**
- **Current – Pressure to reduce further approaching background**

Major Tensions in Setting Standards

- **Role of Science**
  - **Scientists want to see "their science" used**
  - **Mixing science and personal ideology as to policy outcome**
  - **Lower is better (Really?)**
  - **Politicians like to use the "cloak of science"**
- **In USA, cost cannot be considered in setting NAAQS**
- **Reluctance or refusal of scientists to share raw data**
- **Establishing "causality" for diseases with multiple etiologies**
- **Determining exposure-response relationships for "low exposures"**
- **Blurred boundary between personal exposure (home, work place, commuting, recreation), ambient and work place**
- **Increased pressure to tighten occupational exposure limits**
- **Focus on small "relative risks" and ignoring non-identified attributable risk that dominates baseline**
- **Lack of recognition of role of technological advances in reducing hazard/risk**

Summary

- Diesel technology continues to be a major contributor to the economic health of the world and helps improve public health
- Diesel technology has undergone revolutionary advances to improve its use and reduce emissions to de-minimis levels
- Improved work place and ambient air quality dependent on pace of implementing new technology
- Need for scientific community and regulatory agencies to recognize advances and re-prioritize issues and allocation of resources
- "How low is low enough" for any agent is a political decision that should be informed by the best available science. Science alone cannot establish what is sufficiently safe.

SELECTED REFERENCES

Attfield MD, Schleiff PL, Lubin JH, Blair A, Stewart PA, Vermeulen R, Coble JB, Silverman DT. The diesel exhaust in miners study: a cohort mortality study with emphasis on lung cancer. J Natl Cancer Inst 104:1-15, 2012.

Crump, K. and C.V. Landingham. Evaluation of an Exposure Assessment Used in Epidemiological Studies of Diesel Exhaust and Lung Cancer in Underground Mines. Crit. Rev. in Toxicol. 42(7): 599-612, 2012.

Gamble, J.F., M.J. Nicolich and P. Boffetta. Lung Cancer and Diesel Exhaust: An Updated Critical Review of the Occupational Epidemiology Literature. Crit. Rev. in Toxicol. 42(7): 549-598, 2012.

Hesterberg, T.W., W.B. Bunn, R.O. McClellan, G.A. Hart and C.A. Lapin. Carcinogenicity Studies of Diesel Engine Exhausts in Laboratory Animals: A Review of Past Studies and a Discussion of Future Research Needs. Crit. Rev. in Toxicol. 35: 379-411, 2005.

Hesterberg, T.W., C. Long, W.B. Bunn, C. A. Lapin, R.O. McClellan and P. Valberg. Product Stewardship and Science: Safe Manufacture and Use of Fiber Glass" *Reg. Toxicol. Pharmacol*. 62(2): 257-277, 2012. The linkage for on-line open access is: http://www.sciencedirect.com/science/article/pii/S0273230012000037.

McClellan, R.O. Role of Science and Judgment in Setting National Ambient Air Quality Standards: How Low is Low Enough? *Air Quality, Atmosphere and Health Journal* 5(2): 243-258, 2012. The linkage for on-line open access is: http://www.springerlink.com/content/?k=mcclellan+vol%3a(5)+iss%3a(2)+p%3a(243)

McClellan, R.O., T.W. Hesterberg and J. C. Wall – Evaluation of Carcinogenic Hazard of Diesel Engine Exhaust Needs to Consider Revolutionary Changes in Diesel Technology, *Reg. Toxicol. Pharmacol* 63(2): 225-258, July 2012. The linkage for on-line open access is: http://www.sciencedirect.com/science/article/pii/S0273230012000694.

Silverman DT, Samanic CM, Lubin JH, Blair AE, Stewart PA, Vermeulen R, Coble JB, Rothman N, Schleiff PL, Travis WD, Ziegler RG, Wacholder S, Attfield MD. The diesel exhaust in miners study: a nested case-control study of lung cancer and diesel exhaust. J Natl Cancer Inst 104:1-14, 2012.