Health Effects of Diesel Exhaust

Ray Copes, MD, MSc
Chief, Environmental and Occupational Health, Public Health Ontario
Associate Professor, University of Toronto
• This presentation is the personal assessment of the speaker and should not be taken as implying any organization view or policy.
Diesel health effects

- Cancer
- Non-cancer
- Exposure, standards
- Policy implications
Is Diesel Exhaust Carcinogenic?

Top Down?

Bottom Up?
Diesel exhaust as a carcinogen

- Complex mixture – particulate and gas phase
- Analogy with other combustion mixtures (tobacco smoke)
- DE contains known carcinogens (e.g. benzene, BaP)
- DPM is a component of ambient PM$_{2.5}$, generally about 6-10% of PM$_{2.5}$ although may be up to 36%
- “Air pollution” now considered Group 1 carcinogen by IARC
- In 2012, IARC moved diesel engine exhaust from Group 2A to Group 1 based on assessment of human evidence since its previous assessment

- Noted emissions are complex – depend on fuel, type and age of engine, tuning and maintenance, emissions control system and use.

- US Miners’ study – Cohort and nested case control adjusted for tobacco use, both showed positive trends for lung cancer risk w/ increasing exposure to DE (used el carbon as proxy), 2-3 fold increased risk in highest cum or average exposure categories.

- US Railroad workers – 40% increased risk in workers exposed to diesel compare to no or low, indirect adjustment for smoking, later revised exposure estimates based on work history and history of dieselization, 70-80% increased risk with duration but not cumulative exp.

- US Truckers’ Study- 15-40% increase in risk in drivers and dockworkers with regular exposure to diesel, trend of increased risk with longer duration of employment, with doubling of risk at 20 years after adjusting for smoking.

- Revised exposure assessment (contemporary measures and exposure reconstruction) showed positive trend for cumulative but not average exposure.

- Bladder cancer also mentioned as outcome in some but not all studies.

- Concluded ‘sufficient evidence’ in humans for the carcinogenicity of diesel engine exhaust.
IARC Assessment 

- IARC also reviewed animal studies on whole diesel engine exhaust, gas phase diesel-engine exhaust and extracts of diesel-engine exhaust particles
- Whole DE caused increased incidence of lung tumours in rats
- Intratracheal DE particles caused benign and malignant lung tumours in rats
- Gas phase DE did *not* increase incidence of respiratory tumours in any species
- Concluded ‘sufficient evidence’ in experimental animals for the carcinogenicity of *whole diesel engine exhaust*, *diesel engine exhaust particles* and *extracts of diesel engine exhaust particles*

- Diesel engine exhaust, diesel exhaust particles, diesel exhaust condensates and organic solvent extracts of diesel engine exhaust particles induced various forms of DNA damage
- This includes: bulky adducts, oxidative damage, strand breaks, unscheduled synthesis, mutations, sister chromatid exchange, morphological cell transformation
- Positive genotoxicity biomarkers of exposure and effect observed in humans exposed to diesel engine exhaust
- Concluded ‘strong evidence’ for the ability of whole diesel engine exhaust to induce cancer in humans through genotoxicity
IARC Assessment

If one accepts IARC assessment -

- Cancer as an outcome related to exposure is established
- Cancer effects attributable to DE particulate
- Genotoxic – no threshold for effect
- IARC does not assess potency (risk)
Dissenting comments? Pallapies et al Arch Tox 87:547-549 2013

• Discrepancies in risk estimates for surface only vs ever underground miners
• Critique of exposure assessment in miners study - can the 1998-2001 respirable elemental carbon measures be applied to 1947-1997?
• Assessment of smoking status also flawed and explanation of antagonism between DE and smoking in miners’ study unconvincing
• Use of some cohort members as controls for more than one case needs explanation
• Most recent uptake of US truckers study does not give significant results without adjusting for duration of work
• Pooled analysis study used by IARC did not include adequate sensitivity analyses and shouldn’t be used for hazard or risk assessment purposes.
• IARC did not distinguish between ‘new technology’ and ‘traditional’ diesel
• If one accepts these criticisms, is IARC conclusion unwarranted?
Meta and pooled analyses
Pooled relative risk estimates and heterogeneity-adjusted 95% confidence intervals for all studies and subgroups of studies

Source:
Diesel Exhaust Exposure and Lung Cancer
Author(s): Rajiv Bhatia, Peggy Lopipero and Allan H. Smith
Source: Epidemiology, Vol. 9, No. 1 (Jan., 1998), pp. 84-91
Published by: Lippincott Williams & Wilkins
Stable www.jstor.org/stable/3702619
Pooled estimates of relative risk (RR) of lung cancer in epidemiological studies involving occupational exposure to diesel exhaust (random-effects models)

Source: Occupational exposure to diesel exhaust and lung cancer: A meta-analysis
Lipsett, Michael; Campleman, Sharon
American Journal of Public Health; Jul 1999; 89, 7; ProQuest pg. 1009
Study-specific odds ratios for the highest quartile of cumulative diesel motor exhaust exposure compared with never-exposed, adjusted for age, sex, cigarette pack-years, time-since-quitting smoking, and ever-employment in a “List A” job

• Are these OR/RR large or small?
• Some suggestion older higher risks in older studies
Other assessments – US EPA from online IRIS listing

Using U.S. EPA's revised draft 1999 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999), diesel exhaust (DE) is likely to be carcinogenic to humans by inhalation from environmental exposures. The basis for this conclusion includes the following lines of evidence:

• strong but less than sufficient evidence for a causal association between DE exposure and increased lung cancer risk among workers in varied occupations where exposure to DE occurs;

• extensive supporting data including the demonstrated mutagenic and/or chromosomal effects of DE and its organic constituents, and knowledge of the known mutagenic and/or carcinogenic activity of a number of individual organic compounds that adhere to the particles and are present in the DE gases;

• evidence of carcinogenicity of DPM and the associated organic compounds in rats and mice by other routes of exposure (dermal, intra-tracheal, and subcutaneous and intra-peritoneal injection); and

• suggestive evidence for the bioavailability of organic compounds from DE in humans and animals.
California From Office of Env Hlth Haz Assess online

- Diesel engine exhaust (DEE) has been demonstrated to cause several toxic effects in animals and humans. These effects include respiratory, cardiovascular and immune system toxicity. DEE has also been demonstrated to be genotoxic and carcinogenic.

- The California Air Resources Board (CARB) listed particulate matter from diesel-fueled engines as a Toxic Air Contaminant (TAC) in 1998, with a cancer unit risk factor of $3 \times 10^{-4}$ ($\mu g/m^3)^{-1}$. 
Effects other than cancer
Non-cancer effects

• Multiple approaches possible

• Treat DE on a constituent by constituent basis – the mix is the sum of its components

• Evaluate DE as a mixture

• Diesel particulate matter is a component of ambient particulate matter, and a portion of ambient PM effects are ‘attributable’ to diesel particulate matter

• Conclusions will vary with approach chosen
Diesel exhaust as a mixture

• Chronic respiratory effects are the principal non-cancer hazard to humans from long-term environmental exposure to DE.

• There is some evidence suggesting that exposure may impair pulmonary function, though the results are not robust. While the increased occurrence of mostly transient symptoms such as cough, phlegm, and chronic bronchitis is clear in occupational studies, the studies are deficient in exposure information.

• Evidence for chronic respiratory effects is based mainly on animal studies showing consistent findings of inflammatory, histopathological (including fibrosis), and functional changes in the pulmonary and tracheobronchial regions of laboratory animals, including the rat, mouse, hamster, guinea pig, monkey, and cat.
Diesel exhaust as a mixture

- Other effects (e.g., neurological, growth and survival, neurobehavioral, lowered resistance to respiratory infection, liver effects) are observed in animal studies at higher exposures than those producing the respiratory effects.
- Other effects (e.g., neurological, growth and survival, neurobehavioral, lowered resistance to respiratory infection, liver effects) are observed in animal studies at higher exposures than those producing the respiratory effects.
- Reproductive toxicity has been evaluated in six studies. No teratogenic, embryotoxic, fetotoxic or female reproductive effects have been observed in mice, rats, or rabbits at inhalation exposure levels lower than those where respiratory effects were observed.
Mode of action non cancer effects

From US EPA IRIS

- In rats, the pathogenic sequence following the inhalation of DPM begins with the phagocytosis of diesel particles by alveolar macrophages (AMs).
- Activated AMs release chemotactic factors that attract neutrophils and additional AMs.
- Aggregations of particle-laden AMs in alveoli adjacent to terminal bronchioles, increases in the number of Type II cells lining particle-laden alveoli
- Neutrophils and AMs release mediators of inflammation and oxygen radicals, and particle-laden macrophages are functionally altered, resulting in decreased viability and impaired phagocytosis and clearance of particles.
- May result in pulmonary inflammation and fibrosis.
Non-Cancer Outcomes associated with ambient air pollution (of which Diesel particulate matter is a subset)
Cardiovascular Mortality

Source: A Systematic Review of the Relation between Long-term Exposure to Ambient Air Pollution and Chronic Diseases, Chen, H, Goldberg, M, Villeneuve, P. REVIEWS ON ENVIRONMENTAL HEALTH VOLUME 23, NO. 4, 2008
Mortality from Coronary Heart Disease or Cerebrovascular Disease

Source: A Systematic Review of the Relation between Long-term Exposure to Ambient Air Pollution and Chronic Diseases, Chen, H, Goldberg, M, Villeneuve, P. REVIEWS ON ENVIRONMENTAL HEALTH VOLUME 23, NO. 4, 2008
Risk Assessment?

- Reasonably good agreement that DE is a *probable, likely, or established* human carcinogen
- Debate on how different traditional diesel and new technology diesel are and relevance for carcinogenicity
- Apart from California, no other quantitative estimates of DE cancer potency
- General agreement that the plausible range of potency estimates makes DE one of the leading contributors to cancer risk from ambient PM.
- Based on ambient particulate matter studies, the contribution of DE to non-cancer (e.g. cardiorespiratory morbidity and mortality) is likely as great or greater than its effects as a carcinogen for the general public
Exposure measures and Standards

• For general public/environmental standards, PM$_{2.5}$ likely to remain as the metric, although appreciation that ultrafines (<0.1um diameter) are likely the most biologically active fraction

• Ambient PM$_{2.5}$ objectives and standards likely to be lower in the future, will be driven by additional evidence on non-cancer outcomes as much as recent IARC rating of Group 1 for ‘air pollution’

• Exposure measure in workplace? Respirable elemental carbon has been used in some studies

• Could use in a comparative sense, but would be ‘challenging’ to provide meaningful risk interpretation given uncertainties and inconsistencies in dose-response relationship in available studies
Derivation of EPA RfC for non-cancer effects

<table>
<thead>
<tr>
<th>Critical Effect</th>
<th>Experimental Doses</th>
<th>UF</th>
<th>MF</th>
<th>RfC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary inflammation and histopathology</td>
<td>NOAEL: 0.46 mg/m³</td>
<td>30</td>
<td>1</td>
<td>5µg/m³</td>
</tr>
<tr>
<td></td>
<td>NOAEL&lt;sub&gt;hec&lt;/sub&gt;: 0.144 mg DPM/m³</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If one used California cancer potency factor, what would cancer risk be at this concentration?
Policy implications

• Does it matter if DE is a Group 1 or Group 2A carcinogen?
• Current ambient PM standards are in the range where we know there are effects on the public including mortality
• In practice, they are set on what regulators think is achievable rather than a specified level of protection
• Diesel emissions have been targeted by environmental regulators (esp. US EPA) during the last decade, current engines and fuels much ‘cleaner’ than in past. Off-road likely lags on-road
• Further tightening of emission and fuel standards likely in future leading to further reduction in ambient concentrations
Policy Implications

• Trend towards assessing mixtures rather than single substance
• An OEL for DE?
• Apply ambient standards to workplace?
• Reductions in DPM for vehicles and equipment mandated by environmental standards should also reduce worker exposures.
• No threshold, treat as ALARA?
Policy Implications

• Particulate phase appears to be most active component
• As well as reductions in emissions at source, ventilation, isolation and PPE may reduce exposures
• Lack of threshold does not mean there is ‘no safe level’
• Zero risk is often desired but rarely, if ever, achievable!
Thank You

Questions?