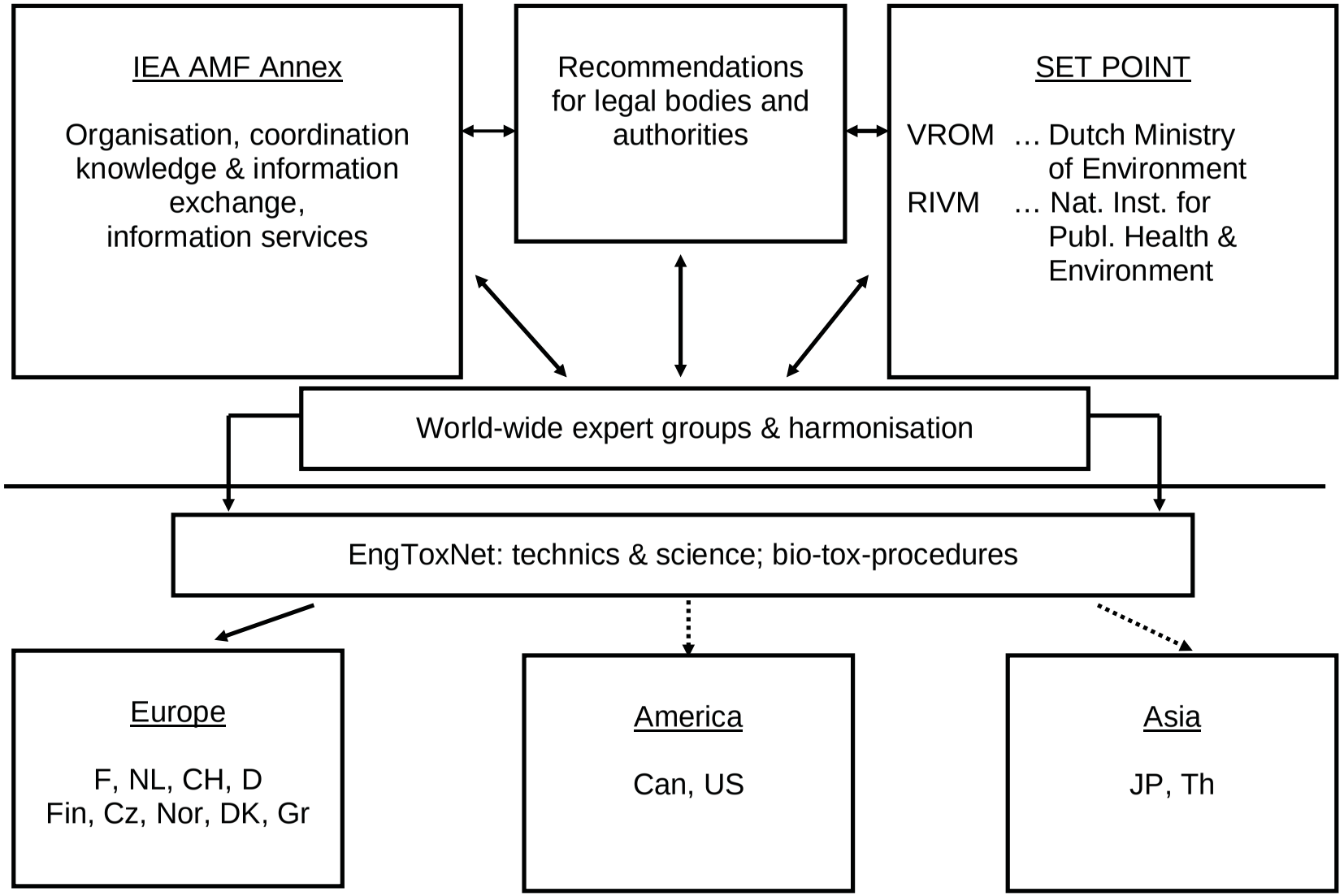
Efforts of Coordination and Information of the Worldwide Research on Toxicity of Exhaust Gases from Engines with Unified Methodology of Aerosol Exposure



[5th final information report for IEA AMF Annex XXXIII, AFHB Sept. 2010, A1]

Toxicological tests – endpoints (examples)

LDH: estimation of membrane integrity which indicates cell viability (toxic conditions → leaky membrane → cytosolic proteins (as LDH) can leave the cell); more LDH – more potential of destroying cells.

WST-1: chemical which is used to measure proliferative ability of cells (do they grow as fast as, expected?) and cell viability. WST-1 is cleaved by mitochondrial activity in viable (healthy) cells and the product (formazan) can be detected colorimetrically. Mitochondrial activity is indicative for the metabolic functioning of a cell; more of the product formazan – cells healthier.

ATP: is a key indicator for intact metabolism (the cells 'energy storage molecule'). The ability for ATP production is strongly affected by toxic conditions; more ATP – intact metabolism, cells OK.

MTT: works in a similar way as WST-1 (also product formazan).

Hoechst: is a dye (and a method) which can get into cells and is actively exported from cells. If the cell is not well, export will not work properly and the amount of the dye in a cell therefore indicates its viability; more Hoechst in the cell – worse condition.

PI exclusion: PI (propidium iodide) is only taken up by severely damaged cells. In principle a similar approach as LDH, but the other way round. Indicates membrane integrity; more PI in the cell is a sign of damage.

Glutathion, GSH: antioxidant molecule produced by the cell, which is sacrificed to oxidative molecules instead of e.g. DNA or important proteins and is used to protect proteins by binding to oxidation susceptible sites. Depletion of reduced GSH indicates high loads of oxidizing chemical species (e.g. ROS ... reactive oxygen species) and gives an estimate of the cell's antioxidant capacity.

NADPH: in principle the same as GSH, but NADPH is a reducing molecule which is used in metabolism (in part: reduce oxidized molecules that could not be protected by GSH); more NADPH means less oxidative stress.

TNF-a, IL-xy etc: cytokines, signal molecules (proteins), used for communication of cells with each other. Measurements of these proteins show the induction of inflammatory responses. ELISA is a method for quantification of such molecules, the amount indicates the strength of responses, (quantifies the crosstalk between cells, the signal exchange in relation to inflammation).

Flow cytometry (sophisticated analysis of shape and surface of the cells):
sorts and counts cells according to their state. E.g. cells in which an inflammatory response has been activated by cytokines have certain patterns/markers molecules on their surfaces, by which they can be sorted, (quantification of the outcome of the signal exchange measured by ELISA).

RT-PCR: reverse transcriptase polymerase chain reaction (analysis of intermediate molecules, which are produced by genes as reaction to the toxic influences):
measures the activity of genes, to what extent they are used by a cell. The information about gene function (e.g. used against oxidative stress) and information about gene activity indicates cellular responses to certain stimuli. Can be used for any response to any stimulus.

Comet assay (by a special method by moving the cells through a carrier substance):
measures the integrity of DNA. The extent of DNA strand breaks, which derive from oxidizing agents, radiation, errors during the process of replication (due to inhibitory chemicals, severe metabolic distortions and many more) can be estimated.

TUNEL: measures how many DNA breaks occurred by labeling the resulting free ends by means of an optical method.

H2AX: is a histone, a protein around which DNA is wrapped in the nucleus, and is involved in the repair of double strand DNA breaks (DSBs). If DSBs are present, H2AX becomes phosphorylated - 'activated' – which can be detected and used as an estimate of the occurrence of DSBs.

Abbreviations:

LDH:	Lactate dehydrogenase
WST-1:	Water soluble Tetrazolium salt 1
ATP:	Adenosin triphosphat
MTT:	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
PI:	Propidium iodid
CCK-8:	Cell counting kit-8
GSH:	reduced glutathion, antioxidant molecule
ROS:	reactive oxygen species
NADPH:	Nicotinamid adenin dinucleotid phosphat
TNF-α:	Tumor necrosis factor-alpha
IL:	Interleukin
ELISA:	Enzyme linked immunosrbent assay
RT-PCR:	reverse transcriptase polymerase chain reaction
TUNEL:	Terminal dUTP nick end labeling (dUTP = deoxyuridine triphosphate)
EMSA:	Electrophoretic mobility shift assay
H2AX:	Histon 2A family, member X

Introduction in test methodologies and some biological processes

Gene expression and proteins

1) A certain signal acts on the promoter region of a target gene.
2) The signal activates the promoter, protein complexes are recruited which transcribe the gene (transcription = production of RNA from a DNA template). Depending on the gene and the signal, a certain lag time between the stimulus and the activation of the gene can be observed.
3) The mRNA is processed and transported out of the nucleus.
4) The mature mRNA is translated to a polypeptide by the action of ribosomes (translation = production of polypeptides from an mRNA template). Depending on the protein and the state of the cell, translation may not occur immediately.

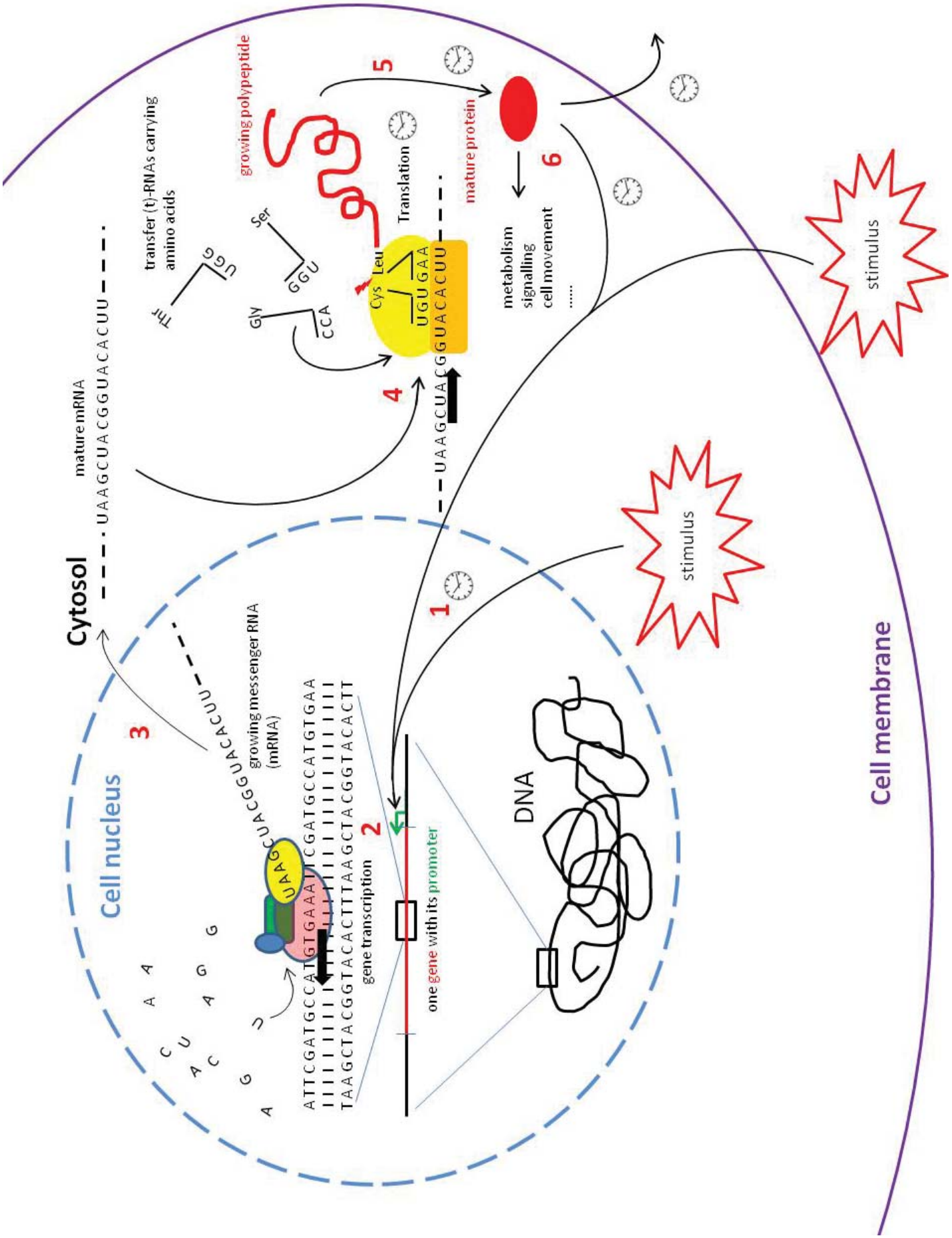
using real-time RT-PCR, we measure the amount of the mRNA of a specific gene relative to the amount of mRNA of a reference gene for which a change in expression has not to be expected upon the experimental treatment.

1) The polypeptide is processed and folded into the protein with the proper conformation. This also may take time.
2) The mature polypeptide exerts its biological action, which in many cases includes the regulation of its own production. Genetic responses are often delayed (depending on the function of the protein).

Proteins can be detected:

- By quantification of the biochemical action (enzymatic activity) of a given protein in a sample, by measuring the amount of the product of the chemical reaction the protein catalyzes. LDH is detected like this

    - By the use of specific antibodies which bind to the protein of interest. Chemical labels attached to the antibodies then allow quantification of how much of the protein is in a sample. This is basically how ELISA (enzyme linked immunosorbent assay) works, which we use for the quantification of TNF-a and IL-8


Cytosol
mature mRNA
U A A G C U A C G G U A C A C U U
transfer (t)-RNAs carrying amino acids
Thr
UGG
Ser
GGU
Gly
CCA
growing polypeptide
Cys
Leu
UGU GAA
Translation
mature protein
metabolism
signalling
cell movement
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stimulus
stimulus
Cell membrane
Cell nucleus
growing messenger RNA (mRNA)
gene transcription
one gene with its promoter
DNA
1
2
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6

Cytokines (TNF-a and IL-8)

Cytokines are small soluble proteins which are released by cells in order to communicate with other cells. When cytokines bind to specific receptors (also proteins) on the cell surface, the receptor triggers a signal cascade inside the cell, finally leading to changes in the gene expression patterns and the behaviour (e.g. movement) of the cell.

Tumor necrosis factor (TNF)-a is a pro-inflammatory cytokine. It is released by cells (most importantly macrophages) upon encountering various kinds of injury and foreign material (antigens). Binding of TNF-a to TNF-receptors on a cell induces (among others) inflammatory reactions which include the production and the release of other cytokines such as IL-8.

IL-8 is produced and released in response to binding of TNF-a to the TNF-receptor. It is a chemotactic factor, meaning that it attracts other cells (immune cells) to the site of injury or infection.

We measure the amount of released cytokine as well as the gene expression level of the two cytokines TNF-a and IL-8. Because mRNA processing, RNA translation , protein processing and release requires time, the proteins can be detected only a certain time after gene expression has started. Furthermore, since proteins are quite stable, they can still be detected after gene expression has stopped.

HMOX1 and SOD1

HMOX1 and SOD1 both are proteins involved in the defence against oxidative stress. The production of both proteins is induced by a large array of stimuli, including radiation, heat, mechanical stress, heavy metals and of course reactive oxygen species. Also nitric oxides are known to be important players. Polyaromatic hydrocarbons have been shown to act antagonizing on HMOX1 and SOD1 production.

SOD1 converts the superoxidide anion O_2^- to O_2 and H_20.

The action of HMOX1 relies in the cleavage of the biomolecule porphyrin, the products of which act anti-oxidative, anti-inflammatory and anti-apoptotic. Importantly, the production of HMOX1 is induced by inflammatory cytokines and HMOX1 induces the production of anti-inflammatory cytokines and represses the production of pro-inflammatory cytokines.

Apoptosis

Apoptosis = programmed cell death, a highly (genetically) regulated energy dependent process in which a cell undergoes a series of changes including for example the breakdown of proteins and DNA and the disintegration of the cell into multiple membrane-enclosed fragments.

This is in sharp contrast to what happens during necrosis. During necrosis, a cell is a passive victim and follows an energy independent mode of death. The cell disintegrates in an uncontrolled way, the cell membrane eventually disrupts, leading to the release of various factors into the surrounding tissue. This cell debris usually affects other cells and causes inflammation.

The biological roles of apoptosis include renewal and shaping of tissues (e.g. the tissue between the fingers is eliminated during the embryonal development via apoptosis), elimination of self-intolerant immune cells, and elimination of damaged and infected cells.

FAS is a protein which is released by cells that get into contact with cell that should be eliminated. On the surface of such cells, the FAS receptor (also a protein) is present. Binding of FAS to the receptor triggers a chain of signals within the cell which finally result in apoptosis. This apoptotic pathway is referred to as the extrinsic one.
Severly damaged cells can induce their own apoptosis by signals originating from intracellular components that detect metabolic imbalances, DNA damages, and regulatory defects. This pathway is referred to as the intrinsic induction of apoptosis.

The intracellular apoptotic signal cascades of both pathways involve a large array of proteins which translate the apoptotic stimulus into the execution of apoptosis. Caspases are the most prominent group of these proteins and their production is transiently up-regulated during certain stages of apoptosis (which is also true for FAS and the FAS receptor).

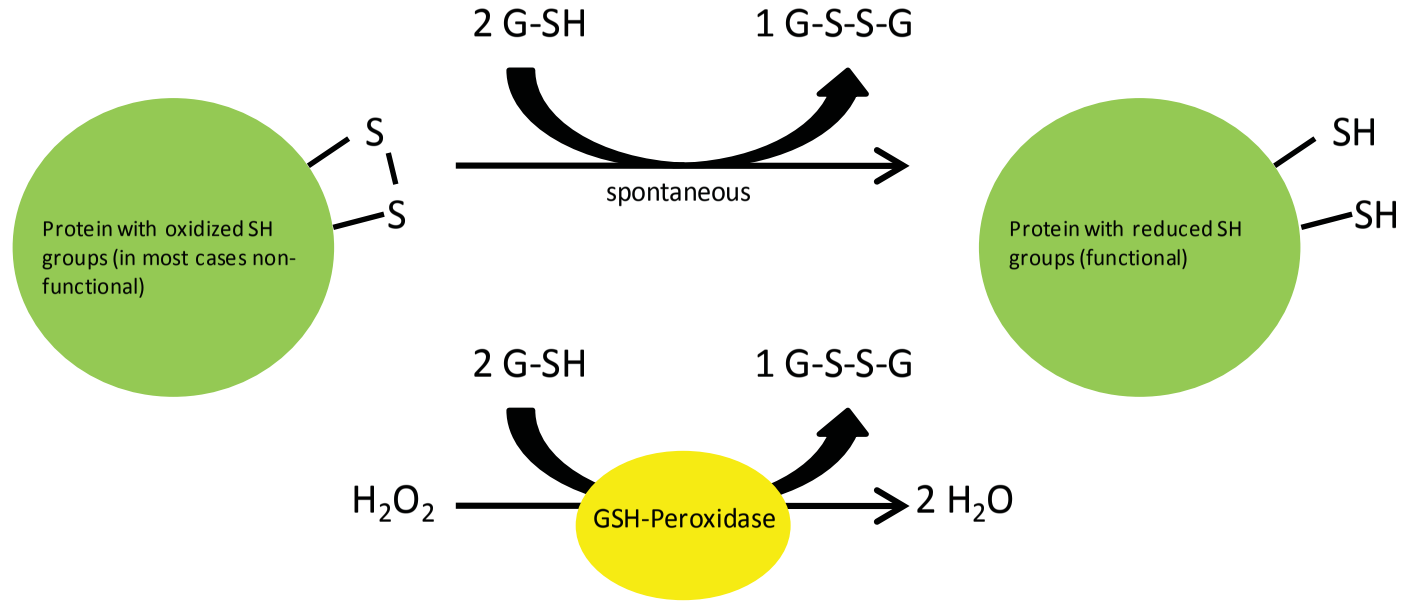
We measure apoptotic responses by real-time PCR and not on the protein level. Since the upregulation is only transient, it can happen that the peak of the expression of such pro-apoptotic genes is missed if samples are only taken at a certain time point.

Changes in the expression levels of CASPASE7 indicate an apoptotic (or anti-apoptotic) response independently on whether the intrinsic or the extrinsic pathway is active. When a change in FAS expression is detected as well, it must be assumed that the extrinsic pathway is active. No changes in FAS expression imply the activity of the intrinsic pathway.

GSH

Glutathion is a tripeptid, composed of the three amino acids glutamate, cystein and glycin.
The important feature of this molecule is the presence of a sulfhydryl (–SH) group in cystein
Its main functions are:

1) protection of SH groups in proteins from oxidation
2) detoxificatio of H_2O_2 (by the enzyme GSH-peroxidase)



The cellular pool of reduced GSH is continuously replenished by the action of the enzyme GSSG reductase. For this, NADPH (the cell's main reducing agent) is needed as an electron donor. Strongly oxidizing conditions may overburden the kinetics of GSH-peroxidase or may result in the depletion of the NADPH pool. Measurement of the concentration of reduced GSH gives a measure for how oxidative a cell experiences a certain condition.

LDH

Lactate dehydrogenase is a protein involved in the glucose metabolism and based on ist biochemical function has nothig to do with cytotoxicity. Under normal conditions, it is present in high amounts as a soluble protein in the cytosol.

Cytotoxic conditions affect the integrity of the cell membrane. This may happen directly (the cell membrane is damaged, for example by peroxidation of membrane lipids) and indirectly (the cellular membrane synthesis, maintenance and repair mechanisms are inhibitied).

LDH detection outside cell therefore gives a measure of the extent to which the membrane is damaged, which in turn is indicative for the the overall cytotoxicity of a certain treatment.

If a high LDH release is detected, it must be assumed that the cell is not able to show normal responses anymore. This is because damages in the cell membrane affect all regulatory mechanisms and the whole cellular homeostasis. Therfore, if high LDH release is observed, the cells should not be used for further endpoint measurements.

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REVIEW ARTICLE

Lung cancer and diesel exhaust: an updated critical review of the occupational epidemiology literature

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Abstract

A recent review concluded that the evidence from epidemiology studies was indeterminate and that additional studies were required to support the diesel exhaust-lung cancer hypothesis. This updated review includes seven recent studies. Two population-based studies concluded that significant exposure-response (E-R) trends between cumulative diesel exhaust and lung cancer were unlikely to be entirely explained by bias or confounding. Those studies have quality data on life-style risk factors, but do not allow definitive conclusions because of inconsistent E-R trends, qualitative exposure estimates and exposure misclassification (insufficient latency based on job title), and selection bias from low participation rates. Non-definitive results are consistent with the larger body of population studies. An NCI/NIOSH cohort mortality and nested case-control study of non-metal miners have some surrogate-based quantitative diesel exposure estimates (including highest exposure measured as respirable elemental carbon (REC) in the workplace) and smoking histories. The authors concluded that diesel exhaust may cause lung cancer. Nonetheless, the results are non-definitive because the conclusions are based on E-R patterns where high exposures were deleted to achieve significant results, where *a posteriori* adjustments were made to augment results, and where inappropriate adjustments were made for the "negative confounding" effects of smoking even though current smoking was not associated with diesel exposure and therefore could not be a confounder. Three cohort studies of bus drivers and truck drivers are in effect air pollution studies without estimates of diesel exhaust exposure and so are not sufficient for assessing the lung cancer-diesel exhaust hypothesis. Results from all occupational cohort studies with quantitative estimates of exposure have limitations, including weak and inconsistent E-R associations that could be explained by bias, confounding or chance, exposure misclassification, and often inadequate latency. In sum, the weight of evidence is considered inadequate to confirm the diesel-lung cancer hypothesis.

Keywords: Cumulative exposure, diesel exhaust, elemental carbon, epidemiology, exposure-response, latency, lung cancer, odds ratio

Abbreviations: CO_2, carbon dioxide; CO, carbon monoxide; COD, cause of death; COPD, chronic obstructive pulmonary disease; DE, diesel exhaust; DEMS, diesel exhaust in miners study; DME, diesel motor exhaust; DOC, diesel oxidation catalyst; EM, elemental carbon; E-R, exposure-response; HR, hazard ratio; HEI, Health Effects Institute; IH, industrial hygiene; IARC, International Agency for Research on Cancer; JEM, job exposure matrix; NCI/NIOSH, National Cancer Institute/National Institute of Occupational Safety and Health; NTP, national toxicology program; NO_2, nitrogen dioxide; NOx, nitrogen oxides; NMRD, nonmalignant respiratory disease; NTDE, non-traditional diesel exhaust; OR, odds ratio; PAHs, polynuclear aromatic hydrocarbons; REC, respirable elemental carbon; SES, socioeconomic status; SMR, standardized mortality ratio; TDE, traditional diesel exhaust; TB, tuberculosis; UG, underground

Table of Contents

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Results from the case-control study (Silverman et al, 2012) are considered the most relevant for evaluating the diesel-lung cancer hypothesis and assessing the weight of evidence. These results are adjusted for smoking and other potential confounders. Primary analyses included all cases and controls without exclusion based on tenure or restriction of exposure. The authors' concluded that DE increases the risk of lung cancer with significant E-R trends. The study is large with 198 cases with well-defined time of initial DE exposure and adequate latency.

Exposure assessment results are uncertain, however, and have not been replicable. REC exposure is based on extrapolations from HP to CO to REC where the correlations are low, variable, and not linear based on independent analyses; and the CO data are of questionable precision with such a high proportion of non-detectable samples. Uncertainty in the exposure estimates raises questions about the pattern of E-R trends and detracts from the reliability of reported E-R associations. Exposure assessment results need further analyses and independent confirmation to assure reliability.

Significant E-R associations are found only with 15-year lagged REC cumulative exposure. There are no biological gradients based on crude unadjusted ORs. Adjustments for potential confounding effects of smoking are implausible. Smoking does not appear to be confounder based on the apparent lack of association with REC exposure. Smoking adjustments may be inappropriate based on the authors' citation of inappropriate comparisons of smoking prevalence in high versus low exposed tertiles for UG workers instead of for all cases and controls, and on the implausibly large effects of adjusting for potential confounders. Results are considered indefinite until these questions are resolved.

Overall weight of evidence

The weight of evidence from these studies is not definitive and is inadequate to conclude that workplace exposure to TDE increases the risk of lung cancer. E-R trends tend to be weakly positive which may be suggestive of causal associations. However, close inspection of these trends indicates potential biases or hidden limitations that complicate interpretation. These include such factors as:

(i) Adjustments for smoking may produce an apparent "negative confounding" effect that biases E-R trends because current smoking was not associated with DE exposure, and therefore was not a confounder (Silverman et al., 2012; Attfield et al., 2012). Thus, confirmation of the 'true' relationship by independent investigators is required.

(ii) Sometimes there is a sharp increased risk that remains at the same level even as DE exposure increases. That is, there may be a plateau of increased risk at higher exposures but no apparent E-R trend (Laden and al 2006; Attfield et al., 2012; Silverman et al., 2012).

(iii) In the German potash worker cohort there is a significant overall deficit in lung cancer mortality and the estimated SMR in the referent group is even lower. The observed E-R trend may be due to an inadequate referent group, and it is the unusually low lung cancer mortality rate in that group that produces the trend (Neumeyer-Gromen et al., 2009). Some potash miners had worked in uranium mines, and when this hazardous employment was adjusted for, statistical significance disappeared (Möhner 2012)

(iv) In the UK Study, inclusion of all coal mines showed a statistically significant E-R trend that was produced by one pit that had much higher exposures but only slightly higher mortality. Omission of this pit produced inverse E-R trends. The authors suggest a possible regional effect (Johnston et al., 1997).

(v) One of the strongest E-R trends is among the least biologically plausible workers due to the relatively low DE exposures of Teamsters (Steenland et al., 1998).

(vi) The strength of associations is with RRs less than 2.0 at the highest exposure levels. E-R trends tend to be positive but do not provide consistent or convincing evidence of clear associations with DE exposure because the results could be due to chance or residual confounding when there is a possible trend.

We conclude that the DEMS results are indeterminate because of numerous inconsistencies and unanswered questions. More definitive conclusions must await responses from the authors and independent analyses to address the multiple limitations that have been noted.

Overall, in these occupational cohort studies with the better estimates of DE exposure and adjustments for smoking, the weight of evidence remains inadequate to conclude that there is a causal association between DE exposures and lung cancer. As a result, the epidemiological evidence remains indeterminate regarding the association between traditional diesel exhaust and risks of lung cancer.

10. Overall conclusions

The publication of recent meta-analyses, cohort studies, and case-control studies relating to the possible association of occupational exposures to diesel exhaust and an increased incidence of lung cancer has raised the question whether the available epidemiological evidence is different from what the International Agency for Research on Cancer (IARC) determined it to be in 1989 – "limited." IARC's conclusion in 1989 (IARC 1989) regarding the limited nature of the available epidemiological data was echoed by the U.S. EPA in its 2002 Health Assessment Document (EPA 2002) and by the Health Effects Institute, both of which noted significant uncertainties in the underlying exposure-response (E-R) relationships, uncertainties that precluded the derivation of any confident quantitative estimate of cancer risk.

This review paper examined in detail the seven recent epidemiology studies that have been published since the

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data of our prior review (Gamble 2010). Those seven studies are: Birdsey et al., 2010; Merlo et al., 2010; Petersen et al., 2010; Olsson et al., 2011; and Villeneuve et al., 2011 (collectively, the "population and pooled analyses"); and Attfield et al., 2012; and Silverman et al., 2012 (collectively, the "Diesel Exhaust in Miners Study" or "DEMS"). As detailed in our critical review, neither the results of the population and pooled analyses nor the DEMS results (which include a cohort and case-control study) are sufficient to change the conclusion that the available epidemiological data base is inadequate to support a definitive causal association between occupational exposures to diesel engine exhaust and increased risks for lung cancer.

More specifically, the population and pooled analyses suffer from inherent defects in job groupings and exposure estimations, insufficient latency periods, inconsistent *a posteriori* sub-analyses based on cell type, non-significant E-R trends after adjustment for potential cofounders, and failures to adjust for the rates of dieselization or for the evolution of diesel engines and fuels (and thus exposure levels) over time.

The DEMS results are similarly questionable. For the entire cohort, surface workers had higher SMRs than underground miners even though the underground miners' estimated exposures to diesel emissions were 75 times higher than those for surface workers.

Exposure estimates are based on presumed correlations between estimated CO emissions from diesel engines and estimated PM emissions (the marker for respirable elemental carbon). It was further assumed that estimated CO emission levels could be derived from estimates of engine horsepower and mine ventilation rates. None of those assumptions is robust or supported by the available data or literature.

In addition, what many appear to have glossed over is the fact that based on the study's *a priori* analyses, DEMS cohort was a negative study: **"Initial (i.e., a priori defined) analyses from the complete cohort did not reveal a clear relationship of lung cancer mortality with DE exposure.** The hazard ratios (HRs) for the upper three quartiles of cumulative REC exposure were all less than 1.0." [Bold added.]

Faced with these negative results, the DEMS authors moved to sub-analyses based on worker location. But even then, the results obtained were counter-intuitive. This led to still more sub-analyses of the underground workers only. In those additional analyses, the most significant E-R results were premised entirely on what appear to be unjustified *a posteriori* truncations of the data, including: exposure levels were arbitrarily cut off at 1280 $\mu g/m^3$ year to eliminate an apparent leveling-off or plateauing of any response; a 15-year lag was added to improve the "fit" of the model; an additional minimum 5-year tenure of underground work was added for the highlighted sub-analyses, again to enhance the calculated hazard ratios.

In the case-control study a "negative" confounding effect of smoking was observed in UG workers. Adjustments for purported confounding from smoking in the complete cohort of cases and controls produced a similar "negative confounding" effect to that observed in UG workers. This appears to be an incorrect adjustment for confounding as current smoking is not associated with DE exposure, so smoking cannot be a confounder, and if "confounding" adjustments are made the effect should be negligible. The effect of the unjustified adjustments for current smoking produced spuriously elevated ORs that were incorrectly attributed to DE exposure. The slope of E-R trends using crude ORs are flat, similar to initial results from the cohort study, and are suggestive of inconclusive E-R trends and potentially no association of lung cancer and DE exposure in this study population. Case-control results also do not allow a definitive regarding the association of lung cancer and DE in the DEMS studies.

In sum, the recent publication of new epidemiology studies has not altered the state of the epidemiological data base to the point where the epidemiological data can be deemed sufficient to support a definitive causal association between occupational exposures to diesel engine exhaust and an increased risk of lung cancer. To the contrary, the evidence remains "limited" and inconclusive.

In sum, the evidence is inadequate to adequately test the diesel-lung cancer hypothesis for potential effects of TDE or transitional diesel exhaust on humans.

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Declaration of interest

John Gamble helped prepare this review during the normal course of his work as an independent consultant with financial support from CONCAWE (CONservation of Clean Air and Water in Europe), a European trade association of oil companies working on environmental, health, and safety issues in refining and distribution. CONCAWE has nominated him as an industry observer for the IARC (International Agency for Research on Cancer) Monograph 105 Working Group Meeting June 5-12, 2012. The IARC Monograph is focused on diesel and gasoline engine exhaust. He also received financial support from CONCAWE for preparation of a previous review of diesel exhaust and lung cancer published in Critical Reviews in Toxicology in 2010. He retired from ExxonMobil Biomedical Sciences, Inc (EMBSI) in 2005.

Mark Nicolich is an independent consultant and helped prepare this review during the normal course of work with financial support from CONCAWE (CONservation of Clean Air and Water in Europe), a European trade association of oil companies working on environment, health,

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and safety issues in refining and distribution. He has not previously published any work concerning diesels engine exhaust. He was previously employed by ExxonMobil Biomedical Sciences, Inc (EMBSI).

Paolo Boffetta worked on this review as a consultant to the Mining Awareness Resource Group (MARG). He has been the principal investigator of several epidemiologic studies of diesel exhaust exposure and cancer. MARG is a coalition of mining companies and engine manufacturers and now includes FMC Wyoming, Tata Minerals, Morton Salt, Cargill Deicing, Mosaic Potash, Detroit Salt and Navistar. Two of the papers reviewed were prepared by scientists with the National Cancer Institute and the National Institute of Occupational Safety and Health and are the subject of litigation involving MARG (Case No. 11-30812, currently pending in the United State Court of Appeals for the Fifth Circuit).

This review was conducted independently by the authors and the interpretations and opinions offered are solely those of the authors and do not necessarily represent the views of CONCAWE, MARG or any other public or private clients of the authors.

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Original Contribution

Exposure to Diesel and Gasoline Engine Emissions and the Risk of Lung Cancer

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Pollution from motor vehicles constitutes a major environmental health problem. The present paper describes associations between diesel and gasoline engine emissions and lung cancer, as evidenced in a 1979–1985 population-based case-control study in Montreal, Canada. Cases were 857 male lung cancer patients. Controls were 533 population controls and 1,349 patients with other cancer types. Subjects were interviewed to obtain a detailed lifetime job history and relevant data on potential confounders. Industrial hygienists translated each job description into indices of exposure to several agents, including engine emissions. There was no evidence of excess risks of lung cancer with exposure to gasoline exhaust. For diesel engine emissions, results differed by control group. When cancer controls were considered, there was no excess risk. When population controls were studied, the odds ratios, after adjustments for potential confounders, were 1.2 (95% confidence interval: 0.8, 1.8) for any exposure and 1.6 (95% confidence interval: 0.9, 2.8) for substantial exposure. Confidence intervals between risk estimates derived from the two control groups overlapped considerably. These results provide some limited support for the hypothesis of an excess lung cancer risk due to diesel exhaust but no support for an increase in risk due to gasoline exhaust.

case-control studies; environmental pollutants; gasoline; lung neoplasms; motor vehicles; occupational exposure; vehicle emissions

Pollution from motor vehicles constitutes one of the most ubiquitous environmental health problems of our era (1, 2). There has been increasing recognition, based in part on studies of workers exposed to diesel engine emissions, that such exposure may be carcinogenic to humans (3–12). However, drawing inferences regarding effects of diesel exhaust is difficult because of methodological limitations and the indirect nature of the evidence. Namely, most studies have used job titles (such as truck driver or railroad worker) as proxies for occupational exposure to diesel exhaust, but job titles can be misleading (13). Few studies were able to control for the potential confounding effect of the most powerful risk factor for lung cancer, cigarette smoking, and of other occupational exposures such as asbestos. Many of the studies had low statistical power. The number of diesel-powered vehicles is increasing in many countries. Given the significant scientific and public policy implications (14, 15), it is important to derive more definitive inferences regarding the potential human carcinogenicity of diesel emissions.

Because of the predominant role of gasoline as a motor vehicle fuel, the effects of gasoline engine emissions are potentially an even greater problem. However, there has been less research on possible carcinogenic effects of gasoline exhaust than on diesel exhaust. The purpose of this paper is to present epidemiologic evidence on the lung carcinogenic effects of diesel and gasoline engine emissions from a unique data set in which both of these substances could be measured and their effects contrasted.

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elevated, as it was in several of the subgroups examined. The increases were of borderline statistical significance and were higher for men exposed at high concentration levels. When cancer controls were studied, the only increased risk was seen in the high concentration subgroup. The association with diesel exhaust was strongest for squamous cell tumors, a pattern similar to that for cigarette smoking (35). Moreover, we observed elevated risks with diesel exhaust exposure for both smokers and nonsmokers. The increased risk was not concentrated in any particular diesel-exposed occupation. These findings, although not persuasive by themselves, nevertheless support other epidemiologic and experimental findings.

There is convincing evidence that chronic exposure to a high concentration of whole diesel engine exhaust causes lung tumors in rats, whereas results for other rodent species have been mixed (32). The relevance of these toxicologic results for human exposure in most general and occupational environments is questionable (4). Carcinogenicity of diesel exhaust is hypothesized to originate from mutagenic and carcinogenic organic compounds adsorbed to the particles or from an overloading of particle clearance from the lung by macrophages, resulting in chronic inflammation, cell proliferation, and lung tumors (36).

Considerable epidemiologic data have accumulated on lung cancer risk in some occupations presumed to entail exposure to diesel emissions, such as railroad workers, miners, heavy-equipment operators, truck drivers, bus drivers, and vehicle and truck mechanics (3, 5, 7, 37–53). Several studies, including meta-analyses (10, 54), support the notion that these jobs are associated with an excess risk of lung cancer.

Our results are also in line with the positive associations reported in most studies that assessed diesel exhaust exposure per se by using either self-reports (50, 55), a job-exposure matrix (56), expert ratings (57–60), or indices based on fuel and equipment use (61). Previous null findings may have resulted from errors in self-reported exposure (62, 63) or from low exposure levels (64).

If diesel exhaust is carcinogenic and operates through a mechanism similar to that of tobacco smoke, then one would expect their joint effect to be additive (65). In fact, the joint effect was close to additive in our data. This finding is compatible with most (57) but not all (66) previous results on the joint effects of smoking and urban air pollution on lung cancer.

While the evidence on diesel exhaust and lung cancer remains controversial (14, 25, 67–70), there is increasing evidence in favor of the hypothesis. However, there are still few data on the quantitative aspects of the diesel exhaust–lung cancer relation. What the relative risk might be at the low levels found in the general population remains speculative. Indeed, recall that the workers who we considered ''unexposed'' were in fact exposed to general environmental levels; if such levels in fact carry some excess risk of lung cancer, then our estimates would have underestimated the relative risks compared with a truly unexposed population. Nonetheless, given the complex nature of urban air pollution from diverse mobile and stationary sources, it is unlikely that epidemiologic methods alone will suffice to quantify the relative magnitude of the effects of specific causal components (71). In conclusion, results from this study provide some limited support for the hypothesis of an excess lung cancer risk due to diesel exhaust but no support for an increase in risk due to gasoline exhaust.

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The fieldwork was supervised by Lesley Richardson, and the chemical coding was carried out by Dr. Michel Gerin, Dr. Louise Nadon, Denis Begin, and Ramzan Lakhani.

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APPENDIX

The exposure coding in this study was based on not only the occupational codes that workers may be ascribed but also the unique characteristics of the job as related by the worker himself. To illustrate this point, consider four workers who were motor vehicle mechanics and who were all given the same 7-digit code (8581-110) according to the *Canadian Classification and Dictionary of Occupations* (1971 edition) (72). This 7-digit code applies to workers who repair automobiles, buses, and trucks.

Job 1: This mechanic worked from 1975 to 1984 in a big garage in which 12 mechanics worked on as many as 30 trucks at the same time. In this workplace, there was no venting of engine emissions to the outside. Our team attributed a high confidence score that exposure to diesel exhaust had occurred in this job, that the frequency of exposure was high (e.g., over 30 percent of the workday), and that the exposure concentration would have been high (compared with other jobs in our study).

Job 2: This mechanic worked from 1973 to 1979 in a big garage in which 10 mechanics worked on trucks. There was a policy of venting engine emissions to the outdoors by means of hoses attached to the exhaust pipes. However, the worker reported that there were nevertheless fumes in the garage because the exhaust hoses frequently leaked. Accordingly, our team attributed high confidence and high frequency of exposure to diesel exhaust to this job; however, the concentration was coded as medium rather than high because of the partial venting of fumes.

Job 3: This truck mechanic worked from 1953 to 1965 in a small truck garage that could handle four trucks and in which four mechanics worked at a time. This mechanic indicated that he worked exclusively on gasoline-powered trucks, and, given our knowledge of local conditions in that era, this was quite plausible. However, our experts had sufficient doubt about whether all of the mechanics in the garage would have worked on only gasoline-powered trucks that they coded exposure to diesel exhaust for this worker, but with a low confidence level. This worker's exposure to diesel exhaust would have been sporadic and quite indirect. He was given a frequency code of medium and a concentration code of low.

Job 4: This mechanic worked from 1960 to 1969 in a garage that repaired only automobiles. He was not assigned diesel exhaust exposure at all.

These examples illustrate that exposures were not attributed automatically according to job title. Rather, our experts evaluated the idiosyncratic nature of each job.

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Exposure to Diesel Motor Exhaust and Lung Cancer Risk in a Pooled Analysis from Case-Control Studies in Europe and Canada

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***Rationale*: Diesel motor exhaust is classified by the International Agency for Research on Cancer as probably carcinogenic to humans. The epidemiologic evidence is evaluated as limited because most studies lack adequate control for potential confounders and only a few studies have reported on exposure–response relationships.**

***Objectives*: Investigate lung cancer risk associated with occupational exposure to diesel motor exhaust, while controlling for potential confounders.**

***Methods*: The SYNERGY project pooled information on lifetime work histories and tobacco smoking from 13,304 cases and 16,282 controls from 11 case–control studies conducted in Europe and Canada. A general population job exposure matrix based on ISCO-68 occupational codes, assigning no, low, or high exposure to diesel motor exhaust, was applied to determine level of exposure.**

***Measurements and Main Results*: Odds ratios of lung cancer and 95% confidence intervals were estimated by unconditional logistic regression, adjusted for age, sex, study, ever-employment in an occupation with established lung cancer risk, cigarette pack-years, and time-since-quitting smoking. Cumulative diesel exposure was associated with an increased lung cancer risk highest quartile versus unexposed (odds ratio 1.31; 95% confidence interval, 1.19–1.43), and a significant exposure–response relationship (P value < 0.01). Corresponding effect estimates were similar in workers never employed in occupations with established lung cancer risk, and in women and never-smokers, although not statistically significant.**

***Conclusions*: Our results show a consistent association between occupational exposure to diesel motor exhaust and increased risk of lung cancer. This association is unlikely explained by bias or confounding, which we addressed by adjusted models and subgroup analyses.**

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Diesel motor exhaust is currently classified as a probable lung carcinogen.

What This Study Adds to the Field

Our results from a very large pooled study show a small, consistent association between occupational exposure to diesel motor exhaust and lung cancer, after adjusting for potential confounders, such as smoking and other occupational exposures. The effect is similar for non–small cell and small cell lung carcinoma.

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Keywords: epidemiologic studies; lung neoplasm; occupational exposure; vehicle emissions

Diesel motor exhaust (DME) consists of a complex mixture of components in gas or particulate form. The particulates are mainly composed of cores of elemental carbon; traces of metallic compounds; and adsorbed organic materials including aromatic hydrocarbons, polycyclic aromatic hydrocarbons, aldehydes, and nitrogen oxides (1, 2). The composition of DME

the use of diesel engines over time, and it was not possible to estimate absolute concentration levels for DME.

Our results reflect the effects of the DME exposure present before and up to the time when the studies were conducted. Modern engine emissions have become cleaner in the last 20 years (e.g., by the use of low-sulfur fuel and particle traps on vehicles) (35). However, the number of emitted particles may still be high and the consequences on the potential carcinogenicity are not clear. In addition, old types of engines and other sources of DME (e.g., ships, generators, diesel powered tools, paving equipment, and so forth) continue to lead to DME exposure; our results suggest that DME exposure may contribute to the current lung cancer burden.

Conclusions

Our results show a small consistent association between occupational exposure to DME and lung cancer risk, and significant exposure–response trends. When the exposure score was categorized in quartiles, the OR associated with the highest quartile was statistically significant. This association is unlikely to be entirely explained by bias or confounding, which we addressed by adjusted models and analyses in subgroups not exposed to potential confounders. Cohort studies among heavily exposed occupations with quantitative exposure measurements may shed further light on the risk assessment.

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Occupational exposure to diesel engine emissions and risk of lung cancer: evidence from two case-control studies in Montreal, Canada.

Pintos J, Parent ME, Richardson L, Siemiatycki J.

Unit of Population Health, Centre de recherche du CHUM, Université de Montréal, Montreal, Quebec, Canada.

Abstract

OBJECTIVE: To examine the risk of lung cancer among men associated with exposure to diesel engine emissions incurred in a wide range of occupations and industries.

METHODOLOGY: 2 population-based lung cancer case-control studies were conducted in Montreal. Study I (1979-1986) comprised 857 cases and 533 population controls; study II (1996-2001) comprised 736 cases and 894 population controls. A detailed job history was obtained, from which we inferred lifetime occupational exposure to 294 agents, including diesel engine emissions. ORs were estimated for each study and in the pooled data set, adjusting for socio-demographic factors, smoking history and selected occupational carcinogens. While it proved impossible to retrospectively estimate absolute exposure concentrations, there were estimates and analyses by relative measures of cumulative exposure.

RESULTS: Increased risks of lung cancer were found in both studies. The pooled analysis showed an OR of lung cancer associated with substantial exposure to diesel exhaust of 1.80 (95% CI 1.3 to 2.6). The risk associated with substantial exposure was higher for squamous cell carcinomas (OR 2.09; 95% CI 1.3 to 3.2) than other histological types. Joint effects between diesel exhaust exposure and tobacco smoking are compatible with a multiplicative synergistic effect.

DISCUSSION: Our findings provide further evidence supporting a causal link between diesel engine emissions and risk of lung cancer. The risk is stronger for the development of squamous cell carcinomas than for small cell tumours or adenocarcinomas.

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The policy relevance of wear emissions from road transport, now and in the future

Workshop report

Date	May 2012
Author(s)	H.A.C. Denier van der Gon, PhD, M. Jozwicka, MSc (TNO) F.R. Cassee, PhD and M.E. Gerlofs-Nijland, MSc (RIVM)
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The policy relevance of wear emissions from road transport, now and in the future

An International workshop

Amsterdam, 22 June 2011

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Contents

SWISS SAPALDIA Study & Health Institutes

The SAPALDIA cohort study
http://www.sapaldia.net/en/

SAPALDIA (Swiss study on Air Pollution and Lung Disease in adults) is a cohort study in the Swiss population, which studies the effects of air pollution on the respiratory and cardiovascular health in adults. The SAPALDIA study (Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults) is a multi-center study in eight geographic areas representing the range of environmental, meteorological and socio-demographic conditions of Switzerland.

It was initiated in 1991 (SAPALDIA 1) with a follow-up assessment in 2002 (SAPALDIA 2). This study has allowed to assess 1) prevalence and development of major respiratory and allergic symptoms and diseases and the age-related decline in lung function, 2) the distribution of heart rate variability in the general population over age 50, 3) the association of these health indicators with individual long term exposure to air pollution, other toxic inhalants, life style and molecular factors.

The WHO and the European Research authorities have acknowledged the importance of SAPALDIA as one of the very few population-based adult cohort studies in Europe. It is well positioned to address crucial questions of air pollution epidemiology and important environmental health policy-related questions in the coming years.

When SAPALDIA was initiated in 1991, 9'651 subjects, aged 18 to 60 years, were recruited for a detailed computer-based interview and more than 90% of them underwent lung function and atopy testing. More than 7'000 of the subjects had bronchial reactivity tested by a methacholine challenge. SAPALDIA shares parts of its study protocol with the European Community Respiratory Health Survey (ECRHS) with which it is linked through the study center of Basel.

Since 1991 SAPALDIA has been carefully following address histories of its participants. In the 2002 follow-up, 8'047 (83%) provided health information, 6'528 persons underwent physical re-examination, and 6'345 provided blood samples to establish an extensive blood, plasma, serum and DNA bank. In addition, 1'813 subjects aged 50 or older participated in 24h-ECG Holter monitoring to provide detailed data on parameters of heart rate variability. With the inclusion of cardiovascular endpoints, SAPALDIA is one of the first studies examining effects from long-term exposure to air pollution on cardiovascular health parameters as well as mutual influence between the respiratory and the cardiovascular system.

The SAPALDIA bio-bank has allowed scientific publications on the association between some genetic profiles (gene polymorphism) and the propensity to develop asthma, allergic diseases, or accelerated lung function decline with age. Ongoing studies are focusing on gene-environment interactions a crucial question to understand why some persons suffer more from the effect of air pollution than others.

Swiss Tropical and Public Health Institute (TPH)

Department: Epidemiology and Public Health

Unit: Environmental Exposures and Health

http://www.swisstph.ch

The department of Epidemiology and Public Health (EPH) develops and applies advanced epidemiological, biostatistical and modelling methods to advance innovation, validation, and application in the field of public health. Through our focus on designated research topics and interdisciplinary collaborations within and across groups, units and other Swiss TPH departments, EPH contributes to health and policy making worldwide, especially in Switzerland, Europe, and low- and middle-income countries in Africa and Asia. Our activities focus on the distribution of diseases, the environmental, ecological, social, gender and molecular contexts of health and illness, the effectiveness of interventions and health systems, and patterns of access to and use of health services. Strategic priorities include the long-term follow up of large national and international cohorts; integrated analyses of health databases with social, cultural, environmental, molecular and genetic information (biobanking); and modelling and mapping diseases and exposures.

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Research Topics

We focus on a range of methods linking diseases, environmental and ecological, genetic and biological, and socio-cultural factors, life styles, and health systems to efficiently approach public health and prevention.

Institute for Work and Health

http://www.i-s-t.ch/en

Affiliated to the universities of Lausanne and Geneva, IST (Institut universitaire romand de Santé au Travail, Institute for Work and Health) is a foundation under private law, mainly supported by the cantons of Vaud and Geneva. Its mission is teaching, research, assessment and consultancy as well as promotion in the field of occupational health. IST has no inspection or monitoring function; it only acts as a consultant or expert in the field.

Lists of publications can be found under the given internet addresses.

BioToxDi/EngToxDi

Progress Report, October 2012

Sandro Steiner
Adolphe Merkle Institute
University of Fribourg

Abstract

The aim of the research project BioToxDi/EngToxDi is to gain insight into how the toxicity of diesel engine emissions is influenced by exhaust after-treatment systems such as a diesel particle filter (DPF) and oxidative catalysts, different fuel types (e.g. biodiesel), different lubrication oils (differing in the amount and kind of additives they contain) and fuel additives. The experimental approach is to compare the toxicity measured for exhaust produced under defined reference engine settings to the toxicity measured for exhaust that for example passed through a DPF or was produced using biodiesel. The project focusses on the toxicity of emissions produced in urban centers, therefore a passenger diesel car, in its technology comparable to a large fraction of the current diesel vehicle fleet in Switzerland, is used a test vehicle. Since the respiratory tract is the main site of interaction between air pollution and the human body, an *in vitro* model of the human epithelial airway barrier serves as a biological test system. BioToxDi/EngToxDi is a collaboration between the Bern University of Applied Sciences (AFHB), the Adolphe Merkle Institute at the University of Fribourg (AMI), the Paul Scherrer Institute (PSI) Villigen, the Swiss Federal Laboratories for Materials Science and Technology (EMPA) in Dübendorf and the Skobeltsyn Institute of Nuclear Physics at the Moscow State University (SINP). As major partners, AFHB provides technical know-how as well as the test vehicle, the exposure system and the location for the exposure experiments and AMI provides the biological and toxicological know-how and the necessary biological laboratories. The PSI, EMPA and SINP provide knowledge about exhaust chemistry and atmospheric chemistry and perform detailed chemical analyses of collected exhaust fractions. PSI further provides an exhaust aging chamber needed for experiments with aged exhaust samples.

Project outline

As depicted in Table 1, the project is made up of five basic work packages. In a first step (work package 0), a baseline exposure setting is defined and the resulting baseline toxicity is measured.
Further exposure experiments (comprised in work packages 1, 2 and 4), in each of which a single parameter of the baseline engine-setting is changed, allow estimating how exhaust toxicity is influenced by such interventions. According to the original project matrix, these intervention include the installation of a low oxidative potential diesel particle filter (lox-DPF), the use of alternative fuels (100% rapeseed methyl-ester (RME, B100) and a blend of 20% RME in baseline diesel (B20)), the use of low- and zero SAPS lubrication oils, the artificial addition of NO_2 (50ppm) to the exhaust, the aging of the exhaust within a mobile aging chamber (newly developed by the PSI) and the use of a catalytically active diesel additive (fuel-borne catalyst (FBC)).
Work package 3 is reserved for repetitions, cross-combinations and new tasks and its content depends on the outcome of previous experiments.
In parallel to each exposure experiment, diesel exhaust particles (DEPs) are collected on PallFlex filters and will later be used for detailed chemical analysis and for genotoxicity studies.

Table 1: Project matrix listing the major exposure experiments

work package 0: September-December 2010					
evaluation of the optimal experimental settings					
fuel	**lube oil**	**DPF**	**NO2**	**FBC**	**aging**
B0	high	---	---	---	---
work package 1: January-November 2011					
fuel	**lube oil**	**DPF**	**NO2**	**FBC**	**aging**
B0	high	yes	---	---	---
B20	high	---	---	---	---
B100	high	---	---	---	---
B0	low	---	---	---	---
B0	zero	---	---	---	---
work package 2: December 2011					
fuel	**lube oil**	**DPF**	**NO2**	**FBC**	**aging**
B0	high	---	yes	---	---
work package 3: January-December 2012					
Repetitions, cross-combinations, new tasks					
fuel	**lube oil**	**DPF**	**NO2**	**FBC**	**aging**
B20/B100	high	-	-	-	-
B0	high	-	yes	-	-
B0	DEA 2%	-	-	-	-
B0	high 2%	-	-	-	-
work package 4: August-December 2012					
fuel	**lube oil**	**DPF**	**NO2**	**FBC**	**aging**
B0	high	---	---	---	yes
B0	high	---	---	yes	

Experimental procedure

Test vehicle and vehicle settings: As a test vehicle an Opel Astra X20DTL (registration date 1998, running on a dynamometer at a constant velocity of 35 km/hr (corresponding to an engine speed 2180rpm) with a force of 66N at the wheel) is used. Under baseline settings, the vehicle is operated with low sulfur diesel (>10mg sulfur/kg, Greenergy SA) and the recommended lubrication oil (V10.237, Motorex) all pre-installed parts of the exhaust after-treatment system have been removed.
Biological system: A triple-cell co-culture is used (Figure 1, described in Blank et al. 2007, Steiner et al. 2012), which in its architecture simulates the three dimensional structure of the human airway epithelium.

Exposure system: The exposure experiments are conducted using a well-established exhaust exposure system (Figure 2, described in Müller 2010). It is located in the laboratory for IC-engines and exhaust gas control of the Bern University for Applied Sciences in Nidau, where also the experiments take place. Exhaust samples can be taken directly at the tailpipe, diluted with any gaseous matrix to a ratio of choice and brought to the cell cultures with a delay ranging from 30 seconds to a time period of choice. Throughout the exposure experiments, the composition of the diluted exhaust is monitored on-line (concentration of hydrocarbons (HC), carbon monoxide (CO), nitrogen oxides (NO_x), nitrogen monoxide (NO), and particle concentration). The conditions in the system are kept stable (37°C, 5% CO_2, and 80% relative humidity). The number of particles deposited in the exposure system and hence on the cell cultures is counted by transmission electron microscopy (TEM).

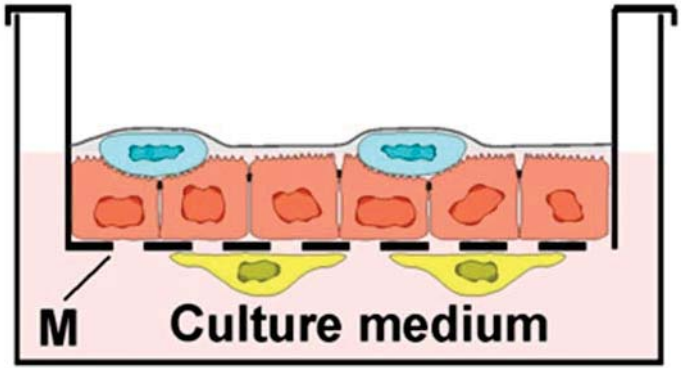

Figure 1 (adapted from Blank et al., 2007): A triple cell co-culture, simulating the structure of the human epithelial airway barrier. On the upper side of the supporting porous membrane (M), a confluent layer of epithelial cells is cultured (16HBE14o- cell line, orange), on top of which human peripheral blood derived macrophages are placed (blue). Human peripheral blood derived dendritic cells (yellow) are placed beneath the membrane. Only the dendritic cells and the epithelial cells are in direct contact with the culture medium, whereas macrophages and the apical side of the epithelial layer is in contact with the exhaust samples.

Exposure experiments: An individual engine setting is tested in four subsequent days, at the first of which (with a few exceptions) exposures under baseline settings are repeated followed by three days of exposure under the specified setting. For each experiment and dose, four sets of cell cultures are processed: i) an untreated control left in the incubator is needed to assure the integrity (health) of the cell cultures, ii) a positive control is needed to assure that the cell cultures are able to respond to a given stimulus, iii) a reference set which is exposed to a stream of filtered air, and iv) a fourth set which is exposed to a stream of exhaust samples (ten-fold diluted with filtered air). The cell cultures exposed to filtered air or exhaust are kept under identical conditions throughout the experiment and subtracting the biological responses detected upon filtered air exposure from the ones observed upon exhaust exposure therefore allows eliminating any non-exhaust related effects.

The triple cell co-cultures are exposed at the air-liquid interface for two hours (low dose) or six hours (high dose), followed by six hours post-incubation. Exhaust exposures as well as post-incubation takes place under constant conditions of 37°C, 5% CO_2, and 80% relative humidity. Following the post-incubation the cell cultures and the cell culture media are harvested and conserved in adequate ways to allow for later analysis of the biological responses.

Biological analysis: The analysis of the biological samples is conducted according to well established, standardized protocols (described in Steiner et al. 2012) and comprises the investigation of exhaust related effects towards cellular morphology (fluorescent microscopy), the induction of necrotic cell death (quantification of extracellular levels of the cytosolic protein lactate dehydrogenase (LDH)) and/or apoptotic cell death (measurement of the transcriptional activity of the two pro-apoptotic genes caspase7 (*CASP7*) and *FAS*), the induction of oxidative stress (quantification of the total cellular levels of the anti-oxidant molecule glutathione (GSH) and the according cellular responses (measurement of the transcriptional activity of the two oxidative stress responsive genes superoxide-dismutase 1 (*SOD1*) and heme-oxygenase 1 (*HMOX1*)), and the induction of inflammatory responses (measurement of the transcriptional activity of the two pro-inflammatory genes tumor necrosis factor (*TNF*) and interleukin-8 (*IL-8*) and quantification of the extracellular protein concentrations of their gene products (TNF-α and IL-8) into the cell-culture medium).

Figure 2: The exhaust exposure system, located at the Bern University for Applied Sciences in Nidau Prof. J. Czerwinskis lab. *A*) test vehicle, *B*) exhaus sampling, *C*) characterization of the particulate exhaust fraction *D*) cell exposure system.

Current state of the project

The exposure experiments of work packages 0-2 have been completed according to the project matrix. Up until now, during work package 3 a repetition of the lox-DPF, the B100, the B20 and the NO_2 experiments have been conducted and the analysis of the biological samples is completed. Repetitions were necessary in order to increase the robustness of the results and hence the possibility of high impact publication. In addition, new lube oil experiments have been designed in which 2% (v/v) lube oil without any additives (DEA) or the baseline oil (Motorex) were added to the fuel in order to simulate an engine with high oil consumption (~0.1L/100km). The exposure experiments have already been performed and the analysis of the biological samples is currently in progress.
Particles sampled on PallFlex filters during baseline, B20 and B100 exposures have been sent to the Institute of Nuclear Physics at the Moscow State University, where detailed analysis of their elemental composition and their surface chemistry is currently being performed in the group of Prof. Olga Popovicheva.
In parallel to the baseline experiments (work package 0), a side project investigating how a co-exposure of cerium dioxide nanoparticles influence the cellular response to diesel exhaust was included, and the results of this study have been published in Toxicology Letters in 2012 (Steiner et al. 2012). Publication of the lox-DPF, B20 and B100 results (work package 1) is currently in progress.

The data obtained in the low and zero SAPS experiments in work package 1 did not yield conclusive results, and because of the newly designed experiments in which the oil is added to the fuel, no repetitions are planned.

Results

General observations: The results obtained from work package 0 and the subsequent repetitions of exposure experiments under baseline settings revealed a high technical and biological reproducibility. This confirms that comparison of results obtained from exposures conducted under specific settings to results obtained under baseline settings is a valuable method to investigate how changes in the technical setting of a diesel engine influence the toxicity of the engine emissions.
Independently on the exposure setting and the dose, no changes in cellular morphology and no ruptures in the epithelial cell layer have been detected so far. Also, the assessment of necrotic and apoptotic cell death revealed no cytotoxicity and/or pro-apoptotic effects. It was rather found that diesel exhaust in general reduces the activity of pro-apoptotic gene expression, which can be interpreted as an anti-apoptotic effect. Because of relatively high levels of noise in the gene expression data for the pro-apoptotic genes however, this observation would have to be confirmed by further experiments in order to be considered as a fact.
Baseline settings: The results show a considerable level of GSH oxidation, indicative for the induction of severe oxidative stress. An increase in the transcriptional activity of oxidative stress-responsive genes could however, only be detected for *HMOX1*, but not for *SOD1*. Pro-inflammatory responses were observable for both assessed cytokines. *TNF* expression was increased upon high dose exposures only, whereas TNF-α secretion was increased by both doses, with a weak dose effect being detectable. It can be assumed that the genetic response to the low dose exposures was already terminated in the moment the cell cultures were harvested. *IL-8* expression but not IL-8 secretion was increased, with no dose effect being detected. The absence of an increased IL-8 secretion by simultaneous gene expression indicates that the production/secretion of the protein had not reached a detectable level in the moment the cells were harvested.
Lox-DPF: In comparison to the baseline settings, the introduction of a lox-DPF did not significantly change the chemical composition (CO, NO, NOx, HC) of the exhaust. Changes in the composition of the HC-fraction cannot be ruled out however. As expected based on the well-known high performance of modern DPFs, the particulate exhaust fraction was almost completely removed. Compared to the baseline exposures, exposures with lox-DPF filtered exhaust resulted in slightly lower levels of GSH oxidation. This effect appeared however, not be sufficient to be reflected in the transcriptional responses of *HMOX1* or *SOD1*, for both of which no significant difference between baseline and lox-DPF could be observed. Except for *TNF* expression, all assessed pro-inflammatory endpoints showed a significantly lower response upon exposure to lox-DPF filtered exhaust than upon exposure to baseline exhaust. It can be concluded that the removal of the particulate exhaust fraction is sufficient to suppress pro-inflammatory responses, at least in the case of short term exposure.
B20 and B100: Upon B20 exposures, a slightly lower level of GSH oxidation was measured compared to the baseline exposure, which is also reflected in the lower level of

transcriptional induction of *HMOX1*. The same is true for low dose B100 exposures, whereas the high dose B100 results are less conclusive. The transcriptional induction of *TNF* and *IL-8* is clearly lower upon B20 and low dose B100 exposure, whereas high dose B100 exposures resulted in comparable (*TNF*) or even higher (*IL-8*) induction of gene activity. The results of the measurement of the extracellular TNF-α and IL-8 concentrations are not in line with the gene expression data but rather imply the absence of an effect.
The particle concentration in the exhaust was comparable between B20 and baseline and for B100, a distinct peak of particles in the size range of 10-30nm not present in baseline exhaust was observed. In contrast, B20 and B100 resulted in considerably lower particle deposition in the exposure system and it has therefore to be assumed that B20/B100 exhaust contains a large number of semivolatile particles that are not detectable by TEM. It is reasonable to hypothesize that it is the smaller number of solid (non-volatile) particles on the cell cultures which is responsible for the observed difference in the biological responses to baseline and B20/B100 exhaust exposure.
Low/zero SAPS lubrication oil: No conclusive results could be obtained from these exposure experiments. For proper data interpretation, a higher number of experimental repetitions would be needed, however, since new experiments with lubrication oil were designed, no such repetitions will be conducted.
NO_2: A ten-fold increase of the NO_2 concentration in the diluted exhaust (50ppm) surprisingly resulted in lower levels of GSH oxidation and accordingly in lower levels of *HMOX1* expression compared to the baseline exposure. Pro-inflammatory responses were comparable to what was observed upon baseline exposure or even lower. This finding is surprising since it indicates a minor contribution of NO_2 to the overall exhaust toxicity.

Outlook

According to the project matrix (Table 1), as soon as the exhaust-aging and the FBC experiments have been performed, the main part of the project in which different engine settings are tested fort their effect on emission toxicity will be completed.
The exposure experiments with artificially aged diesel exhaust are scheduled for November or December 2012, the exact date being dependent on the availability of the exhaust aging system (provided by the PSI). The experiments with FBC additized fuel will take place in January-March 2013. Because the FBC will enduringly contaminate the engine (memory-effect) and hence cannot be performed until no other experiments are needed, the date for their realization depends on when the aging experiments can be performed and on whether additional exposures (repetitions) will be needed.
During the last six month of the project, in order to confirm the data obtained so far and to gain a more detailed picture of how diesel exhaust exposure influences cellular signalling, in depth analysis of genetic responses to the performed exposure experiments will be performed using the genetic material that has been isolated form the biological samples in the previous exposure experiments. This will be done using PCR arrays covering whole signaling pathways, i.e. the cellular responses to oxidative stress, pro-inflammatory responses, apoptotic responses and the activation of the cellular DNA repair machinery. For which engine settings these in depth analyses will be performed has not been decided yet.

Further, the mutagenic potential of the DEPs collected on PallFlex filters during the exposure experiments will be assessed using the comet assay and the Ames-test. Dichlormethane extracts, the DEPs denuded from the organic fraction and native DEPs, but also whole exhaust (using the exposure system) can be used for these studies. The aim of these experiments is to gain insight into the mutagenic potential of diesel exhaust particles and into which fraction of the particles is responsible for the mutagenicity. By comparing the results from the different fractions and the two experimental approaches, they also may contribute to answering the question whether or not the Ames-test is suitable for the assessment of particle-related mutagenicity

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Risk re-classified for carcinogenic everyday substance **6 August 2012**

Empa X-ray expert "decodes" diesel soot

Since June 2012, it is official: The World Health Organisation (WHO) has classified diesel soot as a lung carcinogen. Artur Braun, a physicist at Empa and an X-ray spectroscopy expert, has made crucial contributions to analyzing the structure and composition of soot particles.

Source: Flickr: «eutrophication&hypoxia»

Soot particles are dangerous – there is nothing new in this knowledge. But what is it that makes fine particulates dangerous? Is it only diesel soot from vehicle engines? Does the danger also come from wood-burning stoves in holiday chalets? Or even from grease-laden fryer fumes from the restaurant around the corner? For a long time, these questions have been a hard nut for science to crack. Indeed, fine soot particles were collected in filters and their chemical components were analysed. Yet the question remained: what precisely is the source of the danger? Is it the soot particles themselves that make people ill? Or is it toxic chemicals the soot carries with it – like a wet sponge?

Not all smoke is created equal

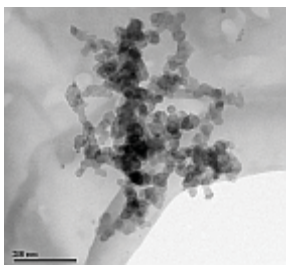
The Norwegian Institute of Public Health wanted to investigate this matter and asked Empa scientist Artur Braun for support. Before joining Empa, Braun had worked at the University of Kentucky and there, in 2002, he analyzed soot particles for the first time on a synchrotron using soft X-rays. Result: diesel particles that have been "born" in the engine under high pressure and immense heat have a graphite structure – this is clearly visible under X-ray light. In the case of soot particles from wood fires, which have been generated under mild atmospheric conditions, this graphite structure is absent. The functional groups are also different: diesel soot was found to contain carboxyl groups such as those occurring in formic and acetic acid molecules; in the wood smoke, Braun found hydroxyl groups as in ethanol and methanol. There is thus a fine difference between smoke and smoke.

Pitch black diesel soot from the exhaust of a US truck (Image: US Environmental Protection Agency EPA)

Analyse separately, fight together

The Norwegian toxicologists then went a step further and asked Braun's colleagues at the University of North Dakota to isolate the soot particles from the adherent chemical toxic substances using solvents. Braun then analysed the components individually under X-ray light: first the "bare" soot particles, then the solution with the suspected carcinogenic chemicals previously bound to the soot. Braun again found various functional groups on the carbon structure and was able to compare them with the findings of his earlier work.

At the same time, the toxicologists tested the effect of the two soot fractions on human lung cells in culture. For the first time separate investigations had been carried out to establish what is so dangerous in soot. The study, which recently appeared in the journal "Toxicology Letters", is, in Braun's opinion, the first to combine the methods of X-ray absorption spectroscopy (NEXAFS) with toxicological methods.



Conjoined diesel soot particles under the electron microscope (Image: Naresh Shah, Consortium for Fossil Fuel Sciences, Lexington, Kentucky)

The WHO response

The results of the study were quite unambiguous: The "bare" soot particles triggered a genetic detoxification mechanism in the cell cultures. The cells had therefore been under “toxic attack”. However, the washed out substances previously adhering to the soot also exhibited an effect: they caused inflammatory

reactions in the cells and also acted as a cellular toxin. The World Health Organization (WHO) responded simultaneously. A number of new studies – including those by Braun and his colleagues from Norway and the USA – had indicated the carcinogenic effect of soot and sufficiently explained the underlying mechanisms.
It was now no longer possible to speak, as had been the case since 1988, of a probable risk of cancer ("probably carcinogenic to humans"). Reclassification followed on 12 June 2012. Diesel soot is now considered a cause of lung cancer "based on sufficient evidence"; what's more, there is a certain probability that diesel soot also increases the risk of bladder cancer.

X-ray research at Empa – measurements in Berkeley and Stanford

Physicist Artur Braun – after his " assistance" in the field of health research – is resuming his duties as group leader in Empa's High Performance Ceramics Laboratory, a position in which he also continues to work on synchrotrons in the USA and in Europe. He is regularly at the ALS radiation source in Berkeley (California) and at the Stanford synchrotron (SSRL) for measurements. For Empa, the expert uses synchrotron radiation methods for materials research into energy storage devices and converters.
Currently, there is another publication in preparation on the subject of fine particulates from wood combustion, to which Braun has also made crucial contributions. The cooperation between the disciplines will not end there. According to Braun, "The medical scientific potential of synchrotron methods for analyzing the biological interaction of cells with pathogenic substances is still far from being exhausted".

- Media release (PDF-File, 197 KB)
- News-Archive
- Mediacorner

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Sub-micrometer particulate air pollution and cardiovascular mortality in Beijing, China

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ABSTRACT

Background: While the link between particulate matter and cardiovascular mortality is well established, it is not fully investigated and understood which properties of the aerosol might be responsible for the health effects, especially in polluted mega-city areas.
Objectives: Our goal was to explore the association between daily cardiovascular mortality and different particle metrics in the sub-micrometer range in Beijing, China.
Methods: We obtained daily counts of cause-specific cardiovascular deaths in the Beijing urban area for the period March 2004 to August 2005. Concurrently, continuous measurements of particle number size distributions were performed. Particle number concentrations (NC) between 0.003 μm and 0.8 μm were converted to particle mass and surface area concentrations assuming spherical particles. Semi-parametric Poisson regression models adjusting for trend, seasonality, day of the week, and meteorology were used to estimate immediate, delayed and cumulative particle effects. Additionally, effect modification by air mass origin was investigated.
Results: We observed associations between daily cardiovascular mortality and particle NC for a 2-days delay. Moreover, nearly all particle metrics showed 2-days delayed associations with ischemic heart disease mortality. The strongest association was found for particle NC in the size range 0.03–0.1 μm (7.1% increase in daily mortality with a 95%-confidence interval of 2.9%–11.5%, per an increase of 6250 particles/cm^3). Results for surface and mass concentrations with a lag of two days indicated effect modification by air mass origin, whereas effects of particle NC were not modified.
Conclusions: Results show an elevated risk of cardiovascular mortality in Beijing from short-term exposure to particulate air pollution in the sub-micrometer range. Results also indicate that locally produced smaller particles and regionally transported particles may exhibit different effects in Beijing.
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Abbreviations: ACP, accumulation mode particles; CDC, Center for Disease Control; CPC, Condensation Particle Counter; CI, confidence interval; DF, degrees of freedom; DMA, Differential Mobility Analyzer; GCV, generalized cross validation; ICD-10, International Classification of Disease, Tenth Revision; IQR, interquartile range; MC, mass concentrations; MC_1, particle MC for particles in the range below 0.8 μm; PAH, polycyclic aromatic hydrocarbons; PACF, partial autocorrelation coefficient; PKU, Peking University; PM, particulate matter; PM_{10}, particulate matter with an aerodynamic diameter <10 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter <2.5 μm; PM_1, particulate matter with an aerodynamic diameter <1 μm; NC, number concentrations; NC_1, particle NC for particles in the range below 0.8 μm; SC, surface area concentrations; SC_1, particle SC for particles in the range below 0.8 μm; TDMPS, Twin Differential Mobility Particle Sizer; UFP, ultrafine particles (particles with an aerodynamic diameter <0.1 μm).

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Research activities in the Czech Republic

New state-of-the-art engine testing laboratory at VTP Roztoky / Czech Technical University

New engine and vehicle testing laboratory has been constructed at the Science and Technology Park in Roztoky (VTP Roztoky), a small town just north to the Dejvice, Prague campus of the Czech Technical University. The laboratory, co-financed by EU funds, houses five transient engine dynamometers, one single cylinder research engine, all-wheel-drive light duty chassis dynamometer, and dynamometers and test stands for electric motors and transmissions. For emissions measurements, the laboratory is equipped with a full-flow dilution tunnel, several sets of gaseous emissions analyzers, two particle sampling systems, particle number measurement systems, and particle classifier and counter. In addition to the Department of Mechanical Engineering and the Department of Electrical Engineering of the Czech Technical University, the laboratory also houses the engine and vehicle certification and testing group of TÜV SÜD Czech.

MEDETOX project - ongoing

The major activities were done within the LIFE+ EU project LIFE10 ENV/CZ/651 "Innovative Methods of Monitoring of Diesel engine exhaust toxicity in real urban traffic" (MEDETOX, www.medetox.cz)

1. Miniature proportional sampling system under development

Miniature sampling system has been constructed as a complement the existing portable, on-board emissions monitoring system providing on-line measurements, and is being refined. Working version of the system has undergone trial runs on a diesel powered motorized rail unit and is also evaluated in the laboratory.

2. Exploratory measurements in real-world city operation

Exploratory measurements have been carried in real traffic with on-board monitoring system on a scooter, on passenger cars powered by gasoline, blends of ethanol with gasoline and blends of butanol with gasoline, and on diesel powered passenger trains. Particle emissions were measured with semi-condensing nephelometer calibrated to particle mass concentrations, with a measuring ionization chamber providing total particle length measurements, and with a proportional gravimetric sampling system. The focus was on the testing methodology and on preliminary assessment of patterns in particle emissions.

It was found that operation in congested urban areas can be very challenging, as exhaust emissions tend to be, compared to the operating conditions experienced under legislated tests, much higher during both extreme low-load (idle, low-speed "creep") and transient high-load (abrupt accelerations) operation. This problem is compounded by the immediate proximity of the "source" (tailpipes) and the "receptors" (citizens perusing traveled street and nearby buildings and areas).

Reference: Vojtisek-Lom M.: Consideration of congested urban traffic in exhaust toxicity assessment. 16th ETH Conference on Combustion Generated Nanoparticles, Zurich, Switzerland, June 24-27, 2012.

3. Biofuels and emissions of polyaromatic hydrocarbons (PAH)
Study on emissions of polyaromatic hydrocarbons in exhaust of biodiesel and rapeseed oil powered diesel engines, and of biodiesel engines with catalytic aftertreatment devices, was published in Atmospheric Environment. This study presents a compilation of Czech and Swiss results on a total of four engines. Among others, the study concludes that neat biodiesel reduces the toxicity equivalent of PAH by an average of 73%, regardless of the set of toxicity equivalents and analytical method used.
Reference: Vojtisek-Lom M., Czerwinski J., Lenicek J., Sekyra M., Topinka J.: Polycyclic aromatic hydrocarbons (PAHs) in exhaust emissions from diesel engines powered by rapeseed oil methylester and heated non-esterified rapeseed oil. Atmospheric Environment 60, 2012, 253-261.

4. Pilot study on genotoxicity of the organic extracts from particulate engine emissions
The study was performed to identify possible genotoxicity induced by organic extracts from particulate matter in the exhaust of two typical diesel engines run on diesel fuel and neat heated fuelgrade rapeseed oil: a Cummins ISBe4 engine tested using the World Harmonized Steady State Test Cycle (WHSC) and modified Engine Steady Cycle (ESC) and a Zetor 1505 engine tested using the Non-Road Steady State Cycle (NRSC). In addition, biodiesel B-100 (neat methylester of rapeseed oil) was tested in the Cummins engine run on the modified ESC. Our findings suggest that the genotoxicity of particulate emissions from the combustion of rapeseed oil is significant and is comparable to that from the combustion of diesel fuel. A more detailed study is ongoing to verify and extent these preliminary findings.
Reference: Topinka J., Milcová A., Schmuczerová J., Mazač M., Pechout M., Vojtíšek M.: Genotoxic potential of organic extracts from particle emissions of diesel and rapeseed oil powered engines. Toxicology Letters, 212, 2012, 11-17.

5. Optimisation of toxicity assays
The methodology for the extraction of particles from filters was established and verified. The toxicity tests in cell free system (DNA adduct analysis by ^{32}P-postlabelling method, analysis of the oxidative damage of DNA) were tested with the organic extracts from the diesel emissions under laboratory conditions. Simultaneously, use of human embryonic lung fibroblasts (HEL 12469) was optimized for *in vitro* toxicity tests with: cytotoxicity, DNA adducts, oxidative damage of DNA, proteins and lipids, DNA strand breaks by Comet assay, and automated analysis of micronuclei (cytogenetic analysis).

6. Exploration into engine history and unstable emissions effects
Exploration into the effects of engine operating history was motivated by online particle measurements from a diesel-electric locomotive, where particle emissions were often unsteady even during seemingly steady-state operating conditions.
Reference: Vojtisek-Lom M.: Inference of steady-state non-road engine exhaust emissions values from non-stabilized data. SAE Technical Paper 2012-01-1673, Society of Automotive Engineers, 2012.

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ARTICLE

The Diesel Exhaust in Miners Study: A Nested Case–Control Study of Lung Cancer and Diesel Exhaust

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Background Most studies of the association between diesel exhaust exposure and lung cancer suggest a modest, but consistent, increased risk. However, to our knowledge, no study to date has had quantitative data on historical diesel exposure coupled with adequate sample size to evaluate the exposure–response relationship between diesel exhaust and lung cancer. Our purpose was to evaluate the relationship between quantitative estimates of exposure to diesel exhaust and lung cancer mortality after adjustment for smoking and other potential confounders.

Methods We conducted a nested case–control study in a cohort of 12315 workers in eight non-metal mining facilities, which included 198 lung cancer deaths and 562 incidence density–sampled control subjects. For each case subject, we selected up to four control subjects, individually matched on mining facility, sex, race/ethnicity, and birth year (within 5 years), from all workers who were alive before the day the case subject died. We estimated diesel exhaust exposure, represented by respirable elemental carbon (REC), by job and year, for each subject, based on an extensive retrospective exposure assessment at each mining facility. We conducted both categorical and continuous regression analyses adjusted for cigarette smoking and other potential confounding variables (eg, history of employment in high-risk occupations for lung cancer and a history of respiratory disease) to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Analyses were both unlagged and lagged to exclude recent exposure such as that occurring in the 15 years directly before the date of death (case subjects)/reference date (control subjects). All statistical tests were two-sided.

Results We observed statistically significant increasing trends in lung cancer risk with increasing cumulative REC and average REC intensity. Cumulative REC, lagged 15 years, yielded a statistically significant positive gradient in lung cancer risk overall (P_{trend} = .001); among heavily exposed workers (ie, above the median of the top quartile [REC $\geq$ 1005 μg/m^3-y]), risk was approximately three times greater (OR = 3.20, 95% CI = 1.33 to 7.69) than that among workers in the lowest quartile of exposure. Among never smokers, odd ratios were 1.0, 1.47 (95% CI = 0.29 to 7.50), and 7.30 (95% CI = 1.46 to 36.57) for workers with 15-year lagged cumulative REC tertiles of less than 8, 8 to less than 304, and 304 μg/m^3-y or more, respectively. We also observed an interaction between smoking and 15-year lagged cumulative REC ($P_{interaction}$ = .086) such that the effect of each of these exposures was attenuated in the presence of high levels of the other.

Conclusion Our findings provide further evidence that diesel exhaust exposure may cause lung cancer in humans and may represent a potential public health burden.

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The question of whether diesel exhaust causes lung cancer in humans has been investigated in many studies since the 1980s. In 1989, the International Agency for Research on Cancer (IARC) classified diesel exhaust as a "probable" carcinogen (IARC classification: Group 2A) based on "sufficient" experimental evidence and "limited" evidence of carcinogenicity in humans (1). Two meta-analyses (2,3) of epidemiological studies have estimated the summary relative risk for lung cancer for those ever occupationally exposed to diesel exhaust as 1.33 (95% confidence interval [CI] = 1.24 to 1.44) (2) and 1.47 (95% CI = 1.29 to 1.67) (3), based on more than 35 studies. A pooled analysis (4) of 13 304 case subjects and 16 282 control subjects from 11 lung cancer case–control studies in Europe and Canada yielded an odds ratio (OR) of 1.31 (95% CI = 1.19 to 1.43) for subjects in the highest vs lowest quartile of cumulative diesel exposure based on a job exposure matrix (4). Although these meta-analyses (2,3) and the pooled analysis (4) suggest a modest but consistent effect, the excesses are in a range that could be explained by confounding (5), particularly from

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Our findings are important not only for miners but also for the 1.4 million American workers and the 3 million European workers exposed to diesel exhaust (29), and for urban populations worldwide. Some of the higher average elemental carbon levels reported in cities include Los Angeles (4.0 μg/m^3) (30), the Bronx (a borough in New York City) (6.6 μg/m^3) (31), nine urban sites in China (8.3 μg/m^3) (32), Mexico City (5.8 μg/m^3) (33), and Estarreja, Portugal (11.8 μg/m^3) (34). Environmental exposure to average elemental carbon levels in the 2-6 μg/m^3 range over a lifetime as would be experienced in highly polluted cities approximates cumulative exposures experienced by underground miners with low exposures in our study. Because such workers had at least a 50% increased lung cancer risk, our results suggest that the high air concentrations of elemental carbon reported in some urban areas may confer increased risk of lung cancer. Thus, if the diesel exhaust/lung cancer relation is causal, the public health burden of the carcinogenicity of inhaled diesel exhaust in workers and in populations of urban areas with high levels of diesel exposure may be substantial.

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Evaluation of carcinogenic hazard of diesel engine exhaust needs to consider revolutionary changes in diesel technology

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ABSTRACT

Diesel engines, a special type of internal combustion engine, use heat of compression, rather than electric spark, to ignite hydrocarbon fuels injected into the combustion chamber. Diesel engines have high thermal efficiency and thus, high fuel efficiency. They are widely used in commerce prompting continuous improvement in diesel engines and fuels. Concern for health effects from exposure to diesel exhaust arose in the mid-1900s and stimulated development of emissions regulations and research to improve the technology and characterize potential health hazards. This included epidemiological, controlled human exposure, laboratory animal and mechanistic studies to evaluate potential hazards of whole diesel exhaust. The International Agency for Research on Cancer (1989) classified whole diesel exhaust as – "probably carcinogenic to humans". This classification stimulated even more stringent regulations for particulate matter that required further technological developments. These included improved engine control, improved fuel injection system, enhanced exhaust cooling, use of ultra low sulfur fuel, wall-flow high-efficiency exhaust particulate filters, exhaust catalysts, and crankcase ventilation filtration. The composition of New Technology Diesel Exhaust (NTDE) is qualitatively different and the concentrations of particulate constituents are more than 90% lower than for Traditional Diesel Exhaust (TDE). We recommend that future reviews of carcinogenic hazards of diesel exhaust evaluate NTDE separately from TDE.
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1. Introduction

Diesel engines have found increasingly wide application in industry and in the transportation of goods and people around the world from the time of invention of the technology by Rudolph Diesel in the 1890s to the present day. Rudolph Diesel, with an eye to the future, wrote on October 2, 1892 – "This machine is destined to completely revolutionize engine engineering and replace everything that exists" (Mollenhauer and Tschoeke, 2010). His prophecy was only partially realized during the first century of diesel technology development. He could not have anticipated the recent revolutionary advances that have been made in diesel engine and fuel technology in response to more stringent emission regulations. Those advances in technology and the resulting major reductions in diesel engine exhaust emissions are the subject of this paper.

Diesel engine exhaust is a complex mixture of carbon dioxide, oxygen, nitrogen, nitrogen compounds, carbon monoxide, water vapor, sulfur compounds and numerous low and high molecular weight hydrocarbons, and particulate matter. As will be related in this paper, the relative contribution of each of these compounds or classes of compounds have changed with advances in engine and fuel technology. A key concept well established in the internal combustion engine field is that emissions are influenced by both the engine (and exhaust after-treatment system) and the fuel being combusted. Pre-1980 diesel engines fueled with high sulfur content fuel produced exhaust that contained high concentrations of carbonaceous particulate matter with associated high concentrations of polycyclic aromatic hydrocarbons. The exhaust also contained high concentrations of nitrogen oxide (NO_x) and gas phase hydrocarbons. That exhaust was of concern because of its impact on visibility and for its potential health hazard. Concern for health impacts and especially, cancer intensified when it was discovered that organic solvent extracts of the exhaust particulate matter were mutagenic in the Ames bacterial assays.

The finding that extracts of diesel exhaust particulate matter contained mutagenic chemicals was viewed as presumptive evidence that exposure to diesel exhaust particulate matter could pose a carcinogenic hazard. This presumptive evidence had three related impacts. First, it stimulated a multi-faceted international research effort to clarify the potential health hazards of exposure to diesel exhaust. This included epidemiological studies, controlled

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In recent years, the issue of evaluating the hazards of a wide range of poorly soluble particulate material has received additional scientific attention resulting in a number of publications concerning the extrapolation of laboratory animal findings on poorly soluble inhaled particulate material to humans. For example, Pauluhn (2011) has recently offered a unifying approach for evaluating the toxicity of poorly soluble submicron particulate matter which would include the hallmark DEP found in TDE. The outcome of the discussions on the role of particle overload in rats leading to an excess of lung tumors will have implications for deciding on the weight of evidence to be assigned to the finding of excess lung tumors in rats exposed for long periods of time at high concentrations in the overall evaluation of the cancer hazard of TDE. Whatever the outcome of the discussion, it is important to recognize that NTDE is essentially devoid of the hallmark DEP found in TDE.

In the section on "animal studies" for NTDE, it is important that the 2012 Monograph provide a clear description of the ACES chronic bioassay in rats being conducted with NTDE. In short, this description will serve as a promissory note of results yet to be obtained that will be valuable in any future hazard evaluation of NTDE. Recall that a key objective of the ACES program was to test the "null" hypothesis that emissions from diesel engines compliant with the EPA's 2007 emission standards "will not cause an increase in tumor formation – at the highest concentration of exhaust that can be used."

It is to be anticipated that the section on "mechanistic and other relevant data" for TDE will consider the overload mode of action discussed above and the significance of the DEP associated hydrocarbons in evaluating human cancer hazards. It is our view that the excess lung tumors observed in rats chronically exposed to high concentrations of diesel exhaust is a species-specific effect occurring as a result of the overload phenomena. It is not necessary to invoke a role for particle-associated hydrocarbons in explaining these findings in rats. The absence of an excess of lung cancer in mice and Syrian hamsters chronically exposed to high concentrations of diesel exhaust raises questions as to whether the hydrocarbon fraction of diesel exhaust has been demonstrated to cause cancer. For example, the Mauderly et al. (1996) report of an absence of excess lung tumors in mice exposed concurrently with rats that exhibited lung tumors related to the overload phenomena (Mauderly et al., 1987; Wolff et al., 1987) serves as a dramatic illustration of the role of the overload phenomena and species differences in response.

Consistent with the recommendations we have offered earlier, it is our view that the "summary" and "evaluation and rationale" sections of the 2012 IARC review should provide for separate evaluation of TDE and NTDE. In our opinion, the scientific information available on NTDE supports placing NTDE in Group 3, not classifiable as to its carcinogenicity in humans. When the results of the ACES chronic bioassay in rats exposed to the Maximum Tolerated Dose (more correctly concentration and time) becomes available, the cancer hazard classification of NTDE should be re-evaluated.

12. Summary

The information reviewed above comparing NTDE to TDE has shown that in the case of technology-specific emissions (such as diesel exhaust), technological advances can have a profound impact on reducing and changing the composition of emissions. This situation is in sharp contrast to that for a particular chemical agent that has physical properties, including those that determine its hazard potential, which never change.

Major revolutionary advances have been made in diesel technology, especially during the last decade, which have impacted on exhaust emissions. Those advances which are integrated as a system include: (a) engine improvements including the use of exhaust gas recirculation; (b) use of ultra-low sulfur diesel fuel; (c) exhaust after-treatment including oxidative catalysts and wall-flow particulate matter traps; and (d) electronic sensing and computerized control systems. The new systems are extraordinarily effective in substantially reducing and changing particulate matter exhaust as compared to TDE emissions. The key changes are: lower particulate mass emissions, different chemical composition, lower particle number emissions, altered composition of the semi-volatile fraction, and lower concentrations of unregulated pollutants. Thus, the NTDE emissions are substantially different, both quantitatively and qualitatively, than TDE emissions. Moreover, the NTDE emissions are now similar to or lower than those of modern CNG or modern gasoline–fueled engines.

The extensive characterization of NTDE has clearly established that the emissions are substantially lower than the applicable, very stringent regulatory emission standards. Moreover, the detailed chemical characterization gives confidence that the emissions do not contain any unique constituents that might pose a hazard to human health. The new technology heavy-duty engines with ultra-low particulate emissions were introduced into the market for on-road use in 2007 as required by US regulations, and have been well received by customers. Starting in 2010, the engines marketed in the USA continue to have ultra-low particulate mass emissions and, in addition, even lower NO_x emissions than the 2007 model engines. In future years, the number of NTDE units will increase and the number of TDE units will decrease in the on-road fleet. Moreover, a similar shift will follow with off-road diesel-power equipment.

To further validate the lack of health hazard of NTDE, exhaustive investigations are now underway in which mice and rats are being exposed to graded concentrations of whole NTDE. The highest concentrations being studied are a dilution of only 40:1 of engine-out emissions, a dilution selected to limit potential effects of the NO_2. However, the high concentration NO_2 component at the highest exposure level was expected and has produced minimal/limited modest histopathological changes in the respiratory tract. The bioassay with rats exposed for 30 months (16 h/day, 5 days/week) is similar in design to the earlier studies with TDE in which an excess of lung tumors was observed at the highest particulate mass concentrations (the lowest dilutions of whole TDE). Thus, the results of the NTDE and TDE cancer bioassays can be directly compared when the NTDE bioassay is completed and reported in 2013. Moreover, it is clear that the results of the NTDE bioassay will provide a direct evaluation of the ACES core (null) hypothesis that the NTDE exposure "will not cause an increase in tumor formation or substantial toxic health effects in rats and mice at the highest concentration of exhaust that can be used – compared to animals exposed to "clean air," although some biological effects may occur."

Based on the remarkable differences in concentration and composition of NTDE compared to TDE, it is our recommendation that NTDE should be evaluated and classified separately from TDE by the IARC Working Group in June 2012.

13. Conclusions

The use of diesel engines as reliable and efficient sources of power to move goods and people and meet other critical needs of society has steadily grown over the past century. During the past half century, concerns arose over the impact of diesel engine exhaust on visibility and human health and more recently on climate change. Those concerns were soon reflected in increasingly more stringent regulations to limit engine emissions. The need for progressively lower emission standards was reinforced by increasingly stringent National Ambient Air Quality Standards for Particulate Matter, Ozone and Nitrogen Dioxides.

In response to the stringent regulations, the manufacturers of diesel engines and refiners of diesel fuel made evolutionary and, more recently, revolutionary advances in diesel technology including improved engines, exhaust after-treatment and use of improved, ultra-low sulfur fuels. This new technology is being rapidly introduced into the market to replace traditional diesel engines and fuels. The particulate matter concentration in NTDE is remarkably lower than in TDE and the composition of NTDE is distinctly different than that of TDE. The TDE particles illustrated in Fig. 1, with their core of elemental carbon and substantial amount of associated hydrocarbons, are simply not present in NTDE. It is clear that there have been paradigm-shifting advances in the control of diesel exhaust emissions in response to progressively more stringent regulations.

The earlier IARC (1989) review classified whole diesel exhaust, which we characterize as TDE, as a "probable human carcinogen, Group 2A." The same IARC Working Group classified whole gasoline exhaust, which we characterize as traditional gasoline exhaust, as a "possible human carcinogen, Group 2B." IARC in June 2012 will again review the carcinogenic hazard classification of diesel exhaust and gasoline exhaust. Since the previous IARC review, substantial new information has been published on epidemiological observations relating to workers exposed to TDE and on the mechanisms by which protracted exposure to high concentrations of TDE and other poorly soluble particles produces lung tumors in rats. That new information will need to be critically evaluated by the IARC working group as it considers appropriate carcinogenic hazard classifications for whole diesel exhaust. It is our view that whatever classification is given, it should be specifically identified as being applicable to TDE. We recommend, in recognition that NTDE is fundamentally different than TDE, that IARC evaluate and classify NTDE separately from TDE. Likewise, it is appropriate for IARC to recognize that sufficient information is now available for gasoline exhaust to separately evaluate TGE and MGE. This is the approach shown schematically in Table 6. This approach would be similar to the approach taken by IARC (2002) in an earlier review and classification of newly developed biosoluble glass wool fibers as "not classifiable as to human carcinogenicity, Group 3." It is our recommendation, based on current scientific information, that it would be appropriate to classify NTDE as "Group 3, not classifiable as to human carcinogenicity." Classifying NTDE in Group 3 will serve to distinguish the new technology diesel engine and fuel from the old traditional diesel technology that produced TDE. Most importantly, this distinction will encourage the deployment of ultra-clean diesel technology around the world with a resulting profoundly positive impact in improving ambient air quality and public health.

Conflict of interest statement

The authors have had a long association with private sector firms and organizations striving to develop ultra-clean diesel technology. Roger O. McClellan has served on numerous advisory committees to the US EPA and other government and private organizations on air quality issues. He was first alerted to issues concerning the potential health effects of diesel exhaust emissions from traditional diesel technology while serving on an EPA Advisory Committee in the 1970s. In the late 1970s, he was responsible for providing leadership for initiating the Lovelace organization's pioneering studies of diesel exhaust. From that time to the present time, he has served in an advisory role to the Health Effects Institute, the Engine Manufacturers Association and private firms concerned with diesel technology and its potential health impact. In addition, he has served in an Advisory Role to the US Environmental Protection Agency on setting of air quality standards, including service as Chair of the US Environmental Protection Agency Clean Air Scientific Advisory Committee (CASAC) and service on CASAC Panels for the revision of National Ambient Air Quality Standards for all the criteria pollutants. He served from 1985 to 1987 as a Member of the Advisory Committee on Standards and Regulations for Diesel Powered Equipment in Underground Coal Mines, Mine Safety and Health Administration, Department of Labor. He served as a member of the Working Group that prepared the IARC (1989) Monograph on Diesel and Gasoline Exhaust and Some Nitroarenes. Thomas W. Hesterberg has been employed by Navistar International since 2002 and has responsibility for coordinating that firm's product stewardship program of which a major component is the development of improved diesel technology. John C. Wall has been employed by Cummins, Inc. since 1986 and has a leadership role in that firm's programs to develop improved diesel technology. Both Cummins, Inc. and Navistar International are major international producers and marketers of diesel engines.

The three authors have sole responsibility for the final manuscript. The analyses, interpretations and recommendations in the manuscript reflect their professional expertise and judgments and do not necessarily reflect the views of their employers, the Engine Manufacturers Association (EMA) or other EMA member companies.

Acknowledgments

The authors extend a note of appreciation to their many colleagues who have made major contributions to the evolutionary and revolutionary developments in diesel technology since the 1970s and the remarkable advances that have been made in understanding the potential health impacts of diesel emissions. Many of those individuals contributed to the development of information cited in this review and, in some cases, offered specific suggestions that improved the quality of the manuscript. In particular, we acknowledge the helpful review comments by Imad A. Khalek, Southwest Research Institute, and Z.G. (Jerry) Liu, Cummins, Inc. Their reviews were especially useful because they and their colleagues have been major contributors to the literature on the characterization of New Technology Diesel Exhaust. The authors would also like to specifically note the valuable input of Charles Lapin, an independent consultant, and Christopher Long and Peter Valberg, Gradient, Consultants to Navistar International. We especially acknowledge the comments of three anonymous reviewers whose comments prompted us to make several changes, including adding selected material and references that improved the manuscript.

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For MECA Members Only

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SPECIAL REPORT
Health Effects Institute's 2012 Annual Conference in Chicago

The Health Effects Institute (HEI) held its annual conference on April 15-17, 2012 in Chicago, IL. MECA's Jamie Song attended the conference. This year's conference included sessions on studies looking at carcinogenicity of diesel emissions, long-term exposure to photochemical oxidants and chronic disease, results from HEI's National Particle Component Toxicity Initiative, and health effects of ultrafine particles.

Topics discussed at the conference include:

Highlights from the conference of interest to MECA members include:

- With the recent introduction of innovative aftertreatment technologies, the emissions from new diesel engines are decreasing dramatically, raising opportunities to substantially reduce human exposure and health effects. Data recently released by HEI shows much higher concentrations of PM in emissions from older engines than newer engines and demonstrates the need to differentiate the risks of diesel exhaust of old and new engines.
- John Wall, Cummins, gave a presentation on the evolution of diesel emission control technologies and the characteristics of new technology diesel exhaust.
    - Wall characterizes "Traditional Diesel Exhaust" (TDE) as emissions from unregulated engines (before 1988 U.S. on-road), and transitional diesel exhaust as exhaust from 1998-2006 U.S. on-road engines. He characterizes the "New Technology Diesel Exhaust" (NTDE) as emissions from 2007 and later engines (U.S. on-road).
    - Advances in heavy-duty diesel engine technologies were due to adoption of EPA's 2007-2010 highway engine regulation and low-sulfur diesel fuel standard.
        - "Revolutionary" step in diesel technology came with development of DPF/DOC in conjunction with ULSD.

  - PM levels in NTDE are more than 100-fold lower than in TDE.
    - NTDE NOx and PM mass emissions are comparable to CNG and gasoline engines.
    - NTDE PM is chemically different from TDE PM.
      - Has lower particulate numbers
      - Has less hydrocarbon (fuel + lube derived) and elemental carbon + ash but has higher sulfate/nitrate levels.
    - Lower volatile organic compounds and aldehyde emissions
    - Lower polycyclic aromatic hydrocarbon emissions
- Jake McDonald, Lovelace Respiratory Research Institute, gave a presentation on the biological response to inhaled 2007 compliant diesel emissions (NTDE). As part of Phase 3A of the Advanced Collaborative Emissions Study (ACES), HEI conducted animal inhalation studies to test HEI's hypothesis that 2007-compliant on-road diesel emissions "will not cause an increase in tumor formation or substantial toxic effects in rats and mice at the highest concentration of exhaust that can be used…although some biological effects may occur". HEI-sponsored work has previously shown that emissions from such engines contain very low levels of diesel particles and other pollutants. Emissions from older diesel engines have been evaluated by HEI and others in similar studies in the past, but this is the first, and so far the only study, to focus on emissions from new engines now on the market, which comply with stringent emissions regulations now in force. HEI investigators have recently completed analysis of the first health results (1-, 3-, and 12-month animal exposures) from a comprehensive bioassay using exhaust from a new engine.
  - Exposed mice and rats for 16 hours each day, 5 days a week, to diluted emissions from a 2007 compliant 500 hp engine equipped with a DPF.
  - Rats were evaluated by respiratory function, hematology, serum chemistry, bronchoalveolar lavage, lung cell proliferation, and histopathological assays after 1 and 3 months of exposure.
  - Mice were evaluated after 1 and 3 months of exposure with assays identical to those used in rats, with the exception of respiratory function.
  - Results:
    - Majority of the analyses showed no difference between diesel exhaust exposure and clean air control. Exposures produced mild to no response in the mice and minimal inflammatory, tissue remodeling and respiratory function changes in rats.
    - Mild biological responses were observed in lungs after both 3 and 12 months of exposure. The findings were mostly observed at the highest exposure concentration,
    - Minimal but statistically significant trends were observed in lung diffusion capacity of rats at both 3 and 12 months.
    - Pulmonary function assessments in rats showed slight differences in exposed rats compared with control after 3 months of exposure.
  - Chronic rat exposures are currently on-going for 24-month study and are expected to be completed during the fall of 2012.
    More information on this study is available at:
    http://pubs.healtheffects.org/view.php?id=372,

- Eric Garshick, VA Boston Healthcare System, gave an update on lung cancer and diesel emissions.
    - Effects of diesel exhaust on lung is challenging to epidemiologists because lung cancer takes years to develop and prospective studies have not been feasible.
    - Epidemiology studies rely on occupational registries/work records not designed for health studies.
        - Need to ensure quality linkage between job/work records and quantitative or semi-quantitative exposure estimates.
        - Need to assess factors other than diesel, such as smoking.
    - Pooled Case-Control Study conducted by International Agency for Research on Cancer (IARC): 11 pooled studies
        - Objective was to investigate the risk of lung cancer following occupational exposure of vehicle diesel exhaust, while controlling for smoking and other occupational exposures.
        - 13,304 cases/16,282 controls (from around 1990 to 2005).
        - The Institute for Risk Assessment Sciences at Utrecht University developed a job exposure matrix to determine level of exposure to occupational vehicle diesel exhaust.
        - The response rate was 82% among cases and 66% among controls.
        - Cumulative vehicle diesel exhaust exposure was associated with an increased lung cancer risk.
    - Railroad Worker Cohort Study:
        - The U.S. Railroad Retirement Board (RRB) maintained a computerized record of work history since 1959.
        - In 1981, men 40-64 years of age with 10-20 years of railroad service in 1959 were selected for data extraction.
        - Sampled 56,208 workers in 39 job codes that were identified. Among these workers, 4,351 died of lung cancer through 1996.
        - Study showed increased lung cancer risk in diesel exposed jobs. The relative risks for lung cancer and exposure to diesel exhaust on the basis of job held in 1959 were inversely related to age in 1959; workers who were 40 to 44 years of age and working in a job category with exposure to diesel emissions in 1959 experienced an increase in lung cancer mortality compared with those who were in that age category but held unexposed jobs in 1959.
    - Railroad Worker Case-Control Study:
        - Conducted a case-control study of RRB registrants who died between March 1, 1982 and February 28, 1982.
        - Among 650,000 active and retired male railroad workers born in or after 1900 who had at least 10 years of railroad employment, 15,059 deaths were reported to the RRB.
            - Most common underlying causes of death among both older (age at death ≥ 65) and younger (age at death ≤ 64) controls were diseases of the circulatory system; deaths from nonmalignant respiratory disease were also included. Overall, 1,256 lung cancer cases and 2,385 controls were considered in the analysis.

- Conducted separate analyses for younger workers and older workers because heavy cumulative exposure to diesel exhaust was more likely among the workers who died at a younger age.
- No excess risk of death from lung cancer in association with exposure to diesel exhaust was observed among the older workers.
- Among the younger workers, with diesel exposure modeled as a continuous variable, more than 20 years of exposure to diesel exhaust was associated with a crude relative risk (RR)=1.4 (95% CI: 1.0, 1.8) for lung cancer mortality.

- Trucking Industry Particle Study:
  - Conducted a national exposure assessment of combustion particles to complement epidemiologic data on lung cancer mortality for workers in the U.S trucking industry, including drivers.
  - Retrospective cohort study with 54,319 male Unionized trucking company workers.
    - Employed in 1985 in 4 U.S. companies.
    - Looked at lung cancer mortality experience through 2000.
  - Driver exposures were measured at 36 truck freight terminals across the U.S., sampling for a 1 –week period at each terminal and visiting a new terminal approximately every month during 2001-2005.
    - Drivers were asked to perform their normal driving activities with a sampling box mounted in the cab to measure particle concentrations in their work environment.
  - Found 779 lung cancer cases among ≥ 40 in 1985.
  - Study suggest that driver exposures were significantly impacted by a number of individual factors, including smoking status, ambient particle concentrations, truck age, window status and weather characteristics.
- Diesel Exhaust in Miners Study:
  - National Cancer Institute (NCI) and National Institute of Occupational Safety and Health (NIOSH) conducted two studies to clarify the relationship between exposure to diesel engine exhaust and the risk of death from lung cancer.
  - Conducted cohort study of 12,315 miners from 8 U.S. nonmetal mines.
    - Miners had average of 8 years of underground work.
    - Researchers developed a quantitative estimate of occupational exposure to diesel exhaust based on many sources of information, including mining company records and air samples collected in the mines.
    - Analysis showed statistically significant increases in the risk of lung cancer mortality among underground workers as the level of diesel exposure increased, especially in those who worked for more than 5 years.
  - Conducted nested case-control study:
    - 198 subjects who died from lung cancer in the full cohort study were compared with matched control subjects from the cohort.

- Conducted next-of-kin interviews for information about workers' history of smoking, employment in jobs associated with a high risk of lung cancer and nonmalignant respiratory disease.
- Results showed that workers with heavy exposure to diesel exhaust were three times more likely to die from lung cancer than workers with the lowest exposures, after taking smoking and other lung cancer risk factors into account.

        - These studies are driving calls for EPA to reassess its 2002 risk assessment of diesel exhaust, which classified the substance as a likely carcinogen but did not set a quantitative risk limit. However, industry and others are urging EPA and others to bifurcate any new assessment of diesel exhaust to account for differences between emissions from old and new engines.
    - From these various studies, it can be concluded that:
        - Lung cancer risk elevated in studies with quality linkage between job/work records and exposure.
        - Risk increases with cumulative exposure in miner and trucking industry studies.
        - Exposures overlap in truckers.
        - Risk not explained by smoking.
- Nigel Clark, West Virginia University, discussed his recent work that looks at trying to correlate PM emissions with gaseous emissions from diesel engines. Prof. Clark examined several large emission databases developed by CRC and others for both on- and off-road engines to examine possible relationships. His analysis found only a weak relationship between CO emissions and PM emissions. The details of this work are discussed in his recent SAE paper, SAE paper no. 2012-01-1346.
- Robert O'Keefe, HEI, gave a presentation on the new developments in air quality regulations.
    - There has been strong progress in reducing air pollution despite growth in economy and population.
    - There are ongoing questions about the health effects of low levels of PM and ozone.
    - Many countries are setting and revisiting PM and ozone standards.
        - After a period of decline, Asian emissions of PM and ozone are on the rise again.
    - U.S. National Ambient Air Quality Standards:
        - PM NAAQS set for review for 2013.
        - Ozone NAAQS set for review by 2013.
        - NO_2 NAAQS set for its first review.
    - Europe:
        - Conducting review of the air quality limit value for PM, NO_2, ozone, SO_2, CO, Pb, and metals.
        - World Health Organization is conducting a study to provide European Commission with advice on health aspects of air pollution. The result will support revisions to EU air quality policies due in 2013. Draft of this study will be released in September 2012.

        - WHO Expert Review of Policy Implementation draft due in January 2013.
    - China:
        - Newly set ozone and $PM_{2.5}$ interim ambient targets that are comparable to WHO levels.
        - Monitoring network will be phased-in over the next 4 years.
    - Major worldwide challenge is to meet GHG and fuel economy standards.
    - Next steps in mobile source regulation:
        - U.S.: Tier 3.
        - Europe: new drive cycle with emission implications.
        - China, India and Mexico: enhanced fuel and lower vehicle emission standards.
- Exposure to ozone has been associated with a range of acute adverse health effects and with irreversible changes in lung structure and function. When exposure to $PM_{2.5}$ is taken into account, cohort studies of long-term exposure to ozone find some evidence of an effect of ozone on mortality from respiratory disease, but little, if any, evidence of effects of cardiovascular mortality.
- Kenneth Demerjian, University of Albany, gave a presentation of estimating human exposure to photochemical oxidants.
    - Ozone formation processes in polluted environments are closely coupled with formation of many other oxidants including: nitric oxide (NO_2), formaldehyde (H_2CO), peroxyacyl nitrates (PAN), nitric acid (HNO_3), hydrogen peroxide (H_2O_2), and nitrate (NO_3).
    - Ozone plays a major role in chemical transformations in the near-road environment
    - Modeled photochemical oxidants suggest a close coupling between ozone and NO_2, PAN and H_2O_2.
    - Diurnal trends of ozone and NO_2 measurements indicate changes in exposure patterns with NOx emission reductions that may confound health outcomes.
    - Reductions in PM precursor emissions have altered PM composition and its potential toxicity.
- HEI's 4-year National Particle Component Toxicity Initiative (NPACT) was designed to address whether some components of particle matter are more harmful to health than others. NPACT has included integrated toxicologic and epidemiologic studies of cardiovascular outcomes in U.S. cities with different composition of particulate and gaseous co-pollutants.
    - Morton Lippman and George Thurston, New York University, gave a presentation on the results from the NPACT Study at New York University. PM is a complex mixture of chemical constituents that affect PM health risks. Current health-based PM standards are limited to mass concentrations: within $PM_{2.5}$, which is largely attributable to combustion products; and PM_{10}, which includes larger-sized mechanically-generated dusts. Both size fractions have been associated with excess mortality and morbidity.
        - Conducted four sub-studies within NYU's integrated 4-year NPACT program.
        - U.S. EPA Chemical Speciation Network data enable the study of: the influence of $PM_{2.5}$ components on short-term human morbidity and

mortality; and associations of long-term average concentrations with annual mortality rates.

- There is a need for a better chemical speciation monitoring network because it is currently limited with too few monitoring sites.

- Also conducted a series of 6-month sub-chronic inhalation exposure studies (6 hrs/day, 5 days/week) of concentrated ambient air $PM_{2.5}$ in mice, in which they measured daily mean concentrations of $PM_{2.5}$ mass, black carbon, and 16 elements in each of five different U.S. airsheds.
- Collected, for the same 5 airsheds, winter and summer samples of $PM_{10-2.5}$, $PM_{2.5-0.2}$.
- Identified $PM_{2.5}$ constituents and sources that elicited both short- and long-term health-related responses.
- Across all four sub-studies, fossil-fuel combustion sources (coal combustion and vehicle emissions) were most consistently associated with both short- and long-term cardiovascular disease effects.
  - The short-term cardiovascular disease effects were most closely associated with the constituents originating from residual oil combustion and traffic, while the long-term effects were more closely associated with effluents from coal combustion. Long-term exposure to $PM_{2.5}$ from traffic gave mixed results.
  - May warrant focusing PM regulations on these types of emissions.

- Sverre Vedal, University of Washington, presented NPACT study on estimating individual-level long-term concentrations of selected $PM_{2.5}$ constituents in two cardiovascular cohorts: the Multi-Ethnic Study of Atherosclerosis (MESA); and the Women's Health Initiative (WHI). The goal of the study was to estimate the associations between estimated exposure to $PM_{2.5}$ constituents and sub-clinical markers of atherosclerosis and cardiovascular events.
  - Results from the study showed that some combustion-derived $PM_{2.5}$ constituents or secondary organic aerosols, as reflected by organic carbon, may have more cardiovascular toxicity than $PM_{2.5}$ constituents from other sources. To the extent that elemental carbon is a reflection of diesel exhaust particles, diesel exhaust particles may not have as much cardiovascular toxicity.

- Ultrafine particles (UFP) continue to be the focus of research and regulatory interest. Last year, HEI convened an expert panel to conduct a critical evaluation of what they know, and don't know, about the potential for ultrafine particles to cause harm to human health. A report from this study will be published soon. Several academics and others said that while ongoing research underscores a growing need to assess the risk of UFP, a lack of adequate data, uncertainty over the health effects of UFP, a need to better define the components of UFP and other limitations prevent any solid conclusions on the particles. Successfully resolving these questions could give EPA the scientific basis to try and regulate UFP in the future if it deems it necessary to reduce UFP levels in order to protect public health. EPA's primary method for reducing PM is its mass-based existing NAAQS to reduce $PM_{2.5}$ and PM_{10} levels.

- Leonidas Ntziachristos, Aristotle University of Thessaloniki, gave a presentation on the extent to which motor vehicles contribute to ultrafine particle emissions.
    - Mobile source for $PM_{0.1}$ accounts for 54% of total $PM_{0.1}$emissions in California's South Coast Air Basin.
    - Mobile source of PM (particle number <300nm) in Europe account for 51% of total emissions.
    - Diesel engines have been an important source of PM.
    - Diesel particle number emissions are declining due to Euro 4 regulation and the use of DPFs.
    - Ultrafine particles from GDI engines are still an issue.
    - DPF regeneration produces particles but not continuously.
    - Size and composition of the PM is changing:
        - Due to decrease in elemental carbon from use of DPFs; decrease in sulfur in fuel in western world; and use of oxygenated fuels.
        - Therefore, there is less of an accumulation mode (>50 nm) and relatively higher organic content.
    - More understanding is still developing in:
        - Alternative fuels and biofuels: biodiesel and renewable diesel; bioethanol, especially in GDI engines; and natural gas and LPG in buses.
        - Small engines: two strokes in scooters and handheld machinery.
    - Aerosol changes as we move away from the source.
    - UFP number is among the fastest decaying pollutants with distance.
        - Prevalent mechanisms for UFP scavenging are: dilution; evaporation; and particle-to-particle interaction.
    - Overall, highest UFP concentrations occur in proximity to traffic.
    - Information on assessing outdoor exposure to UFP is relatively scarce.
        - Routine monitoring in cities or countries are limited;
        - Poor spatial coverage by monitors; and
        - Methods are not standardized.
    - Particles change as they are transported indoors. The fraction of outdoor particles penetrating indoors is dependent on size and composition.
- Mark Frampton, University of Rochester Medical Center, gave a presentation on experimental studies on animal and human exposure to ultrafine particles.
    - In humans, there is increased lung deposition and slower clearance, which leads to increased accumulation.
    - UFP enters blood and translocates systemically.
    - UFP enters brain through olfactory nerve.
    - In animal exposure studies:
        - Show little or no lung inflammation.
        - Effects of on- and near-road exposures:
            - Decrease in heart rate;
            - Allergen responses;
            - Progression of atherosclerosis;
            - Brain inflammation;
            - Shows support for traffic effects.
    - In human studies: variable findings

        - Show airway inflammation;
        - Pulmonary function;
        - Vascular function;
        - Cardiac repolarization.
    - The studies indicate that laboratory exposure studies are limited by technology.
    - Ambient exposure studies are unable to sort out effects of individual pollutants.
    - Gaps in the studies in that there are no long-term animal exposure studies.

A copy of the presentation slides presented during the conference is posted at: http://www.healtheffects.org/annual.htm.

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ORIGINAL ARTICLE

Occupational exposure to diesel engine emissions and risk of lung cancer: evidence from two case–control studies in Montreal, Canada

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ABSTRACT

Objective To examine the risk of lung cancer among men associated with exposure to diesel engine emissions incurred in a wide range of occupations and industries.

Methodology 2 population-based lung cancer case–control studies were conducted in Montreal. Study I (1979–1986) comprised 857 cases and 533 population controls; study II (1996–2001) comprised 736 cases and 894 population controls. A detailed job history was obtained, from which we inferred lifetime occupational exposure to 294 agents, including diesel engine emissions. ORs were estimated for each study and in the pooled data set, adjusting for socio-demographic factors, smoking history and selected occupational carcinogens. While it proved impossible to retrospectively estimate absolute exposure concentrations, there were estimates and analyses by relative measures of cumulative exposure.

Results Increased risks of lung cancer were found in both studies. The pooled analysis showed an OR of lung cancer associated with substantial exposure to diesel exhaust of 1.80 (95% CI 1.3 to 2.6). The risk associated with substantial exposure was higher for squamous cell carcinomas (OR 2.09; 95% CI 1.3 to 3.2) than other histological types. Joint effects between diesel exhaust exposure and tobacco smoking are compatible with a multiplicative synergistic effect.

Discussion Our findings provide further evidence supporting a causal link between diesel engine emissions and risk of lung cancer. The risk is stronger for the development of squamous cell carcinomas than for small cell tumours or adenocarcinomas.

What this paper adds

- The International Agency for Research on Cancer classified diesel engine emissions as probably carcinogenic to humans (group 2A) in 1989 based on limited evidence in humans and sufficient evidence in experimental animals.
- Our findings provide further evidence supporting a causal link between diesel engine emissions and risk of lung cancer.
- The risk is stronger for the development of squamous cell carcinomas than for small cell tumours or adenocarcinomas.

INTRODUCTION

Lung cancer is the most common malignancy worldwide after skin cancer.[1] Tobacco smoking is by far the main determinant of lung cancer, accounting for approximately 90% of the cases among men. Estimates of the fraction of lung cancers attributable to occupational exposures have varied widely, from 5% to 15%.[2 3]

Diesel engine emissions (also referred to as diesel exhaust) are highly complex mixtures that vary widely depending on engine type, fuel type and operating conditions. The components of exhaust most often quantified in occupational setting are particles, carbon monoxide and nitrogen oxides, but polycyclic aromatic compounds and aldehydes have also been measured in work environments.[4] The International Agency for Research on Cancer classified diesel engine emissions as probably carcinogenic to humans (group 2A) in 1989, based on limited evidence in humans and sufficient evidence in experimental animals.[4]

Since then, several epidemiological studies have found an increased risk of lung cancer among exposed workers, either in specific occupations and industries, such as truck and bus drivers, railroad workers, maintenance workers,[5 6] and miners[7] or in a wide range of occupations.[8–10] However, some authors have hypothesised that these positive associations could reflect biases, including inadequate control of confounding, and that a causal link between diesel engine emissions and lung cancer cannot be confirmed.[11–14]

In the early 1980s, we carried out a population-based case–control study in Montreal, Canada, to explore the possible associations between hundreds of occupational substances and multiple cancer sites, including lung cancer (labelled here as study I). In the late 1990s, we carried out a similar study in the same region, this time focusing on respiratory cancers (labelled here as study II). These two investigations offered the possibility of examining the effect of occupational exposures at different levels and in a wide range of occupations. The purpose of the present study was to examine the risk of developing lung cancer associated with occupational exposure to diesel engine emissions under conditions of exposure experienced in diverse occupational settings, while properly controlling for major confounders, such as tobacco smoking and other occupational exposures. As secondary aims, we examined effect–measure modification by smoking and whether the risk differs by major

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subjects, even those we labelled as 'substantial' exposure, were lower than those of some previously studied cohorts.

Our findings are consistent with those of case–control investigations that used expert-based assessments of occupational exposures.[8 9 26 28 31] All these studies found an increased risk of lung cancer associated with exposure to diesel engine emissions. Our results are also in line with the positive associations reported in studies that assessed diesel exhaust exposure using either self-reports[32] or job exposure matrices.[10 33]

We found a stronger association with squamous cell carcinomas than with small cell carcinomas, and we failed to find any link between diesel exhaust and adenocarcinomas. This specificity of associations supports the view that our positive results are unlikely to be explained by information, selection or confounding bias. If any of these biases played a major role, it should influence in a similar way the risk estimation for all histological types. Stronger associations between diesel exhaust and squamous cell carcinomas were also found by Villeneuve *et al*[9] and by Boffetta *et al*.[31]

Few studies have assessed the joint effects of diesel exposure and smoking, and the results are not consistent. Some authors found a stronger effect of diesel exhaust among smokers compared with non-smokers[10]; others found that the effect of each of these exposures was attenuated in the presence of high levels of the other[7] and some others found an additive effect.[34] We clearly found an increased risk due to diesel exhaust in each stratum of smoking. As for the nature of the interaction between smoking and diesel, the pattern of results seems to support more a multiplicative than an additive model, but wide CIs preclude any strong inferences in this regard.

In summary, our findings provide further evidence supporting a causal link between diesel engine emissions and risk of lung cancer. The risk is stronger for the development of squamous cell carcinomas than for small cell tumours or adenocarcinomas.

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Contributors All coauthors contributed significantly to the research. JS designed both studies (I and II) included in this manuscript, developed the methods for assessment of occupational exposures and supervised its implementation. M-EP helped to direct study II and participated in planning analyses. JP conducted the literature review, statistical analysis and prepared the first draft of the article. LR contributed to the design of the studies and the development and coordination of the data collection methods. All coauthors participated in the editing and correction of the final text.

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Competing interests None.

Patient consent Signed by all participants. For deceased subjects, it was signed by next of kin.

Ethics approval Ethical approval was obtained for both studies from each participating hospital and university.

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International Agency for Research on Cancer

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IARC: DIESEL ENGINE EXHAUST CARCINOGENIC

Lyon, France, June 12, 2012 -- After a week-long meeting of international experts, the International Agency for Research on Cancer (IARC), which is part of the World Health Organization (WHO), today classified diesel engine exhaust as **carcinogenic to humans (Group 1)**, based on sufficient evidence that exposure is associated with an increased risk for lung cancer.

Background
In 1988, IARC classified diesel exhaust as *probably carcinogenic to humans (Group 2A)*. An Advisory Group which reviews and recommends future priorities for the IARC Monographs Program had recommended diesel exhaust as a high priority for re-evaluation since 1998.

There has been mounting concern about the cancer-causing potential of diesel exhaust, particularly based on findings in epidemiological studies of workers exposed in various settings. This was re-emphasized by the publication in March 2012 of the results of a large US National Cancer Institute/National Institute for Occupational Safety and Health study of occupational exposure to such emissions in underground miners, which showed an increased risk of death from lung cancer in exposed workers (1).

Evaluation
The scientific evidence was reviewed thoroughly by the Working Group and overall it was concluded that there was *sufficient evidence* in humans for the carcinogenicity of diesel exhaust. The Working Group found that diesel exhaust is a cause of lung cancer (*sufficient evidence*) and also noted a positive association (*limited evidence*) with an increased risk of bladder cancer (Group 1).

The Working Group concluded that gasoline exhaust was possibly carcinogenic to humans (Group 2B), a finding unchanged from the previous evaluation in 1989.

Public health
Large populations are exposed to diesel exhaust in everyday life, whether through their occupation or through the ambient air. People are exposed not only to motor vehicle exhausts but also to exhausts from other diesel engines, including from other modes of transport (e.g. diesel trains and ships) and from power generators.

Given the Working Group's rigorous, independent assessment of the science, governments and other decision-makers have a valuable evidence-base on which to consider environmental standards for diesel exhaust emissions and to continue to work with the engine and fuel manufacturers towards those goals.

Increasing environmental concerns over the past two decades have resulted in regulatory action in North America, Europe and elsewhere with successively tighter emission standards for both diesel and gasoline engines. There is a strong interplay between standards and technology – standards drive technology and new technology enables more stringent standards. For diesel engines, this required changes in the fuel such as marked decreases in sulfur content, changes in engine design to burn diesel fuel more efficiently and reductions in emissions through exhaust control technology.

However, while the amount of particulates and chemicals are reduced with these changes, it is not yet clear how the quantitative and qualitative changes may translate into altered health effects; research into

IARC: Diesel engines exhaust carcinogenic

this question is needed. In addition, existing fuels and vehicles without these modifications will take many years to be replaced, particularly in less developed countries, where regulatory measures are currently also less stringent. It is notable that many parts of the developing world lack regulatory standards, and data on the occurrence and impact of diesel exhaust are limited.

Conclusions
Dr Christopher Portier, Chairman of the IARC working Group, stated that "The scientific evidence was compelling and the Working Group's conclusion was unanimous: diesel engine exhaust causes lung cancer in humans." Dr Portier continued: "Given the additional health impacts from diesel particulates, exposure to this mixture of chemicals should be reduced worldwide."(2)

Dr Kurt Straif, Head of the IARC Monographs Program, indicated that "The main studies that led to this conclusion were in highly exposed workers. However, we have learned from other carcinogens, such as radon, that initial studies showing a risk in heavily exposed occupational groups were followed by positive findings for the general population. Therefore actions to reduce exposures should encompass workers and the general population."

Dr Christopher Wild, Director, IARC, said that "while IARC's remit is to establish the evidence-base for regulatory decisions at national and international level, today's conclusion sends a strong signal that public health action is warranted. This emphasis is needed globally, including among the more vulnerable populations in developing countries where new technology and protective measures may otherwise take many years to be adopted."

Summary evaluation
The summary of the evaluation will appear in The Lancet Oncology as an online publication ahead of print on June 15, 2012.

(1) JNCI J Natl Cancer Inst (2012) doi:10.1093/jnci/djs034
http://jnci.oxfordjournals.org/content/early/2012/03/05/jnci.djs034.abstract; and
JNCI J Natl Cancer Inst (2012) doi: 10.1093/jnci/djs035
http://jnci.oxfordjournals.org/content/early/2012/03/05/jnci.djs035.abstract

(2) Dr Portier is Director of the National Center for Environmental Health and the Agency for Toxic Substances and Disease Registry at the Centers for Disease Control and Prevention (USA).

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Link to the **audio file** posted shortly after the media briefing:
http://terrance.who.int/mediacentre/audio/press_briefings/

About IARC
The International Agency for Research on Cancer (IARC) is part of the World Health Organization. Its mission is to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control. The Agency is involved in both epidemiological and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships.

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Annexes

Evaluation groups - Definitions

Group 1: *The agent is carcinogenic to humans*.
This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.
This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

- **Group 2A:** The agent is *probably carcinogenic to humans*.
  This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

- **Group 2B:** The agent is *possibly carcinogenic to humans*.
  This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is *not classifiable as to its 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.
Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.
Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations.

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Group 4: The agent is *probably not carcinogenic to humans*.
This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

Evidence for studies in humans - Definition

As shown previously, the evidence relevant to carcinogenicity is evaluated using standard terms. For studies in humans, evidence is defined into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

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Carcinogenicity of diesel-engine and gasoline-engine exhausts and some nitroarenes

In June, 2012, 24 experts from seven countries met at the International Agency for Research on Cancer (IARC; Lyon, France) to assess the carcinogenicity of diesel and gasoline engine exhausts, and some nitroarenes. These assessments will be published as Volume 105 of the IARC Monographs.[1]

Diesel engines are used for on-road and non-road transport (eg, trains, ships) and (heavy) equipment in various industrial sectors (eg, mining, construction), and in electricity generators, particularly in developing countries. Gasoline engines are used for cars and hand-held equipment (eg, chainsaws).

Emissions from these engines are complex, with varying composition. The gas phase consists of carbon monoxide, nitrogen oxides, and volatile organic compounds such as benzene and formaldehyde. Particles consist of elemental and organic carbon, ash, sulfate, and metals. Polycyclic aromatic hydrocarbons and nitroarenes are distributed over the gas and the particle phase. The qualitative and quantitative composition of exhausts depends on the fuel, the type and age of the engine, the state of its tuning and maintenance, the emission control system, and pattern of use. Diesel-engine exhaust from engines with no or limited emission controls contains more particulate matter.[2]

In the past two decades, progressively tighter emission standards for on-road vehicles, introduced in North America, Europe, and elsewhere, have triggered advances in diesel technology that resulted in lower emission of particulate matter, nitrogen oxides, and hydrocarbons. Emission standards in non-road applications are lagging and therefore are still largely uncontrolled today. Moreover, in many less developed countries standards are not in place for both on-road and non-road use of diesel and gasoline engines.

The most influential epidemiological studies assessing cancer risks associated with diesel-engine exhausts investigated occupational exposure among non-metal miners, railroad workers, and workers in the trucking industry. The US miners study included a cohort analysis[3] and a nested case–control analysis that was adjusted for tobacco smoking.[4] Both showed positive trends in lung cancer risk with increasing exposure to diesel exhaust, as quantified via estimated elemental carbon as a proxy of exposure. Trends were significant in the nested case–control study, with a 2–3-fold increased risk in the highest categories of cumulative or average exposure. This study provides some of the strongest evidence of an association between exposure to diesel-engine exhaust and lung cancer since there were few potential confounding exposures in these underground mines, and high diesel exposures were well documented in current surveys.

In another US study,[5] a 40% increased risk for lung cancer was observed in railroad workers exposed to diesel exhaust compared with individuals exposed to low levels of or no emissions. Indirect adjustment for smoking suggested that differences in smoking could not have influenced this excess risk substantially. This study was later extended by estimating diesel exposure on the basis of work history and history of dieselisation of different railroads, and showed a significantly increased risk for exposed workers of 70–80%; risk increased with duration of exposure but not with cumulative exposure.[6]

A large cohort study in the US trucking industry[7] reported a 15–40% increased lung cancer risk in drivers and dockworkers with regular exposure to diesel exhaust. There was a significant trend of increasing risks with longer duration of employment, with 20 years of employment roughly doubling the risk after adjusting for tobacco smoking. When this study was extended with an exposure assessment involving contemporary measurements and exposure reconstruction on the basis of elemental carbon, positive trends were observed for cumulative but not average exposure. These trends were more pronounced when adjustment for duration of work was included.[8]

The findings of these cohort studies were supported by those in other occupational groups and by case–control studies including various occupations involving exposure to diesel-engine exhaust. A positive exposure–response relationship was found in several studies from Europe and the USA, many of which were adjusted for tobacco smoking. Most notably, a pooled analysis of 11 population-based case–control studies from Europe and Canada showed a smoking-adjusted increased risk for lung cancer after exposure to diesel engine exhaust, which was assessed by a job exposure matrix, and a positive dose response in terms of both a cumulative exposure index and duration of exposure.[9]

These epidemiological studies support a causal association between exposure to diesel-engine exhaust and lung cancer. An increased risk for bladder cancer was also noted in many but not all available case–control studies. However, such risks were not observed in cohort studies. The Working Group concluded that there was "sufficient evidence" in humans for the carcinogenicity of diesel-engine exhaust.

The diesel-engine exhausts and their extracts used in carcinogenicity studies with experimental animals were generated from fuels and diesel engines produced before 2000. The studies were considered by type of

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News

	Evidence of carcinogenicity in experimental animals	Mechanistic evidence	Overall evaluation
3,7-Dinitrofluoranthene	Sufficient	Weak	2B
3,9-Dinitrofluoranthene	Sufficient	Weak	2B
1,3-Dinitropyrene	Sufficient	Weak	2B
1,6-Dinitropyrene	Sufficient	Moderate	2B
1,8-Dinitropyrene	Sufficient	Moderate	2B
3-Nitrobenzanthrone	Limited	Strong	2B*
6-Nitrochrysene	Sufficient	Strong	2A*
2-Nitrofluorene	Sufficient	Weak	2B
1-Nitropyrene	Sufficient	Strong	2A*
4-Nitropyrene	Sufficient	Moderate	2B

*Strong mechanistic evidence contributed to the overall evaluation.

Table: **Evaluation of some nitroarenes**

exposure: whole diesel-engine exhaust; gas-phase diesel-engine exhaust (with particles removed); and extracts of diesel-engine exhaust particles. Whole diesel-engine exhaust caused an increased incidence of lung tumours in rats.[10] Diesel-engine exhaust particles instilled intratracheally caused benign and malignant lung tumours in rats,[11] and the particle extracts also caused lung carcinomas in rats and sarcomas at the injection site in mice.[12,13] Gas-phase diesel-engine exhaust did not increase incidence of respiratory tumours in any species tested. The Working Group concluded that there was "sufficient evidence" in experimental animals for the carcinogenicity of whole diesel-engine exhaust, of diesel-engine exhaust particles and of 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, in vitro and in vivo, various forms of DNA damage, including bulky adducts, oxidative damage, strand breaks, unscheduled synthesis, mutations, sister chromatid exchange, morphological cell transformation in mammalian cells, and mutations in bacteria.[14] Increased expression of genes involved in xenobiotic metabolism, oxidative stress, inflammation, antioxidant response, apoptosis, and cell cycle in mammalian cells was observed.

Positive genotoxicity biomarkers of exposure and effect were also observed in humans exposed to diesel engine exhaust. The Working Group concluded that there is "strong evidence" for the ability of whole diesel-engine exhaust to induce cancer in humans through genotoxicity.

Gasoline exhaust and cancer risk was investigated in only a few epidemiological studies and, because of the difficulty to separate effect of diesel and gasoline exhaust, evidence for carcinogenicity was evaluated as "inadequate".

The Working Group considered the animal carcinogenicity studies of gasoline-engine exhaust by type of exposure: whole gasoline-engine exhaust; and extracts of gasoline-engine exhaust condensate. Organic extracts of gasoline engine-exhaust condensate induced a significant increase in lung carcinomas and papillomas of the skin in mice.[15] In rats, the gasoline-exhaust condensate induced a significant increase in lung carcinomas.[16] The Working Group concluded that there was "sufficient evidence" in experimental animals for the carcinogenicity of condensates of gasoline-engine exhaust.

Gasoline-engine exhaust induced chromosomal damage in mice, and changes in gene expression in rat lung that involved pathways related to xenobiotic metabolism and inflammation. In mammalian cells, gasoline-engine exhaust particles and organic extracts thereof induce DNA adducts, DNA strand breaks, oxidative DNA damage, chromosomal aberrations, and morphological cell transformation, as well as gene mutations in bacteria. In mammalian cells, extracts of gasoline-exhaust engine particles altered expression of genes involved in inflammation, xenobiotic metabolism, tumour progression, and cell cycle. The gaseous phase of gasoline-engine exhaust was mutagenic to bacteria. The Working Group concluded that there is "strong evidence" for a genotoxic mechanism for the carcinogenicity of organic solvent extracts of particles from gasoline engine exhaust.

In conclusion, the Working Group classified diesel engine exhaust as "carcinogenic to humans" (Group 1) and gasoline engine exhaust as "possibly carcinogenic to humans" (Group 2B).

Evaluations for ten nitroarenes, all of which have been detected in diesel-engine exhaust, are shown in the table. Biomonitoring studies have shown that workers and the general population are exposed to these substances.[17–19] All the nitroarenes were genotoxic to various extents in different assays. The Working Group reaffirmed the Group 2B classification of seven. Strong evidence for genotoxicity led to an upgrade of 3-nitrobenzanthrone to Group 2B, and similar findings in human cells led to an upgrade of 1-nitropyrene and 6-nitrochrysene to Group 2A.

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Conflicts of interest
DBK has received research funding from Caterpillar and from British Petroleum. MvT has received research funding from Statoil, CONCAWE, and CEFIC. JG has received research funding from CONCAWE. DG is the President of the Health Effects Institute (the Institute's funding comes in equal part from the US Environmental Protection Agency and the makers of motor vehicles for sale in the USA). TH is an employee of Navistar (manufacturer of diesel trucks and engines). TLL served as a consultant to the diesel industry through Cambridge Environmental. RM serves as a consultant for the Engine Manufacturers Association, Navistar International, Cummins Engine Company, Shell Exploration and Production Company, Union Pacific, and the American Petroleum Institute. PM is a member of the Scientific Advisory Group of European Research Group on Environment and Health in the Transport Sector. DP holds stock in Daimler-Benz AG and was employed until 2008 by BASF. JCW is Vice President and Chief Technical Officer of Cummins, and holds stock and patents. SM holds stock in BHP Billiton Limited. All other Working Group members, specialists, representatives, and secretariat declare that they have no conflicts of interest.

See Online for appendix

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Fuel Impact on Exhaust Emissions - Comparison of Two Diesel Fuels

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ABSTRACT

In the EU regulations, specification's for diesel fuel quality is regulated in the standard EN590. Sweden has however for many years used an "Environmental Class 1" (EC1) diesel fuel. In addition to fulfilling the EN590 standard, the main difference today between the Swedish EC1 and the EN590 fuel specifications is that higher levels of aromatics and polyaromatics (PAH) are allowed in the EN590 standard. Aromatics are considered to be potentially mutagenic, and the higher levels of aromatics also lead to increased particle emissions.

Earlier studies of the exhaust emissions from engines using the different fuel qualities have shown significant differences, both regarding regulated emissions and health effects. In these studies, vehicles from emission standard Euro III and older have been used. The scope of this study was to investigate whether the differences persist for a modern Euro V vehicle or not.

Emission results from tests performed on a heavy duty vehicle fuelled with the two different diesel qualities are presented. The tests were carried out on a chassis dynamometer and the vehicle was driven according to the WHVC test cycle. Both regulated and several unregulated components were measured, along with CO2 and fuel consumption. The gaseous components were sampled in bags and measured second-by-second. Particulate matter was collected on filter and also measured second-by-second with a TEOM instrument.

In addition to the particulate mass, the particle size distribution was measured with an ELPI instrument. The unregulated components includes olefins, PAH and aldehydes. Extract of the particulate and semivolatile phase was used to carry out the Ames' bio assay to analyze the level of mutagenicity in the exhausts.

This study has shown that there were significant differences between these two fuel qualities for a modern Euro V vehicle. The emission tests performed with EN590 show higher levels of the regulated components NOx, PM and CO - all of which have shown direct and indirect effects on both health and environment. For the unregulated components, aldehydes are emitted to a greater extent when the vehicle is fuelled with the EN590 fuel. The higher levels of PAH in the EN590 fuel is reflected in the emissions, and the PAH extracts used for the Ames' bio assay show higher levels of mutagenicity for the EN590 fuel.

The WHVC driving cycle can be divided into three subcycles, each representing different driving patterns (urban, rural and motorway). This enables an analysis of emissions relative to the driving pattern, and a comparison of the two fuels. Since HDVs are designed to operate on various conditions such as urban, rural and motorway, the exhausts from all of those conditions have been analyzed. NOx and PM emissions have especially been highlighted as problems in urban areas and the high levels are probably caused by diesel fuelled HDVs and LDVs. Previous studies of real driving emissions have shown that some Euro IV and V HDV emit as much as Euro III vehicles during urban driving.

16th ETH Conference on Combustion Generated Particles
June 24th – 27th 2012

Session 5a: Health Effects **13.00 – 15.10** Chair: B. Rothen-Rutishauser
Brunekreef B. / University of Utrecht, The Netherlands *Health Effects of Airborne Ultrafine Particles: Observations from Epidemiology*
Katsouyanni K. / University of Athens, Greece *Acute Human Health Effects: Epidemiologic Evidence for Relevance of Nanoparticles*
Schins R. / University of Düsseldorf, Germany *Effects of Subchronic Inhalation Exposure to Diesel Engine Exhaust*
Probst-Hensch N. / Swiss Tropical and Public Health Institute, Basel, Switzerland *Gene-Air Pollution Interaction and Beyond*
Clift M. / University of Fribourg, Switzerland *Diesel Exhaust Particles and Human Health; Genotoxicity*

Session 5b: Health Effects **10.10 – 12.30** Chair: P. Gehr
Oberdörster G. / University of Rochester, USA *Effects and Safety Evaluation of Nanoparticles*
Perez L. / Swiss Tropical and Public Health Institute, Basel, Switzerland *The Burden of Near-Road Traffic Related Pollution*
Steiner S. / University of Fribourg, Switzerland *Effect of a Diesel Particle Filter on Toxicity in Lung Cells in Vitro*
Violi A. / University of Michigan, USA *Formation and Uptake of Environmental Nanoparticles*
Walker K. / Health Effects Institute, Boston, USA *Ambient Ultrafine Particles and Health*
Fong K. / VERENUM, Zürich, Switzerland *Health Effects of Wood Combustion Aerosols*
Künzli N. / *Swiss Tropical and Public Health Institute, Basel, Switzerland* *Introduction to Focus Event*

T H E S E S

16th ETH-Conference on Combustion Generated Nanoparticles
24th - 27th June, 2012
ETH Zürich, Zürich, Switzerland

Focus-Event "How to Regulate Ambient Nanoparticles"

27th June, 2012

Recent research indicates gaps of the current policy framework, leaving health relevant fractions of PM pollution unregulated, thus, jeopardizing public health protection among those most exposed to these pollutants, namely the nanosized fraction of particles. The following Theses summarize the rationale to promote additional, source specific regulations to protect people from adverse effects of ambient nanoparticles. They shall contribute to a discussion on how the gaps of the current policy framework may be closed.

A: Current PM regulations

1. The mass concentration of particles with a diameter of ≤10µm (PM_{10}) is an established marker to describe health relevant characteristics of ambient air pollution. PM_{10} are regulated in air quality standards in many countries (including Switzerland), thus, are extensively measured in monitoring networks. PM_{10} does not reflect size distribution and chemical composition of fine particles and is therefore not suited to detect and document changes in size- and composition-specific characteristics of particle related air pollution. PM_{10} correlates best with health risks due to the coarser fraction of fine particles. The PM_{10} fraction between 5 and 10 µm in diameter usually does not reach the lung periphery (alveoli) where the tissue surface (alveolar surface) is separated from the blood (blood capillaries) by less than 1 µm. Thus PM_{10} is not suited to describe risk related to alveolar effects of air pollution.

2. The mass concentration of particles with a diameter of ≤2.5µm ($PM_{2.5}$) is an established marker to describe health relevant characteristics of fine particles in ambient air. $PM_{2.5}$ are regulated in National Air Quality Standards of many countries, including the USA. Particles of 2.5-5 µm in diameter and smaller can reach the alveolar region but cannot penetrate the air-blood tissue barrier in the alveoli. Whilst strongly associated with a broad range of health effects, $PM_{2.5}$ are not well suited to describe exposure to the ultrafine fraction of particle pollution as the latter contribute only marginally to the mass concentration.

3. The mass concentration of particles with a diameter of ≤0.1µm, $PM_{0.1}$ are better indicators to describe the physical characteristics of the ultrafine fraction of particles. Those are called nanoparticles (engineered nanoparticles) or ultrafine particles (ambient nanoparticles). These ultrafine particles are currently not regulated in ambient air. Their interactions with biological systems differ from those of larger particles (see B below). The terms 'combustion-generated

particles' or 'soot' may often refer to this size fraction as well. The particle count or particle number is an alternative marker of $PM_{0.1}$ as $PM_{0.1}$ is highly driven by the particle number.

B: Behaviour of nanoparticles at biological barriers, cells and tissues

4. Only nanoparticles may penetrate in the lung into cells and tissues and, therefore, in the alveolar region through the air-blood tissue barrier into the blood; they can translocate into other organs by the blood circulation, where they may interact with organ specific cells and tissues.
There are further biological barriers, like the blood-brain barrier, the blood-blood placenta barrier, the blood-thymus barrier, the blood-testis barrier a.o. that may be penetrated by nanoparticles.

5. Within cells nanoparticles may cause adverse effects. Moreover, adverse effects have been shown to be caused by nanoparticles in the vascular system.Combustion-generated nanoparticles may cause inflammatory effects in the brain; in most organs, however, the effects which nanoparticles may cause are not fully known yet.
Size matters; nanosized particles are the most critical ones for health

C: Physical, chemical and toxicological properties of nanoparticles and its health relevance

6. Nanoparticles hardly contribute to particle mass and are rather quantified by their number or surface (size, characteristics) for metrological reasons which in turn may be of specific relevance for health as well.

7. Most of the combustion-generated nanoparticles consist of carbon black which is known to be cancerogenic. These particles adsorb genotoxic compounds among other substances and may contain toxic metals and metal oxides.

D: New measuring techniques and regulatory concepts for ambient nanoparticles

8. Measuring techniques and instruments are now available for nanoparticle number/surface and carbon black/metal/metal oxides. However, in view of their practicability for harmonised compliance measurements they differ considerably in terms of complexity, calibration and time resolution.

9. Given availability of techniques, additional air quality standards should now be established for markers of exposure to ambient nanoparticles. Candidates are nanoparticle number or surface which are already measured at some NABEL stations and/or carbon black / elemental carbon, maybe also metal/metal oxides, in addition to PM_{10}. Considering available harmonised measurement techniques, methods for black carbon (BC) are for the time being sufficiently advanced to allow for compliance measurements within short terms.

10. As of 2011 the EU asks diesel as well as gasoline engine emissions of cars to be regulated by nanoparticle number standards (EURO-5b), as of 2014 also for trucks (EURO VI); there are no corresponding particle number-based standards planned yet for ambient concentrations.

Focus Event on "how to regulate ambient nanoparticles" Concluding Remarks

M. Schmitz, C. Leuenberger

The adverse effects of different properties of ambient nanoparticles regarding health and climate are still under discussion. Thus it remains unclear on which components regulation should focus on.

In terms of health effects, however, expert opinions seem to concentrate on two characteristics that might be of major importance. First the size of ambient nanoparticles: ultrafine particles have the highest potential to induce adverse health effects and second the composition of the particles. Here the presence of soot (EC or OC) is assumed to be of major importance. In addition the mixture of components might also play a role.

Besides the question on which characteristics of ambient nanoparticles regulation should focus on, the problem of measurability is of major importance. Under discussion are the following measurement categories: particle number, particle mass, particle composition and particle surface. Each measurement category includes specific problems, advantages and disadvantages.

If particle number is measured, the smallest and most dangerous particles (regarding health effects) become most important. In contrast if particle mass is measured, e.g. PM10, the importance of the smallest particles disappear in relation to the high mass of the larger ones. As a sort of compromise, and for pragmatic reasons, the measurement of PM 2.5, PM 1.0, or even a new smaller category could be measured.

A problem for the measurement of particle number are the secondary organic aerosols (SOA), which are formed in the atmosphere and are mostly in the ultrafine size range. They might produce misleading results since these particles are not all derived from anthropogenic sources. In addition there is no standardized test method available yet.

In summary it can be said that the international scientific community has not agreed on a new measure for ambient nanoparticles yet. Although the disadvantages of PM10 measurements are apparent. There is agreement, however, that new measurement methods must be internationally recognized before they are installed and that this will be a time consuming process.

In terms of fighting air pollution it remains important to use the best available technology known to reduce nanoparticle emissions.

The increasing differentiation of particulate matter regarding size and chemical composition in research makes the use of PM10 more and more questionable. As a sum parameter PM10 contains a large variety of different particles, including harmless mineral salts. In addition, more and more studies have indicated significant increases of health risks with decreasing particle size, because ultrafine particles penetrate deeper into the lungs or even into the bloodstream.

These findings have led to a discussion about which metrics are more important to assess the health risk of particulate matter. Thus in recent studies and some air quality monitoring networks (e.g. Nabel) other metrics such as PM2.5 and PM1 as well as particle number concentration have already been assessed in addition to PM10. Since the international scientific community has not agreed on a new measurement method for ambient nanoparticles yet, the results of these studies are hardly comparable. Thus there is an urgent need to develop new measurement methods which are internationally recognized before they are installed widely.

This will not only be important to improve the comparability of further studies on the health effects of ambient nanoparticles, but also relevant to assess the success of recent air quality measures. For example the low emission zones, which have been introduced in several European countries, do not show a pronounced effect on PM10. In contrast, the particularly harmful carbon fraction (EC / OC) in particulate matter is reduced substantially. Thus, the effect of low emission zones on local air quality can only be shown upon closer inspection. However, as long as only PM10 is regulated by the national authorities such results are not of legal importance.

AECC NEWSLETTER March - April 2012

RESEARCH SUMMARY
First Results from the US ACES Study

The first results from the independent Health Effects Institute (HEI) ACES study, released on 13 April 2012, found few biologic effects from exposure to exhaust from new technology diesel engines.

The peer-reviewed study is a component of the Advanced Collaborative Engine Study (ACES) and is exposing rats and mice for 16 hours a day to emissions from a heavy-duty diesel engine meeting US EPA 2007 emissions standards. The first results of this comprehensive study of the health effects of exposure to new technology diesel engines found no evidence of gene-damaging effects in the animals studied, and only a few mild effects on the lungs.

The study found that exposures lasting one, three, and in some cases up to twelve months had effects on only a few of the many health markers tested; exposures will continue for the lifetime of the rats. The few effects that were reported for the rats were mild hyperplasia (cell proliferation) in the lungs and slightly reduced lung function, and were most consistent with exposure to nitrogen oxides in the engine exhaust, which are being further reduced under 2010 US EPA standards now in effect.

Part 1 of the report describes the core inhalation study with results on general organ toxicity, lung histopathology, pulmonary function, and markers of inflammation and oxidative stress in blood and lung lavage fluid. Parts 2 & 3 describe studies assessing genotoxic endpoints in the exposed rodents.

These results are expected to play an important role in the upcoming risk reviews by international and US agencies of older and new technology diesel engines, including a review of the carcinogenicity of diesel exhaust in June 2012 by the International Agency for Research on Cancer (IARC).

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AECC NEWSLETTER March - April 2012

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