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Carcinogenicity of diesel and gasoline engine exhausts and some nitroarenes

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

Diesel and gasoline engines are internal combustion engines that are the major power sources used in on-road vehicles worldwide. Diesel engines are also used for non-road transport (e.g. trains, ships) and (heavy) equipment in various industrial sectors (e.g. mining, construction) and in electricity generators, particularly in developing countries. Gasoline engines are also used for hand held equipment (e.g. chain saws).

Emissions from these engines are complex with varying composition. The gas phase consists of carbon monoxide (CO), nitrogen oxides (NOx), and volatile organic compounds such as benzene and formaldehyde. Particles consist of elemental and organic carbon (EC, OC), ash, sulfate, and metals. Polycyclic aromatic hydrocarbons (PAHs) and nitroarenes are primarily present in the particle-phase, but some are also found in the gas phase. The qualitative and quantitative composition of the exhausts depends on the fuel, the type and age of the engine, the state of its tuning and maintenance, the emission control system, and the pattern of use. Diesel engine exhaust from engines with no or limited emission controls contains more particulate matter (2).

Over the last 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, NOx and hydrocarbons. Emission standards in non-road applications are lagging and therefore these 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 EC as a proxy of exposure. Trends were statistically 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 a 40% increased risk for lung cancer was observed in railroad workers exposed to diesel exhaust compared to low and non-exposed (95% CI 1.30–1.51) (5). 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 based on work history and the history of dieselization of different railroads and found a significantly increased risk for exposed workers in the order of 70-80%; risk increased with greater duration of exposure but not with cumulative exposure (6).

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

The findings of these cohort studies were supported by studies 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 of these studies from the 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). Taken together 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 of the available case-control studies. However, such risks were not observed in the 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 the year 2000. The studies were considered by type of 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 the incidence of respiratory tumours in any of the 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, and morphological cell transformation in mammalian cells, and also mutations in bacteria (14). Increased expression of genes involved in xenobiotic metabolism, oxidative stress, inflammation, anti-oxidant response, apoptosis and cell cycle in mammalian cells was observed.

Positive genotoxicity biomarkers of exposure and effect were also observed among 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 only investigated in a few epidemiological studies and, because of the difficulty to separate the effect of diesel and gasoline exhaust in these studies, the evidence for carcinogenicity was evaluated as “inadequate”.

The Working Group considered the animal carcinogenicity studies on gasoline engine exhaust by type of exposure: whole gasoline engine exhaust; gas-phase gasoline engine exhaust (with particles removed) 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 carcinomas and sarcomas of the lung (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-exhaust particles and organic extracts of gasoline particles 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-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 (17). 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 Table 1. Biomonitoring studies have shown that workers and the general population are exposed to these substances (18); (19); (20). All the nitroarenes were genotoxic to various extents in different assays. The Working Group reaffirmed the Group 2B classification of seven of theses nitroarenes. Strong evidence for genotoxicity led to an upgrade of 3-nitrobenzanthrone to Group 2B and similar findings in human cells led to an upgrade for 1-nitropyrene and 6-nitrochrysene to Group 2A.

Reference List

(1) IARC. Diesel and gasoline engine exhausts and some nitroarenes. IARC Monogr Eval Carcinog Risks Hum. In press 2012.

(2) Majewski, W. A. and Khair, M. K. Diesel Emissions and Their Control. 2006. Report No.: SAE International R-303.

(3) Attfield MD, Schleiff PL, Lubin JH, Blair A, Stewart PA, Vermeulen R et al. The Diesel Exhaust in Miners Study: A Cohort Mortality Study With Emphasis on Lung Cancer. J Natl Cancer Inst 2012 March 5;104(11):869-83.

(4) Silverman DT, Samanic CM, Lubin JH, Blair AE, Stewart PA, Vermeulen R et al. The Diesel Exhaust in Miners Study: A Nested Case-Control Study of Lung Cancer and Diesel Exhaust. J Natl Cancer Inst 2012 March 5;104(11):855-68.

(5) Garshick E, Laden F, Hart JE, Rosner B, Smith TJ, Dockery DW et al. Lung cancer in railroad workers exposed to diesel exhaust. Environ Health Perspect 2004 November;112(15):1539-43.

(6) Laden F, Hart JE, Eschenroeder A, Smith TJ, Garshick E. Historical estimation of diesel exhaust exposure in a cohort study of U.S. railroad workers and lung cancer. Cancer Causes Control 2006 September;17(7):911-9.

(7) Garshick E, Laden F, Hart JE, Rosner B, Davis ME, Eisen EA et al. Lung cancer and vehicle exhaust in trucking industry workers. Environ Health Perspect 2008 October;116(10):1327-32.

(8) Garshick E, Laden F, Hart JE, et al. Lung Cancer and Elemental Carbon Exposure in Trucking Industry Workers. Environ Health Perspect. In press 2012.

(9) Olsson AC, Gustavsson P, Kromhout H, Peters S, Vermeulen R, Bruske I et al. Exposure to diesel motor exhaust and lung cancer risk in a pooled analysis from case-control studies in Europe and Canada. Am J Respir Crit Care Med 2011 April 1;183(7):941-8.

(10) Heinrich U, Fuhst R, Rittinghausen S, et al. Chronic Inhalation Exposure of Wistar Rats and two Different Strains of Mice to Diesel Engine Exhaust, Carbon Black, and Titanium Dioxide. Inhal Toxicol 1995;7(4):533-56.

(11) Pott F, Roller M. Carcinogenicity study with nineteen granular dusts in rats. Eur J Oncol 2005;10:249-81.

(12) Kunitake E, Shimamura K, Katayama H, Takemoto K, Yamamoto A, Hisanaga A et al. Studies concerning carcinogenesis of diesel particulate extracts following intratracheal

instillation, subcutaneous injection, or skin application. Dev Toxicol Environ Sci 1986;13:235-52.

(13) Grimmer G, Brune H, Utsch-Wenzel R, Dettbarn G, Jacob J, Naujack KW et al. Contribution of polycyclic aromatic hydrocarbons and nitro-derivatives to the carcinogenic impact of diesel engine exhaust condensate evaluated by implantation into the lungs of rats. Cancer Lett 1987 October 30;37(2):173-80.

(14) IARC. IARC monographs on the evaluation of carcinogenic risks to humans. Diesel and gasoline engine exhausts and some nitroarenes. International Agency for Research on Cancer. IARC Monogr Eval Carcinog Risks Hum 1989;46:1-458.

(15) Brune H, Habs M, Schmahl D. The tumor-producing effect of automobile exhaust condensate and fractions thereof. Part II: animal studies. J Environ Pathol Toxicol 1978 July;1(6):737-45.

(16) Grimmer G, Brune H, Utsch-Wenzel R, Dettbarn G, Misfeld J. Contribution of polycyclic aromatic hydrocarbons to the carcinogenic impact of gasoline engine exhaust condensate evaluated by implantation into the lungs of rats. J Natl Cancer Inst 1984 March;72(3):733-9.

(17) Scientific data and findings supporting the conclusion that no revision is warranted to the current IARC assessment (group 2a) of the potential carcinogenic risks to humans from exposures to traditional diesel exhaust. EMA; 2011.

(18) Scheepers PTJ, Velders DD, Martens MHJ, Noordhoek J, Bos RP. Gas chromatographic-mass spectrometric determination of nitro polycyclic aromatic hydrocarbons in airborne particulate matter from workplace atmosphere. Journal of Chromatography A 1994 August 12;677(1):107-21.

(19) Seidel A, Dahmann D, Krekeler H, Jacob J. Biomonitoring of polycyclic aromatic compounds in the urine of mining workers occupationally exposed to diesel exhaust. Int J Hyg Environ Health 2002 February;204(5-6):333-8.

(20) Zwirner-Baier I, Neumann HG. Polycyclic nitroarenes (nitro-PAHs) as biomarkers of exposure to diesel exhaust. Mutat Res 1999 April 26;441(1):135-44.

Table 1: Evaluation of the nitroarenes

Agent	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 (see text).