

# 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.<sup>1</sup>

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.<sup>2</sup>

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<sup>3</sup> and a nested case-control analysis that was adjusted for tobacco smoking.<sup>4</sup> 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,<sup>5</sup> 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.<sup>6</sup>

A large cohort study in the US trucking industry<sup>7</sup> 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.<sup>8</sup>

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.<sup>9</sup>

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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#### 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

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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

	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.<sup>10</sup> Diesel-engine exhaust particles instilled intratracheally caused benign and malignant lung tumours in rats,<sup>11</sup> and the particle extracts also caused lung carcinomas in rats and sarcomas at the injection site in mice.<sup>12,13</sup> 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.<sup>14</sup> 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.<sup>15</sup> In rats, the gasoline-exhaust condensate induced a significant increase in lung carcinomas.<sup>16</sup> 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.<sup>17–19</sup> 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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We declare that we have no conflicts of interest.

For references see appendix.