The IARC Monographs Programme, Vol. 105 The carcinogenicity of diesel engine exhaust, gasoline engine exhaust and some nitroarenes

Kurt Straif, MD MPH PhD

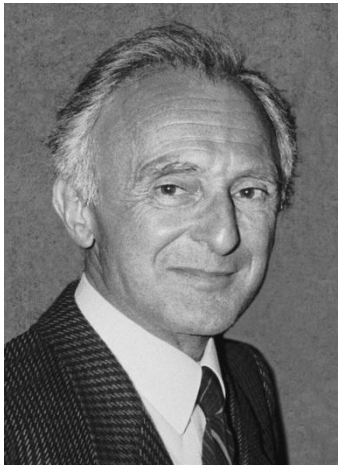
International Agency for Research on Cancer
Lyon, France

International Scientific Symposium
Emerging Issues in Environmental and Occupational Health:
Mining and Construction in Transition Economies
April 22-23, 2013 in Yerevan, Armenia

"The encyclopaedia of carcinogens"

The *IARC Monographs* evaluate

- Chemicals
- Complex mixtures
- Occupational exposures
- Physical and biological agents
- Lifestyle factors



Lorenzo Tomatis
1929-2007

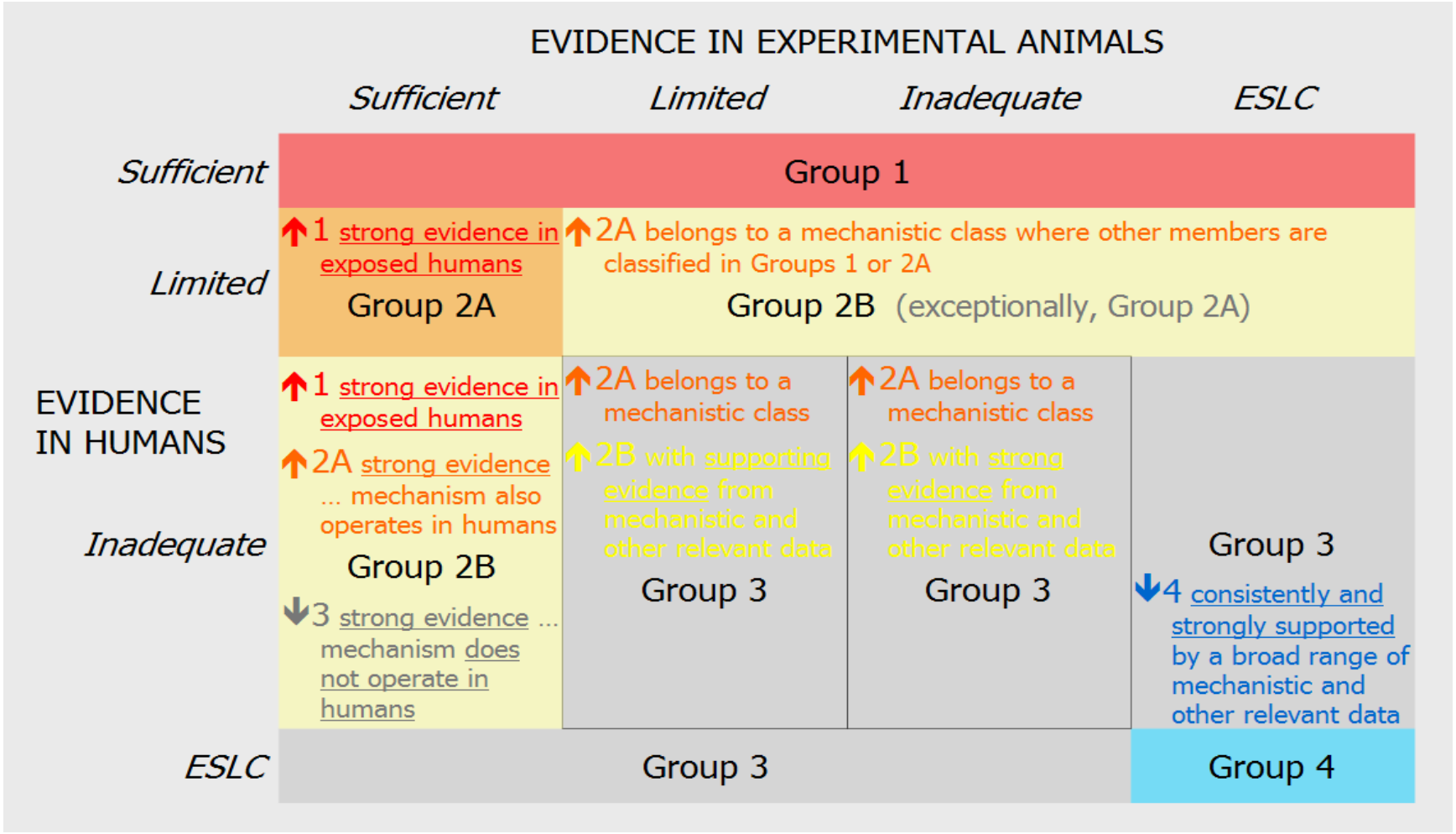
More than 950 agents have been evaluated

- 110 are *carcinogenic to humans* (Group 1)
- 65 are *probably carcinogenic to humans* (Group 2A)
- 274 are *possibly carcinogenic to humans* (Group 2B)

National and international health agencies use the *Monographs*

- As a source of scientific information on known or suspected carcinogens
- As scientific support for their actions to prevent exposure to known or suspected carcinogens

Overall carcinogenicity evaluation



IARC Monographs, Vol 46, 1988

- There is limited evidence for the carcinogenicity in humans of diesel engine exhaust.
- There is sufficient evidence for the carcinogenicity in experimental animals of whole diesel engine exhaust.

Overall evaluation

Diesel engine exhaust is probably carcinogenic to humans (2A).

- There is inadequate evidence for the carcinogenicity in humans of gasoline engine exhaust.
- There is sufficient evidence for the carcinogenicity in experimental animals of condensates/ extracts of gasoline engine exhaust.

Overall evaluation

Gasoline engine exhaust is possibly carcinogenic to humans (2B)

Diesel engine exhaust: exposure (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.
- 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.

Diesel engine exhaust: exposure (2)

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.

Diesel engine exhaust: exposure (3)

- 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.
- In many less developed countries standards are not in place for both on-road and non-road use of diesel and gasoline engines.

Diesel engine exhaust and lung cancer (1)

Study in US miners

- In a large US miners study diesel engine exhaust was quantified via estimated elemental carbon as a proxy of exposure
- Cohort and nested case–control analyses adjusted for tobacco smoking showed positive trends in lung cancer risk with increasing exposure to diesel exhaust, with 2–3-fold increased risk in the highest categories of cumulative or average exposure. (Attfield et al 2012, Silverman et al 2012).

Diesel engine exhaust and lung cancer (2)
Study in US railroad workers

- In US railroad workers exposed to diesel exhaust a 40% increased risk for lung cancer was observed.
- 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;
- Results showed a significantly increased risk for exposed workers of 70–80%; risk increased with duration of exposure but not with cumulative exposure. (Garshick et al, 2004 & Laden et al 2008).

Diesel engine exhaust and lung cancer (3)

Study in the US trucking industry

- A large cohort study in the US trucking industry reported a 15–40% increased lung cancer risk in drivers and dockworkers with regular exposure to diesel exhaust;
- 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 . (Garshick et al, 2008 & 2012)

Diesel engine exhaust and lung cancer (4)

The findings of above 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.
- A pooled analysis of 11 population-based case–control studies from Europe and Canada assessed exposure by a job exposure matrix;
- Results showed a smoking-adjusted increased risk for lung cancer after exposure to diesel engine exhaust and a positive exposure-response for both a cumulative exposure index and duration of exposure (Olsson et al, 2011).

Diesel engine exhaust and bladder cancer

- An increased risk for bladder cancer was noted in many but not all available case–control studies. However, such risks were not observed in cohort studies.

Evaluation, cancer in humans

- The Working Group concluded that there was "sufficient evidence" in humans for the carcinogenicity of diesel-engine exhaust.

Diesel engine exhaust, cancer bioassays

DEE and their extracts used in carcinogenicity studies with experimental animals were generated from fuels and diesel engines produced before 2000.

- Whole diesel-engine exhaust caused an increased incidence of lung tumours in rats.
- Diesel-engine exhaust particles instilled intratracheally caused benign and malignant lung tumours in rats, and the particle extracts also caused lung carcinomas in rats and sarcomas at the injection site in mice.
- Gas-phase diesel-engine exhaust did not increase incidence of respiratory tumours.

Diesel engine exhaust, cancer bioassays Evaluation

- 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.

DEE, mechanisms of carcinogenicity (1)

DEE, DEE particles, DEE condensates, and organic solvent extracts of DEE 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.

DEE, mechanisms of carcinogenicity (2)

- Increased expression of genes involved in xenobiotic metabolism, oxidative stress, inflammation, antioxidant response, apoptosis, and cell cycle regulation 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.

Diesel engine exhaust
Overall Evaluation

- There is sufficient evidence for the carcinogenicity in humans of diesel engine exhaust. Diesel engine exhaust causes lung cancer. Also, a positive association between diesel engine exhaust and bladder cancer has been observed.
- There is sufficient evidence for the carcinogenicity in experimental animals of whole diesel engine exhaust.

Overall evaluation

- Diesel engine exhaust is carcinogenic to humans (Group 1).

Gasoline engine exhaust and cancer

- Gasoline engine 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 concluded that there was "sufficient evidence" in experimental animals for the carcinogenicity of condensates of gasoline-engine exhaust.

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

Carcinogenicity of some nitroarenes, Vol. 105

	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.

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

Published Online
June 15, 2012

In June, 2012, 24 experts from seven countries met at the International Agency for Research on Cancer

The most influential epidemiological studies assessing cancer risks associated with diesel-engine exhausts

with 20 years of employment roughly doubling the risk after adjusting for tobacco smoking. When this study

Acknowledgements

The *IARC Monographs* are supported by grants from

- **U.S. National Cancer Institute (since 1982)**
- **European Commission, DG Employment, Social Affairs and Inclusion (since 1986)**
- **U.S. National Institute of Environmental Health Sciences (since 1992)**