The Director General

Maisons-Alfort, 19 April 2017

Scientific and technical support
NOTE
by the French Agency for Food, Environmental and Occupational Health & Safety

regarding on-road diesel vehicle emissions in France considering IARC Monograph Volume 105 on the carcinogenicity of engine exhaust emissions

(Related Request no. 2014-SA-0156)

On 31 July 2014, ANSES received a formal request from the Directorate General for Health, the Directorate General for Risk Prevention and the Directorate General for Energy and the Climate to investigate the issue of the chemical composition of the particles in ambient air and to define the change in particulate emissions with regard to the French on-road fleet (Request No 2014-SA-0156 in Annex 1). In the framework of this formal request, ANSES was also asked "*its opinion as to the transposition of the conclusions issued in 2012 by the International Agency for Research on Cancer (IARC) on exhaust emissions from diesel engines, to the emissions from on-road diesel vehicles in France*".

A collective expert appraisal is currently under way to respond to the formal request. This scientific and technical support note presents the Agency's response concerning the specific question on emissions from on-road diesel vehicles.

1. BACKGROUND AND PURPOSE OF THE REQUEST

In June 2012, the IARC classified the exhaust emissions from diesel engines as carcinogenic to humans (Group 1) and the exhaust emissions from gasoline engines as possibly carcinogenic to humans (Group 2B). In October 2013, the IARC also classified outdoor air pollution as a whole, and the particulate matter making up this pollution, as carcinogenic to humans (Group 1).

Given the impact of the IARC's classifications and the preponderance of diesel vehicles on French roads, the Ministries of Health and the Environment, which sponsored this formal request, have been largely solicited on this issue.

In this context, this note is intended to provide the sponsors of the formal request with some answers and summarised information, including:

- a summary of the IARC's assessment on the carcinogenicity of diesel and gasoline engine exhausts (Monograph Volume 105) (§ 3.1. pages 2 to 5),
- "questions and answers" on the emissions from on-road diesel vehicles circulating in France considering the conclusions of IARC Monograph Volume 105 (§ 3.2. pages 6 to 10).

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2. ORGANISATION OF THE WORK

This scientific and technical support note was produced by ANSES's Air Risk Assessment Unit, part of the Risk Assessment Department. ANSES received assistance in drafting this note from its Expert Committee (CES) on "Assessment of risk related to air environments" (CES Air). Three expert rapporteurs, members of the CES Air, were mandated to provide their support. The note was presented to the CES for comments at its meeting on 9 March 2017.

3. ANALYSIS AND CONCLUSIONS

3.1. Summary of the IARC's assessment on the carcinogenicity of diesel and gasoline engine exhausts (Monograph Volume 105)

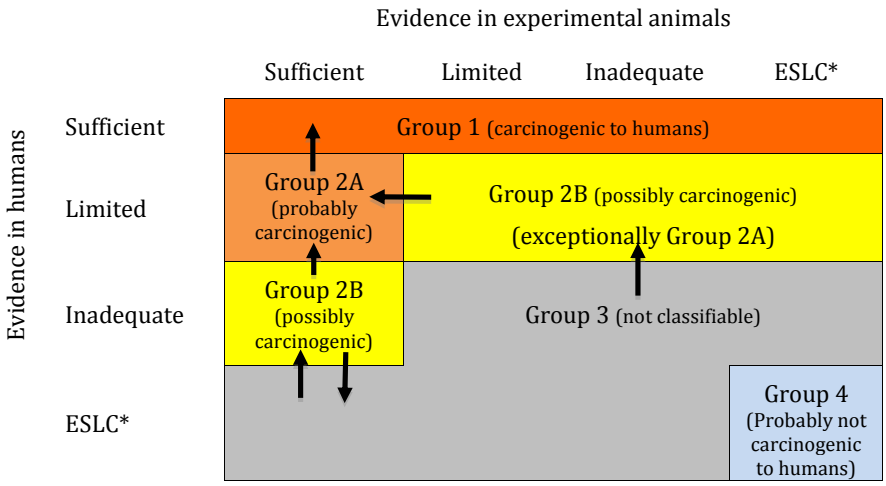
This part summarises the objective and the method followed in the IARC monographs, the conclusions of IARC Monograph Volume 105, and the information from this monograph relating to road vehicle emissions.
For more details, Monograph Volume 105 (CIRC 2014) is available at the following address:
http://monographs.iarc.fr/ENG/Monographs/vol105/

3.1.1. Objective and method followed in the IARC monographs

The objective of the IARC monographs is to examine all the relevant information in order to assess the strength of the available evidence on the carcinogenicity in humans of a chemical, a mixture, an occupational exposure, a physical agent, a biological agent or a lifestyle factor (grouped together below under the term "agent"). The carcinogenicity of an agent is defined as its capability of causing cancer under some circumstances, i.e. to increase the incidence of malignant neoplasms, to reduce their latency or to increase their severity or multiplicity. Carcinogenicity therefore corresponds to a hazard of the agent and not to the risk (probability) of occurrence of the effect of exposure to this agent in a population or in specific conditions. The IARC monographs do not therefore seek to assess the cancer risk from exposure to an agent in a given situation, but to assess the intrinsic capability of the agent to cause cancer in humans.

To assess the strength of the available evidence on the carcinogenicity of an agent in humans, a working group of international experts in the field examines the available scientific data: studies of cancer in humans, studies of cancer in experimental animals and studies of cancer mechanisms.

Following the analysis of these data, the Working Group assigns a classification in Group 1, 2A, 2B, 3 or 4 according to the general diagram below (see Figure).



* ESLC: Evidence suggesting lack of carcinogenicity

Arrows in the figure: Mechanistic data can be pivotal to upgrade or downgrade the agent's classification when the human data are inconclusive

Figure: IARC general diagram of classification (CIRC 2013 figure, translated into English)

The objective and method followed by the IARC and in particular the definition of the strength of evidence categories for an agent's carcinogenicity based on studies in humans and in experimental animals are detailed in Annex 2 (full IARC text provided).

3.1.2. Conclusions of IARC Monograph Volume 105

In 1988, the IARC had classified diesel engine exhausts as probably carcinogenic to humans (Group 2A) and gasoline engine exhausts as possibly carcinogenic to humans (Group 2B).

Following the publication of new epidemiological studies in workers exposed to diesel engine exhausts, and after a 2012 review of all the available data, the IARC concluded that diesel engine exhaust causes lung cancer (sufficient evidence) and observed a positive association (limited evidence) with urinary bladder cancer (CIRC 2014).

To reach its conclusion about diesel engine exhaust, the IARC assessment relied on three major retrospective cohort studies of workers in particular (studies referenced and summarised in Annex 3). These were: a first study of 12,315 US miners exposed to diesel emissions between 1947 and 1967, whose mortality was monitored until 1997, and including a nested case-control study within the cohort on 760 miners (198 cases and 562 controls); a second study of 54,973 US railroad workers followed between 1959 and 1996; and a third study of 31,135 American transport industry workers, whose mortality was monitored between 1985 and 2000. Several of these studies included the quantification of exposure to diesel emissions and an adjustment for individual tobacco smoking. These three studies were the most informative, according to the IARC's assessment. Despite potential biases, they indicate an association between lung cancer and diesel engine exhausts, even after adjustment for tobacco smoking. They all show a moderate but significant excess risk (SMR, OR, HR or RR[1] generally lower than 1.5). This excess risk is significant for different professional situations and different study designs, which limits the risk of unintended and biased results. The study among the most exposed underground miners shows an even higher excess risk (OR of 3.2). The three studies indicate exposure-risk relationships, including relationships with cumulative exposure to diesel engine exhausts. The nested case-control study among the miners also indicates an increased risk in non-smokers associated with an increase in cumulative exposure to elemental carbon (a risk three times higher for the upper tercile compared to the lowest tercile).
Several other cohort studies were regarded as less informative by the IARC, mainly due to less precise definitions of exposure, the use of self-reported exposure, the linking of population data based on the job

[1] SMR: Standard Mortality Ratio; OR: Odds Ratio; HR: Hazard Ratio; RR: Relative Risk.

title with data from national registers for cancer mortality or incidence, the absence of data on tobacco smoking, and/or the absence of information on work history. These studies also support a positive association between lung cancer and exposure to diesel engine exhaust.

All of these epidemiological data contributed to the IARC assessment which concluded that there is "sufficient" evidence in humans for the carcinogenicity of diesel engine exhaust.

The experimental animal studies on which the IARC assessment was based were carried out with diesel fuels and technologies dating from the early 1980s to the late 1990s. Several chronic inhalation exposure studies in rats showed that whole diesel engine exhaust (including the particulate and gas phases) led to a significant increase in the incidence of benign and malignant lung tumours. Studies of exposure to particulate matter from diesel engine exhaust by intratracheal instillation showed that the particles caused a significant increase in benign and malignant lung tumours in rats; one study in mice showed a non-significant increase in lung tumours and lymphomas. The organic extracts of the exhaust particles also caused lung carcinomas in rats and sarcomas at the injection site in mice. Overall, the increases in lung tumours were observed at the highest exposure doses (particle concentrations ≥ 2000 µg/m^3). The study results were negative in hamsters. The study results were also negative for the gas-phase diesel engine exhaust, regardless of the animal species tested (rat, mouse, hamster).

On this basis, the evidence of carcinogenicity in experimental animals was evaluated by the IARC as "sufficient" for whole diesel engine exhaust, diesel engine exhaust particulate matter and the organic fraction of these exhaust particles. Concerning the gaseous fraction, the evidence was evaluated as "inadequate".

The mechanistic data indicate that diesel engine exhaust, exhaust particulate matter and extracts of the exhaust particles induced various genotoxic activities *in vitro* and *in vivo*. The genotoxic mechanisms include DNA damage, gene and chromosomal mutation, changes in relevant gene expression, the production of reactive oxygen species and inflammatory responses. Multiple mechanisms are involved because of the complexity of diesel engine exhausts. Increased levels of biological concentrations of biomarkers of exposure and of genotoxic effects have also been observed in people exposed to diesel engine exhausts, including induction of chromosome aberrations in exposed workers. The co-carcinogenic, cell-proliferative and/or tumour-promoting effects of other known and suspected human carcinogens present in diesel engine exhaust probably contribute to its carcinogenicity.

The IARC evaluation concluded that there is "strong mechanistic evidence" tending to show that diesel engine exhaust as well as many of its components can induce lung cancer in humans through genotoxic mechanisms.

Finally, all this evidence in humans and experimental animals, underpinned by mechanistic data, supports the existence of a causal relationship between diesel engine exhaust and lung cancer.

Concerning gasoline engine exhaust, the evidence for carcinogenicity in humans was evaluated by the IARC as "inadequate". In experimental animals, the evidence for carcinogenicity was evaluated as "inadequate" for whole gasoline engine exhaust and "sufficient" for condensates of gasoline engine exhaust.

In 2012, the IARC concluded that it had sufficient evidence to classify diesel engine exhaust in Group 1 as carcinogenic to humans, with gasoline engine exhaust remaining classified in Group 2B as possibly carcinogenic to humans.

3.1.3. Emissions of on-road vehicle engines and impact of emission control technologies

In its monograph, the IARC discusses changes in diesel emissions and the impact of new emission control technologies.

Diesel engines are present all over the world and are a source of polluting emissions: road transport, off-road transport (marine, rail), machinery for public works (mines, construction), electrical generators. Gasoline engines are used for road transport and hand-held equipment (for example chainsaws).

Diesel and gasoline engines are both internal combustion engines, but differ fundamentally regarding preparation of the air-fuel mixture, ignition, and fuel used. In diesel engines, the combustion conditions lead to the formation of elemental carbon, partially burned fuel, polycyclic aromatic hydrocarbons (PAHs) and carbon monoxide. At the outer edges of the fuel-burning jet, excess air leads to high temperatures and the formation of nitrogen oxides. In gasoline engines, the combustion conditions produce little soot but lead to the formation of carbon monoxide, nitrogen oxides and unburned and partially oxidised hydrocarbons.

Combustion engine exhausts therefore constitute a complex and varied mixture, made up of gases (e.g. carbon monoxide and nitrogen oxides), particulate matter (including elemental and organic carbon, soot, sulphates and metals), various volatile (e.g. benzene) and semi-volatile compounds, and polycyclic aromatic hydrocarbons (PAHs), including oxygen- and nitro-derivatives. The qualitative and quantitative composition of the exhausts depends mainly on the type and quality of the fuel, the lubricating oil, the type and age of the engine, the use of an emission control system, the tuning of the engine, its state of maintenance and its pattern of use (load and acceleration). The combustion by-products in the exhausts represent thousands of chemical components present in the gas and/or particulate phases, some of which have been classified in groups 1, 2A or 2B by the IARC (see Annex 4). Historically, diesel engine exhaust contained larger amounts of particulate matter, whereas those from gasoline engines contained higher levels of certain gases, such as carbon monoxide.

Diesel fuel composition and engine technologies have changed over many years to reduce the impact of engine exhausts from diesel vehicles on air quality. Decreasing the sulphur concentration in fuels [which since 2009 has had to be less than 10 mg/kg in France], and introducing oxidation catalysts [from 1996 in France] and "wall-flow"[2] particle filters [from 2000 in France] led to a significant reduction in emissions of certain pollutants, and changed the exhaust composition. The IARC thus reports that these recent technologies reduce emissions of total particulate matter (typically 99% by mass), sulphates/nitrates, elemental carbon, soot, hydrocarbons, PAHs and nitro-PAHs[3] (52%-99%), dioxins and furans[4] (60%-80%, 99% with catalysed particle filters and SCR systems[5]), number of particles[6] (89% according to a study on five engines) and nitrogen oxides[7].

[2] The "wall-flow" filter is the most common type of particulate filter for transport applications. It is based on a honeycomb structure. By blocking alternate channels, this honeycomb configuration creates a filtration pathway for the gases, forcing them to pass through the porous walls of the channels.

[3] However, several recent studies have shown conflicting results, sometimes with increases in emissions of some nitro-PAHs with some particulate filter systems.

[4] However, some studies have reported an increase in dioxin/furan emissions with the use of copper-based catalytic fuel additives in the presence of high levels of chlorine in the fuel.

[5] SCR: Selective Catalytic Reduction system

[6] However, for some particulate filter systems (non-catalysed particulate filter with an oxidation catalyst upstream), although the number of solid particles emitted is greatly reduced by the particulate filters, the total number of particles emitted can be increased with these particulate filters, with sulphate and ammonium probably being the main particle components.

[7] However, it has been observed on road vehicles whose standard pre-dates Euro 6/VI that some technologies combining oxidation catalysis reinforcement with a particulate filter to manage its regeneration (catalysed particulate filters) led to an increase in NO_2 emissions (AFSSET, 2009).

Gasoline fuel and engine technologies have also changed. Accordingly, in gasoline fuel, tetraethyl lead was prohibited as a fuel additive [from 2000 in France] and the level of benzene, classified as carcinogenic to humans (Group 1), was limited [has had to be less than 1% v/v in France since 2000[8]]. Most gasoline vehicles are now fitted with complex electronic feedback control systems, port fuel injection systems[9] and three-way catalyst systems that have reduced emissions of particulate matter, nitrogen oxides, carbon monoxide and non-methane hydrocarbons, as well as unregulated emissions. To improve their efficiency, the most recent gasoline engines have been fitted with the direct in-cylinder injection system, which may, however, increase emissions of particulate matter.

[8] European Directive No 98/70/EC came into force on 1 January 2000.

[9] With the gasoline port fuel injection system, the air-fuel mixture is formed outside the engine cylinder, in the inlet manifold.

3.2. "Questions and answers" on the emissions from on-road diesel vehicles circulating in France considering the IARC conclusions

Q1: Should it be considered that the emissions from the current French fleet of on-road diesel vehicles are carcinogenic, when the IARC's classification in Group 1 (carcinogenic to humans) is based on, among others, studies in occupational settings with higher exposure to emissions from old diesel engines?

Yes, the emissions from the current French fleet of on-road diesel vehicles must be regarded as carcinogenic, given that:

- The most recent studies on European or North American cohorts followed since the early 1990s indicate positive associations between indicators of traffic-related air pollution exposure and the occurrence of lung cancer and other cancers;

- The current fleet of on-road diesel vehicles includes vehicles not fitted with technologies such as "wall-flow" particulate filters and oxidation catalysts. In 2016, 42% of the diesel passenger cars in circulation had not yet been fitted with a particulate filter (38% in vehicles.km)[10] and very few heavy duty vehicles had been fitted with them. Engine generations prior to the 2000s, for which exhaust carcinogenicity has been demonstrated in experimental animal studies, are still present within the current fleet of on-road diesel vehicles;

- The emissions from the current fleet of on-road diesel vehicles are still characterised by the presence of carcinogenic compounds. In addition to the diesel particulate matter, 35 chemical agents, classified by IARC in Group 1, 2A or 2B, have been identified in diesel and/or gasoline engine exhausts, including polycyclic aromatic hydrocarbons (PAHs), nitro-PAHs, benzene, ethylbenzene, acetaldehyde, formaldehyde, dioxins and dibenzofurans, other organic compounds (1,3 butadiene, propylene oxide and di-2-ethylhexyl phthalate) and metals. These compounds were evaluated by the IARC among the thousands of combustion by-products present in the gas and particulate phases. Several of these agents are genotoxic and can therefore be regarded as having carcinogenic potential without a threshold dose.

Specifically concerning the exhaust emissions from new diesel technologies placed on the market, knowledge is too limited to conclude as to an absence of carcinogenicity of the exhaust emissions from all the new diesel technologies placed on the market. Although these greatly reduce pollutant emissions including particulate matter and PAHs, exhaust emissions remain a complex mixture whose toxicity is difficult to predict. Current knowledge is mainly limited to the results of a programme of experimental studies in rats and *in vitro* studies that did not indicate any carcinogenic, mutagenic and genotoxic potential of exhaust emissions from a recent diesel heavy duty vehicle engine[11]. It is the only major carcinogenicity study to include chronic inhalation exposure to emissions from a recent diesel engine and carried out on a single North American diesel technology.

Although the question here concerns diesel vehicles, it should be remembered that gasoline engine exhausts have been classified by IARC as possibly carcinogenic to humans (Group 2B).

[10] Data from HBEFA v3.2 on the French fleet.
[11] Technology compliant with US EPA 2007 emissions standards.

Given the complexity of combustion engine exhausts and the biological systems that interact with them, as well as the rapid changes in exhaust emission composition due to new technologies, it is unlikely that the toxicity of exhaust emissions can be predicted from their composition in the near future. In addition, given the time needed to obtain epidemiological results, the absence of carcinogenicity in humans cannot be established for exhausts from new diesel and gasoline engine technologies.

Additional details:

*A recent systematic review including a meta-analysis on the relationship between lung cancer and exposure to NO_2 and traffic concluded that there was "*consistent evidence of a relationship between NO_2, as a proxy for traffic-sourced air pollution exposure, and lung cancer*" and that "*studies of lung cancer related to residential proximity to roadways and NOx also suggest increased risk, which may be attributable partly to air pollution exposure*" (Hamra et al. 2015). The results of this meta-analysis were consistent with those of another meta-analysis on the relationship between lung cancer and exposure to traffic-related air pollution (Chen et al. 2015). A study published more recently on a Dutch cohort followed from 1986 to 2003 also indicated positive and statistically significant associations between proxies for exposure to traffic-related air pollution (black smoke, NO_2, traffic proximity and traffic intensity) and lung cancer (Hart et al. 2015). A quasi-experimental study in Tokyo suggested that the diesel emission control ordinance introduced in 2003 reduced the lung cancer mortality rate (-4.9% between 2000-2003 and 2009-2012) (Yorifuji, Kashima, and Doi 2016). Recent studies on cancers other than lung cancer in European or North American populations indicate positive but more rarely significant associations (Cohen et al. 2016, Danysh et al. 2015, Pedersen et al. 2017, Raaschou-Nielsen, Pedersen, et al. 2016), with the exception of acute myeloblastic leukaemia, for which statistically significant associations are reported mainly in children (Boothe et al. 2014, Carlos-Wallace et al. 2016, Janitz et al. 2016, Raaschou-Nielsen, Ketzel, et al. 2016, Symanski et al. 2016). From a mechanistic point of view, genome-wide gene expression microarray analysis using whole blood RNA of non-smoking employees of trucking terminals have provided additional data on a mechanistic link between exposure to traffic-related air pollutants and cancer (Chu et al. 2016). Indeed, multiple gene transcripts were strongly and statistically associated with pollutant exposure concentrations: 48, 260 and 49 transcripts for elemental carbon, organic carbon and $PM_{2.5}$ respectively, including 63 transcripts correlated with at least two of the three exposure indicators. Many of these genes have been implicated in lung cancer and other diseases related to air pollution. A cross-sectional study among workers in a diesel engine truck testing facility indicated higher peripheral blood lymphocyte concentrations in exposed workers compared to the unexposed control group, including after stratification by tobacco smoking status, as well as an exposure-response relationship (Lan et al. 2015). High lymphocyte concentrations play a key role in the inflammation process that is increasingly recognised as a contributor to lung cancer aetiology. Another study among workers in a diesel engine testing facility indicated increased micronucleus, nucleoplasmic bridge, and nuclear bud frequencies in the peripheral blood lymphocytes (Zhang et al. 2015). These studies also provide additional mechanistic evidence.*

Little is still known about the carcinogenicity implications of exhaust from recent diesel and gasoline engine technologies. The experimental carcinogenicity studies supporting the IARC assessment were carried out with diesel fuels and technologies that pre-date the 2000s. Concerning the more modern technologies, there are currently no human studies enabling a direct comparison with the carcinogenicity of older technologies. The results of a research programme including experimental studies in rats and in vitro *studies, did not indicate any carcinogenic, mutagenic and genotoxic potential of exhaust emissions from a heavy duty diesel engine compliant with the US EPA 2007 emissions standards and fitted with a particulate filter and other emission control technologies (McDonald et al. 2015, Bemis, Torous, and Dertinger 2015, Hallberg et al. 2015). One of these studies is a lifetime inhalation carcinogenicity study. It is nevertheless the only major carcinogenicity study to include chronic inhalation exposure to emissions from a recent diesel engine and it was carried out on a single North American diesel technology. Ideally, this type of study should be reproduced considering the other recent technologies in order to draw generalisable conclusions. One* in vitro *study indicates that particles were minor contributors to the genotoxicity of whole exhausts from a Euro 3 diesel engine fitted with a particulate filter and an oxidation catalyst (Andre et al. 2015). In contrast, the gas phase appeared mutagenic directly downstream of the diesel engine tested. After the combined treatments of the oxidation catalyst and the particulate filter, exhausts from the engine tested with a biodiesel (methyl esters of rapeseed oil) appeared weakly but still significantly mutagenic.*

Additional details (continued):

Modern diesel technologies can reduce exhaust levels of genotoxic and carcinogenic pollutants (CIRC 2014, Claxton 2015a). This in no way means that exhaust emissions from the current fleet of on-road diesel vehicles (which moreover includes vehicles not fitted with a particulate filter) should not be regarded as carcinogenic. Indeed, extrapolating effects to low doses is an accepted practice and not specific to diesel engine emissions. This extrapolation is supported by 1/ the fact that it is impossible to identify a human dose without carcinogenic effect, 2/ the exposure-risk relationship that seems linear (Garshick et al. 2012) except at the highest exposure levels (Silverman et al. 2012), 3/ the genotoxic mechanisms of diesel engine exhausts and several of their components including PAHs and nitro-PAHs (it can therefore be considered that there is no threshold dose below which there are no effects), and 4/ the lower end of the range of exposure concentrations in the epidemiological studies used by the IARC being very close to levels reported in ambient air (McDonald et al. 2015, Bemis, Torous and Dertinger 2015, Hallberg et al. 2015). In addition, the IARC recalls that other substances such as radon have taught us that initial studies showing a risk in heavily exposed occupational groups were followed by comparable findings for the general population (CIRC 2012).

It should also be remembered that genotoxic compounds can be generated from non-genotoxic exhaust pollutants during atmospheric transformation processes (Claxton 2015b). On another note, particulate filters can generate other types of ultrafine particles (UFPs), such as UFPs of ammonium sulphate, acid UFPs whose pollution would nevertheless be limited to areas in the immediate vicinity of the emissions, and UFPs of metal oxides (CIRC 2014, Habert and Garnier 2015).

Overall, the exhaust emission toxicity from fuel formulations and technologies introduced in France since 2000 is still poorly characterised and requires additional studies (Claxton 2015a, Habert and Garnier 2015). Given the complexity of combustion engine exhausts and the biological systems that interact with them, it is nevertheless unlikely that the toxicity of these emissions can be predicted from their composition in the near future (Steiner et al. 2016). The need for detailed toxicological studies will become even more critical given the rapid changes in exhaust composition due to new technologies. Recent developments in the field of in vitro *toxicology combined with sophisticated aerosol exposure systems suggest that even though exhaust toxicity is not predictable, fast and reliable assessments of new technologies will be possible, and will be able to contribute to emissions regulations that more effectively protect public health (Steiner et al. 2016).*

In 2016, 42% of the passenger cars in circulation had not yet been fitted with a particulate filter (38% in vehicles.km) according to the data of the Handbook Emission Factors for Road Transport (HBEFA v3.2 on the French fleet) and very few heavy duty vehicles (which have a longer lifespan) are currently fitted with particulate filters. The particulate filter fitment rate is rising with the introduction of new Euro 5 and Euro 6 vehicles within the on-road fleet, and could reach 96% by 2030 (André, Roche and Bourcier 2014). Nevertheless the fleet renewal rate has been slowing down from year to year. The average age of household vehicles in use thus increased from 7.3 years in 2000 to 8.9 years in 2015 (CCFA 2016). In 2015, pre-Euro 3 vehicles (pre-Euro III for HDVs) accounted for 7% of the diesel passenger car traffic (in vehicles.km), 9% for diesel Light Commercial Vehicles, 4% for diesel HDVs and 9% for diesel buses and coaches (CITEPA 2017 data). On-road vehicle emissions of particulate matter and total PAHs (particulate and gas phases) have decreased significantly since the early 1990s as a result of the introduction of new technologies and changes in fuel formulations (Keyte, Albinet and Harrison 2016). Nevertheless, exhaust emissions from diesel engines probably remain a major contributor to the concentrations of carcinogenic PAHs in the outdoor ambient air in France. In the United States, one study indicates that diesel emission is a major contributor to ambient PAHs concentrations according to the fluorene/(fluorene+pyrene) daily concentration ratio (Liu et al. 2017). Concentrations were measured between 1990 and 2014 at 169 measurement stations spread throughout North America. For some carcinogenic nitro-PAHs such as 1-nitropyrene (Group 2A), emissions by on-road vehicles have not decreased in London since the early 1990s, which is probably also the case in urban French agglomerations (Keyte, Albinet and Harrison 2016).

Q2: What is the impact of the emissions from on-road vehicles circulating in France on the cancer risk in the general population?

Recent human observational studies and experimental studies support an impact of outdoor ambient air pollution and traffic-related air pollution on the lung cancer risk of exposed populations. The majority of the general population is exposed to road traffic emissions in France, with 85% of the population residing in urban areas as defined by the French Institute of Statistics and Economic Studies (INSEE). In addition, atmospheric concentrations of carcinogenic pollutants such as particulate matter (in mass and number concentrations), carbon soot, polycyclic aromatic hydrocarbons (PAHs) and benzene are higher in the vicinity of roads and in the passenger compartment of on-road vehicles.

We are unaware of any estimate of the excess risk and the number of cases of cancer attributable to emissions from on-road vehicles circulating in France. The quantitative estimation is complicated, especially given the lack of an exposure-risk relationship specific to vehicle emissions.

Such estimates have, however, been made in other countries such as the United States and at the European scale. According to these recent estimates, the excess risk of death from lung cancer is higher than the risk acceptability benchmark admitted by international institutions: one excess case for 100,000 exposed individuals, due to the general population's exposure to exhaust emissions from diesel engines in the United States and in Europe, characterised by the average concentration in elemental carbon. These figures are based on exposure-risk relationships whose relevance for quantitative risk assessment is still under debate (relatively old diesel engines, retrospective exposure assessment considered too imprecise, time and age factors not taken into account). The authors estimate that around 4.8% of annual deaths from lung cancer at the age of 70 years in the United States and the United Kingdom are due to past environmental exposure to exhaust emissions from diesel engines. Previous estimates for the fraction of lung cancers attributable to traffic-related air pollution in the 2000s ranged between 5% and 7%.

While a precise estimate will always remain inaccessible, given the time needed to obtain the results of epidemiological studies in the exposed population, the orders of magnitude provided by existing estimates of the fraction of cancers attributable to this pollution source can be used to examine the public health issues and thus the opportunity for action.

The carcinogenic effects of exhaust emissions from diesel engines and the genotoxic modes of action (*a priori* carcinogenic effects without a threshold dose) justify the adoption of all measures necessary to reduce exposure to these emissions. The introduction of new diesel technologies is likely to reduce the cancer risk attributable to emissions from on-road diesel vehicles circulating in France, for an equivalent number of kilometres travelled. Other possible measures include for example the development of sustainable transport[12]. There are many guidelines in this field, for example those of the Organisation for Economic Co-operation and Development (OECD)[13] and the THE PEP programme[14] supported jointly by the United Nations Economic Commission for Europe (UN-ECE) and WHO-Europe.

[12] According to the OECD definition, an environmentally sustainable transport system is one where "*transport does not endanger public health or ecosystems, and meets needs for access consistent with (a) use of renewable resources below their rates of regeneration, and (b) use of non-renewable resources below the rates of development of renewable substitutes*".

[13] http://www.oecd.org/env/greening-transport/oecdguidelinestowardsenvironmentallysustainabletransport.htm

[14] https://www.unece.org/thepep/en/welcome.html

Additional details:

We are unaware of any estimate of the health impact of emissions from on-road vehicles circulating in France. The quantitative estimation is currently complicated, especially given the lack of an exposure-risk relationship specific to vehicle emissions. It is even more complicated to make forward-looking estimates, given also the relatively rapid changes in the on-road fleet's technological composition and the little known carcinogenicity implications of exhausts from new diesel and gasoline engine technologies.

Vermeulen et al. (2014) estimated that in the United States, exposure of the general population to exhaust emissions from diesel engines is associated with an excess lifetime risk of 21 deaths from lung cancer for 10,000 individuals exposed to an average concentration of 0.8 µg/m^3 of elemental carbon, exceeding the risk acceptability benchmarks of one excess case for 100,000 or 1,000,000 exposed individuals. This risk estimate was based on a meta-analysis of exposure-risk relationships from the main cohort studies considered by the IARC, i.e. exposure-risk relationships associated with relatively old diesel engines. It should also be considered with caution as it does not take into account the evolution of fuels and technologies, and does not extrapolate to more susceptible subpopulations (children, elderly people, people with pre-existing comorbidities) (HEI Diesel Epidemiology Panel 2015). In addition, the relevance of these exposure-risk relationships is still the subject of debate for quantitative risk assessment, especially given the retrospective exposure assessment regarded as too imprecise and the failure to take into account a potential effect of time- and age-related factors (Crump, Van Landingham and McClellan 2016, Crump et al. 2015, Moolgavkar et al. 2015)[15]*. According to Vermeulen et al. (2014), the slope estimate was roughly consistent with the lung cancer mortality risk associated with long term population exposure to elemental carbon previously estimated by Janssen et al. (2011) based on a conversion of black smoke to elemental carbon from two European studies.*

A more recent study was based on the meta-analysis by Vermeulen et al. (2014) and on some additional sensitivity analyses incorporating other published exposure-risk relationships (Vermeulen and Portengen 2016). This study indicates that median levels of elemental carbon, between 0.5 and 2 µg/m^3 in urban ambient air in Europe and the United States, are higher than the 0.009-0.017 µg/m^3 concentration range calculated for a risk acceptability benchmark of four excess cases for 100,000 exposed individuals[16]*. In occupational environments, the usual levels reported for exposure to elemental carbon vary between 1 µg/m^3 (parking attendants), 2-5 µg/m^3 (professional drivers), 5-10 µg/m^3 (construction workers and mechanics), and >100 µg/m^3 (underground mining). They largely exceed this risk acceptability benchmark and are close to or above the 0.85-1.67 µg/m^3 concentration range calculated for a maximum tolerable risk benchmark of four excess cases for 10,000 exposed individuals.*

The authors roughly estimate that around 4.8% of annual deaths from lung cancer at the age of 70 years in the United States and the United Kingdom are due to past environmental exposure to exhaust emissions from diesel engines (Vermeulen et al. 2014). Previous estimates for the fraction of lung cancers attributable to traffic-related air pollution in the 2000s have ranged between 5 and 7% (Cohen et al. 2005, Vineis, Hoek, and Krzyzanowski 2007).

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[15] The authors of the publications (Crump, Van Landingham and McClellan 2016, Crump et al. 2015, Moolgavkar et al. 2015) declared conflicts of interests, such as the fact that they worked on behalf of, or were funded by, the automotive, mining, rail or oil industries.

[16] Benchmark established for an occupational exposure scenario over 40 years, from the age of 20 to 60 years, and not over the lifetime.

KEYWORDS

Cancer, Centre international de recherche sur le cancer (CIRC), Emission polluant, Gaz échappement, Moteur diesel, Moteur essence, Trafic routier, France, Evaluation risque

Cancer, International Agency for Research on Cancer (IARC), Pollutant emission, Exhaust gas, Diesel engine, Gasoline engine, Road traffic, France, Risk assessment

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ANNEXES

Annex 1: Formal request letter

Annex 2: IARC monographs: objective and assessment method

Annex 3: Summary of studies on the carcinogenicity in humans of diesel engine exhausts

Annex 4: Chemicals and metals assessed by the IARC and found in diesel and gasoline engine exhausts (IARC, 2014)

Annex 1: Formal request letter

2014 -SA- 0 1 5 6

COURRIER ARRIVE
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DIRECTION GENERALE

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MINISTERE DES AFFAIRES ET SOCIALES ET DE LA SANTE

Direction générale de la santé

MINISTERE DE L'ECOLOGIE, DU DEVELOPPEMENT DURABLE ET DE L'ENERGIE

Direction générale de la prévention des risques

Direction générale de l'énergie et du climat

Paris, le 3 0 JUIN 2014

Le Directeur général de la santé

La Directrice générale de la prévention des risques

Le Directeur général de l'énergie et du climat

à

Monsieur le Directeur général
de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES)
27-31 avenue du Général Leclerc
94701 Maisons-Alfort cedex

Objet : Etat des connaissances sur les particules de l'air ambiant (composition chimique et émissions du trafic routier)

Les particules de l'air ambiant représentent un enjeu majeur de santé publique. De très nombreuses publications scientifiques montrent, de par le monde, que l'exposition à court et long terme aux particules de l'air est clairement associée à des effets délétères sur la santé. Durant ces deux dernières années, différentes études, revues et classements confirment l'impact sanitaire des particules, notamment :

- En 2012, les résultats du projet Aphekom[1] montrent que le dépassement de la valeur guide de l'Organisation mondiale de la santé (OMS) pour les particules $PM_{2,5}$[2] (10 µg/m^3 en moyenne annuelle) se traduit chaque année dans 25 grandes villes européennes (39 millions d'habitants) par :
  - o 19000 décès prématurés, dont 2900 pour les 9 villes françaises concernées,
  - o 31,5 milliards d'euros en dépense de santé et coûts associés.

- En juin 2012, le Centre International de Recherche sur le Cancer (CIRC), instance spécialisée de l'OMS, a classé les effluents d'échappement des moteurs Diesel comme cancérogènes pour l'Homme (groupe 1) et les effluents d'échappement des moteurs essence comme possiblement cancérogènes pour l'Homme (groupe 2B). Et en octobre 2013, il a classé, la pollution de l'air extérieur dans son ensemble et les particules en suspension composant cette pollution comme agents cancérogènes pour l'Homme (groupe 1).
- En 2013, l'OMS-Europe dans sa revue de la littérature REVIHAAP (Review of evidence on health aspects of air pollution) met notamment en avant, pour les particules :
  - o un lien de causalité renforcé entre l'exposition aux $PM_{2,5}$ et mortalité cardiovasculaire et respiratoire,

.../...

[1] Cf. le site Internet : www.aphekom.org.
[2] Particules $PM_{2,5}$: particules en suspension de taille inférieure à 2,5 micromètres.

o des publications supplémentaires reliant l'exposition à long terme aux $PM_{2,5}$ et l'athérosclérose, des issues indésirables de la grossesse et de maladies respiratoires chez l'enfant,
o des études émergentes sur l'altération de la fonction cognitive et le diabète,
o l'absence de seuil en deçà duquel les particules n'auraient pas d'effet,
Par ailleurs, plusieurs études récentes renforcent également la connaissance des impacts sanitaires potentiellement associés avec le fait de résider à proximité d'un axe à fort trafic routier (asthme, broncho-pneumopathies chroniques obstructive, etc.).

Selon l'inventaire national des émissions du CITEPA[3] , les émissions primaires de particules par le trafic routier sont principalement liées au parc de véhicules particuliers Diesel. Les véhicules Diesel constituent aujourd'hui environ 60% du parc français de véhicules légers et 72% des ventes en 2011 contre 50% des ventes en 2000. Si les inventaires font état, en France métropolitaine, d'une diminution globale des émissions de PM_{10}[4] et de $PM_{2,5}$ depuis le début des années 1990, celle-ci s'est cependant ralentie depuis une dizaine d'années. Les concentrations de particules (PM_{10} et $PM_{2,5}$) dans l'air mesurées par les différentes stations de mesure françaises restent stables depuis le milieu des années 2000, notamment en raison des particules secondaires, la pollution transfrontalière, les conditions météorologiques, et supérieures aux valeurs guides recommandées par l'OMS, respectivement de 20 et 10 µg/m^3 en moyenne annuelle pour les PM_{10} et les $PM_{2,5}$. Enfin, la France, dont les seuils d'information et d'alerte fixés respectivement en 2010 à 50 et 80 µg/m3 de PM_{10} en moyenne journalière, connaît chaque année plusieurs épisodes de pollution d'ampleur vis-à-vis des particules.

Des interrogations subsistent quant aux effets sanitaires potentiellement associés à la composition de l'aérosol particulaire dont l'évolution au cours des dernières années est vraisemblable, ainsi qu'aux enjeux sanitaires spécifiques associés, le cas échéant, aux particules diesel.

Face à ces constats, le ministère chargé de l'Ecologie (Direction générale de la prévention des risques, DGPR, et Direction générale de l'énergie et du climat, DGEC) et le ministère en charge de la Santé (Direction générale de la santé, DGS) sollicitent l'expertise de l'Anses afin de compléter, sur des volets précis, l'état de l'art actuel sur les enjeux sanitaires que représentent les particules en vue, le cas échéant, d'orienter au mieux le gestionnaire via des recommandations ciblées.

Il est ainsi demandé à l'Anses :

A) D'investiguer la problématique de la composition chimique des particules :
• en compilant les études/données existantes sur la composition des particules de l'air ambiant en France, en tenant compte si possible de la granulométrie et de leur évolution spatio-temporelle, via le recueil de l'ensemble des données auprès du Laboratoire central de surveillance de la qualité de l'air (LCSQA) et notamment au travers du dispositif CARA (CARActérisation des particules) et des différents documents de référencent en la matière ;
• en mettant en perspective cette analyse avec les données toxicologiques et épidémiologiques en lien avec la composition chimique, la granulométrie des particules et son évolution.

Au regard des conclusions que l'agence sera amenée à formuler, il est attendu, le cas échéant, des recommandations ciblées qui permettraient de privilégier les mesures de réduction relatives aux sources d'émission, quelles qu'elles soient, afin de diminuer les conséquences sanitaires tant en situation d'exposition chronique que d'épisode de pollution.

.../...

[3] Centre interprofessionnel technique d'études de la pollution atmosphérique.
[4] Particules PM10 : particules en suspension de taille inférieure à 10 micromètres.

B) Concernant la source « trafic routier », à l'instar des travaux d'expertise de l'agence de 2009 sur les émissions de dioxyde d'azote par les motorisations Diesel, de conduire une expertise visant à :

- définir l'évolution rétrospective et prospective des émissions de particules selon le parc roulant français et des cycles se rapprochant d'usage réel en considérant différents scénarios ;
- d'identifier les impacts différenciés des technologies de dépollution sur les émissions de particules par la source « trafic ».

Ces éléments pourront être mis en regard avec les données d'émission disponibles concernant les autres sources de particules.

Pour ces deux axes, A et B, il est demandé à l'agence d'être particulièrement vigilante à la prise en compte de la formation de particules secondaires.

Enfin, il est demandé à l'Anses son avis quant à la transposition des conclusions émises en 2012 par le CIRC sur les effluents d'échappement des moteurs Diesel, aux émissions émises par les véhicules routiers à moteur Diesel circulant en France.

Nous vous remercions de bien vouloir nous indiquer, dans les meilleurs délais, les modalités de réponse à cette saisine dont le rendu final est attendu pour la fin du premier trimestre de 2016, avec un rendu intermédiaire pour la mi-2015.

Le Directeur général de la santé	La Directrice générale de la prévention des risques	Le Directeur général de l'énergie et du climat
Pr. Benoît VALLET	Patricia BLANC	Laurent MICHEL

Annex 2: IARC monographs: objective and assessment method

The objective and the method are summarised here. More details are available on the IARC website: http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf

Objective:

The IARC monographs programme was initiated in the early 1970s, shortly after the creation of the IARC in 1965. The objective of the IARC monographs is to examine all the relevant information in order to assess the strength of the available evidence on the carcinogenicity in humans of a chemical, a mixture, an occupational exposure, a physical agent, a biological agent or a lifestyle factor (grouped together below under the term "agent"). The carcinogenicity of an agent is defined as its capability of causing cancer under some circumstances, i.e. to increase the incidence of malignant neoplasms, to reduce their latency or to increase their severity or multiplicity.

Carcinogenicity therefore corresponds to a hazard of the agent and not to a risk (probability) of occurrence of the effect from exposure to this agent in a population or in specific conditions. Thus, even if the cancer risk from exposure of the general population is very low at current exposure levels, this does not mean that this agent cannot be classified by the IARC in Group 1, namely carcinogenic to humans.

The IARC monographs do not therefore seek to assess the cancer risk from exposure to an agent, but to assess the intrinsic capability of an agent to cause cancer in humans. The monographs may also indicate where additional research efforts are needed, specifically when data immediately relevant to an evaluation are not available. The monographs are used by national and international authorities to make risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes and decide among alternative options for public health decisions.

Assessment method:

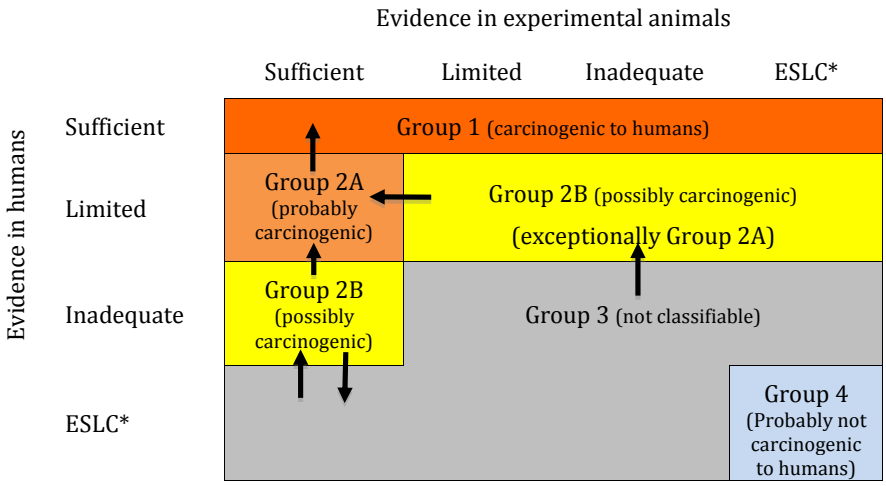
To assess the strength of the available evidence on the carcinogenicity of an agent in humans, the IARC, in collaboration with international experts in the field, begins by collecting the available scientific data and preparing working documents. A working group of international experts is then tasked with carrying out a critical review of the available data and the evaluation. The working group members are selected on the basis of their knowledge and experience, and the absence of real or apparent conflicts of interests. Consideration is also given to demographic diversity and balance of scientific findings and views. The working group is assisted by IARC scientists, as well as invited specialists who have critical knowledge and experience on the subject but have a real or apparent conflict of interests. Representatives of national and international health agencies and observers also attend meetings but do not participate in the evaluation.

The working group examines the available scientific data on an agent, namely:

- studies enabling a contextual description of the sources of and exposures to this agent;
- studies of cancer in humans related to this agent;
- studies of cancer in animals related to this agent;
- studies of biological effects of this agent on human, animal, and cellular organisms and in particular studies of cancer mechanisms related to this agent.

After analysing these available data on the agent and their quality, the strength of evidence for the agent's carcinogenicity in humans is evaluated by the working group, which assigns a ranking from among the following classes (Figure):

- Group 1: Carcinogenic to humans
- Group 2A: Probably carcinogenic to humans
- Group 2B: Possibly carcinogenic to humans
- Group 3: Not classifiable as to its carcinogenicity to humans
- Group 4: Probably not carcinogenic to humans



* ESLC: Evidence suggesting lack of carcinogenicity

Arrows in the figure: Mechanistic data can be pivotal to upgrade or downgrade the agent's classification when the human data are inconclusive

Figure: IARC general diagram of classification (Figure from CIRC 2013, translated into English)

Definition of the strength of evidence categories for an agent's carcinogenicity based on studies in humans (full IARC text provided):

- *Sufficient evidence*: *The Working Group considers that a causal relationship has been established between 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*: *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*: *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 studies can never be excluded.*

Definition of the strength of evidence categories for an agent's carcinogenicity based on studies in experimental animals (full IARC text provided):

- *Sufficient evidence*: *The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence.*

  A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.

- *Limited evidence*: *The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.*

- *Inadequate evidence*: *The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.*

- *Evidence suggesting lack of carcinogenicity*: *Adequate studies involving at least two species are available which show that, within the limits of the test used, the agent is not carcinogenic. A conclusion of evidence suggesting lack of carcinogenicity is inevitably limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied.*

Since 1971, more than 900 agents have been evaluated, of which more than 100 have been classified in Group 1, and more than 300 in Group 2A or 2B.

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Annex 3: Summary of studies on the carcinogenicity in humans of diesel engine exhausts

To reach a conclusion on classifying diesel engine exhausts in Group 1 (carcinogenic to humans), the IARC relied on 119 epidemiological studies, and on three extensive retrospective cohort studies of workers (miners, railroad workers, transport industry workers), several of which quantified exposure to diesel engine exhausts and were adjusted for individual tobacco smoking. The following summary of these studies is based on a review of the health effects of diesel exhaust (Habert and Garnier, 2015), on Monograph Volume 105 (IARC 2014), and on more recent publications re-analysing the data from the three aforementioned cohort studies (Crump, Van Landingham and McClellan 2016, Crump et al. 2015, Moolgavkar et al. 2015).

The first cohort study included 12,315 US miners exposed to diesel engine exhausts between 1947 and 1967, and whose mortality was followed up through 1997 (Attfield et al. 2012). A nested case-control study within the cohort included 760 miners (198 cases and 562 controls) and took potential confounding factors into account, including tobacco smoking and co-exposure to silica, radon, asbestos, PAHs not emitted by diesel engines and respirable dust (Silverman et. al. 2012). Exposure to diesel exhausts was assessed from a retrospective estimate of exposure to respirable elemental carbon (REC) at the work stations, while distinguishing between workers operating at ground level and underground workers. The concentrations of these past REC exposures were estimated by adjusting REC concentrations measured between 1998 and 2001 using carbon monoxide concentrations measured at the same time and measured or modelled for the period before 1976. Both studies showed an increased risk of lung cancer when exposure to diesel exhausts increased. Basically, the cohort study (Attfield et al. 2012) showed a significantly higher standardised mortality ratio (SMR) for lung cancer for the entire cohort (SMR = 1.26; 95% CI: 1.09-1.44) and also for the analysis restricted to miners working at ground level, and hazard ratios (HR) increasing with cumulative exposure to elemental carbon. The risk was maximal and significant for cumulative exposure between 640 and 1280 µg/m^3.year (HR = 5.01; 95% CI: 1.97-12.76), which was higher than the reference (0-20 µg/m^3.year). However, the risk seemed lower and non-significant (HR = 2.39; 95% CI: 0.82-6.94) for the category of highest exposure (≥ 1280 µg/m^3.year). The nested case-control study (Silverman et. al. 2012) showed a risk three times higher for the category of workers with the highest average and cumulative exposure compared with the lowest exposure category (OR = 3.20; 95% CI: 1.33-7.69) and a statistically significant association between lung cancer risk and cumulative and average exposure to elemental carbon. Among non-smokers, the risk also increased with the increase in cumulative exposure to elemental carbon, with a risk three times higher for the upper tercile compared to the lowest tercile.

A second cohort study included 54,973 US railroad workers followed up between 1959 and 1996 (Garshick et al. 2004, Garshick et al. 2006, Laden et al. 2006) and did not include metrological measurements of exposure or adjustment for other occupational risk factors. In the first analysis, exposures were classified on the basis of job title (Garshick et al. 2004). An increased lung cancer risk was found among exposed workers defined as working as either “engineers” (engineers, firemen) or “conductors” (conductors, brakemen, and hostlers) (RR = 1.40; 95% CI: 1.30-1.51); these results were not adjusted for tobacco smoking or for past exposure to risk factors such as asbestos and coal combustion products emitted by steam locomotives until 1959. In the second analysis, the results were adjusted for tobacco smoking and the risk was slightly lower but remained higher among exposed workers (RR = 1.22; 95% CI: 1.12-1.32). The results of these two analyses indicated no relationship with the number of years working in the job; the authors explained this by a "healthy worker effect" and/or by co-exposure to coal combustion products.
In the third analysis (Laden et al. 2006), an estimate of diesel exhaust exposure was integrated into the group of exposed workers (“engineers” and “conductors”) in order to reduce the risk of exposure misclassification. An exposure probability coefficient was calculated for each year and each railroad company, to take account of technical developments between 1945 and 1986. The risks were significantly higher in the exposed workers hired after 1945, the year when diesel locomotives came into operation (RR = 1.77; 95% CI: 1.50-2.09) and with the number of years working in the job, but not with

the cumulative intensity. The results were not adjusted for tobacco smoking or for co-exposure to asbestos and coal combustion products.

A third cohort study of 31,135 American transport industry workers, whose mortality was followed between 1985 and 2000 (Garshick et al. 2008), showed a significant association between lung cancer and the number of years working in jobs involving regular exposure to motorised vehicle exhausts, including after adjustment for tobacco smoking, and with a doubling of the risk after 20 years of exposure (except for long-distance truck drivers). The data from this cohort underwent a second analysis (Garshick et al. 2012) integrating a retrospective estimate of exposure to elemental carbon based on the concentration of elemental carbon measured between 2001 and 2006 at the work stations and on the history of past exposures. A significant association was observed between lung cancer and cumulative exposure to elemental carbon, suggesting a linear exposure-risk relationship. This association was stronger after adjustment for the number of years of work (negative confounding factor). The results were not adjusted for tobacco smoking, considering its non-significant influence in the previous analysis (Garshick et al. 2008), a low risk of differential association with exposure, and confounding factors generally taken into account that are correlated with tobacco smoking (age, year of birth).

A pooled analysis of case-control studies (10 European studies and 1 Canadian study), including a total of 29,586 subjects (Olsson et al. 2011) and relying on a reassessment of the exposure history for diesel engine exhaust between 1985 and 2005 (job-exposure matrix), showed an association between lung cancer and diesel engine exhausts, for the highest quartile of the exposure level compared to the lowest quartile, after adjustment for tobacco smoking.

Apart from the IARC evaluation, the results of these four studies have been the subject of analysis and criticism, regarding certain methodological issues that could bias these results (Crump, Van Landingham and McClellan 2016, Crump et al. 2015, Gamble, Nicolich and Boffeta 2012, Hesterberg et al. 2012 Moolgavkar et al. 2015), mainly:

- the absence of adjustment for tobacco smoking, the exclusion of the most exposed group in the analysis, the failure to take into account a potential effect of time and age factors on the exposure-risk relationship in the cohort study among miners (Attfield et al. 2012), as well as a retrospective assessment of exposure to elemental carbon regarded as too imprecise (Attfield et al. 2012, Silverman et al. 2012),
- the absence of adjustment for the main confounding factors such as tobacco smoking (Garshick et al. 2012) and occupational exposures to other lung cancer risk factors (coal combustion products and asbestos) in the study on the railroad workers (Garshick et al. 2012, Garshick et al. 2004),
- an insufficient adjustment for the other lung cancer occupational risk factors (asbestos, crystalline silica, etc.) and a potential lack of reliability regarding classification of the oldest historical exposures in the pooled analysis of the case-control studies (Olsson et al. 2011).

The authors of these critical analyses nevertheless declared conflicts of interest, such as the fact that they worked on behalf of, or were funded by, diesel engine and vehicle manufacturers (Navistar Inc., Truck and Engine Manufacturers Association, European Automobile Manufacturers Association, American Trucking Association, Alliance of Automobile Manufacturers, International Organization of Motor Vehicle Manufacturers, Alliance of European Research Group on Environment and Health in the Transport Sector, Internal Combustion Engine Manufacturers), associations of automotive equipment manufacturers (Association of Equipment Manufacturers), oil industry associations (CONCAWE, American Petroleum Institute), mining industry and diesel engine manufacturers' associations (MARG, Tronox Specialty Alkali Corporation) and railroad industry associations (Association of American Railroads).

In conclusion, despite potential biases, these studies indicate an association between lung cancer and diesel engine exhausts, even after adjustment for tobacco smoking. They all show a moderate but significant excess risk (SMR, OR, HR or RR[17] generally lower than 1.5). This excess risk is significant for

[17] SMR: Standard Mortality Ratio; OR: Odds Ratio; HR: Hazard Ratio; RR: Relative Risk.

different professional situations and different study designs, which limits the risk of unintended and biased results. The study among the most exposed underground miners showed an even higher excess risk (OR of 3.2). In addition, they often show an exposure-risk relationship, especially with cumulative exposure to diesel engine exhausts, as well as with the average intensity of exposure. Several other cohort studies supported a positive association between lung cancer and diesel engine exhausts. However, the IARC regarded them as less informative, mainly due to less precise definitions of exposure or the use of self-reported exposure estimates, the linking of population data based on the job title with data from national registers for cancer mortality or incidence, the absence of data on tobacco smoking, and/or the absence of data on work history.

All of these epidemiological data contributed to the IARC assessment which concluded that there is "sufficient" evidence in humans for the carcinogenicity of diesel engine exhaust. Also given the "sufficient" evidence for carcinogenicity in experimental animals, and mechanistic data confirming the carcinogenic potential in humans of diesel engine exhausts and many of their components, through genotoxic mechanisms, the IARC has therefore classified diesel engine exhausts as "carcinogenic to humans" (Group 1).

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Annex 4: Chemicals and metals assessed by the IARC and found in diesel and gasoline engine exhausts (IARC, 2014)

Agent	CAS No.	Evaluation	Volume (reference)
Metals			
Antimony compounds	1309-64-4 (Trioxide)	2B	47 (IARC, 1989b)
Arsenic and inorganic arsenic compounds	007440-38-2	1	100C (IARC, 2012a)
Beryllium and beryllium compounds	007440-41-7	1	100C (IARC, 2012a)
Cadmium and cadmium compounds	007440-43-9	1	100C (IARC, 2012a)
Chromium (VI)	018540-29-9	1	100C (IARC, 2012a)
Cobalt and cobalt compounds	007440-48-4	2B	52 (IARC, 1991)
Lead compounds	Inorganic/organic	2A/3	87 (IARC, 2006)
Nickel	Metallic/compounds	2B/1	100C (IARC, 2012a)
Organic chemicals			
1,3-Butadiene	106-99-0	1	100F (IARC, 2012b)
Acetaldehyde	75-07-0	2B	71 (IARC, 1999)
Benzene	71-43-2	1	100F (IARC, 2012b)
Bis(ethylhexyl)phthalate	117-81-7	2B	101 (IARC, 2012c)
Ethylbenzene	100-41-4	2B	77 (IARC, 2000)
Formaldehyde	50-00-0	1	100F (IARC, 2012b)
Propylene oxide	75-56-9	2B	60 (IARC, 1994)
Halogenated and other chemicals			
Dioxin/dibenzofurans	1746-01-6 (TCDD)	1	100F (IARC, 2012b)
Polycyclic aromatic hydrocarbons			
Benz[*a*]anthracene	56-55-3	2B	92 (IARC, 2010)
Benzo[*b*]fluoranthene	205-99-2	2B	92 (IARC, 2010)
Benzo[*k*]fluoranthene	207-08-9	2B	92 (IARC, 2010)
Benzo[*a*]pyrene	5-32-8	1	100F (IARC, 2012b)
Chrysene	218-01-9	2B	92 (IARC, 2010)
Dibenz[*a*,*h*]anthracene	53-70-3	2A	92 (IARC, 2010)
3,7-Dinitrofluoranthene	105735-71-5	2B	This volume
3,9-Dinitrofluoranthene	22506-53-2	2B	This volume
1,3-Dinitropyrene	75321-20-9	2B	This volume
1,6-Dinitropyrene	42397-64-8	2B	This volume
1,8-Dinitropyrene	42397-64-9	2B	This volume
Indeno[1,2,3-*cd*]pyrene	193-39-5	2B	92 (IARC, 2010)
Naphthalene	91-20-3	2B	82 (IARC, 2002)
3-Nitrobenzanthrone	17 117-34-9	2B	This volume
6-Nitrochrysene	7496-02-8	2A	This volume
2-Nitrofluorene	607-57-8	2B	This volume
1-Nitropyrene	5522-43-0	2A	This volume
4-Nitropyrene	57835-92-4	2B	This volume
Styrene	100-42-5	2B	82 (IARC, 2002)

TCDD, 2,3,7,8-tetrachlorodibenzodioxin

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