Review of PM elemental composition in association with
oxidative stress, cancer incidence, cardiovascular and
respiratory disease, health effects in pregnancy and birth
outcome, and mortality

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1. Introduction

Particulate matter is associated with various adverse health effects and mortality. The toxicological mechanism however and the role of particulate matter elemental composition in it is still unclear. The European Study of Cohorts for Air Pollution Effects (ESCAPE) has been launched in 2008 in order to quantify health impacts of air pollution and to reduce the uncertainty. One of these uncertainties is the role of particulate matter elemental composition on adverse health effects and mortality. The ESCAPE project cannot manage to evaluate all elements present in particulate matter. A selection of relevant elements needs to be made based on the current knowledge available.

1.1 Description of airborne particulate matter

Airborne particulate matter is a complex mixture of particles from different size and different chemical composition. In scientific literature and reports 'particulate matter' can be divided into two principle groups: fine particles and coarse particles. The limit between those fractions is fixed at 2.5 µm. Particulate matter (PM) up to 2.5 µm are referred as fine particles or $PM_{2.5}$. PM up to 10 µm is abbreviated as PM_{10}. PM between 2.5 µm and 10 µm is referred as coarse fraction [WHO, 2003].

1.2 Major sources of airborne particulate matter

Airborne PM can be a result of natural emission or anthropogenic activity. The natural sources consist of sea salt, hemispheric activity and terrestrial substances. In anthropogenic activity traffic, industry and refinery, agricultural activity and consumers are the major sources of PM [RIVM, 2005].

1.3 Formation and sources of different types of airborne particulate matter

There are different types of formation and sources of PM leading to different types of PM. The coarse fraction of PM is mechanically produced by the break-up of larger solid particles [WHO, 2003]. There are different sources contributing to the coarse fraction. These sources have different pathways into the eventual formation of PM. Particles from the coarse fraction can be wind-blown dust from agricultural processes, uncovered soil, unpaved roads or mining operations [WHO, 2003]. Traffic produces road dust which is being stirred up by the air turbulence caused by the traffic. Also combustion of fossil fuels such as coal, oil and petrol creates large particles, due to the release of non-combustible materials. In coastal areas the evaporation of sea spray may create large particles. But also particles from biological sources such as pollen grains, mould spores, plant parts and insect parts contribute to the coarse fraction [WHO, 2003].
The fine fraction is largely formed from gasses. The smallest particles of the fine fraction (smaller than 0.1 µm) can be formed by nucleation (nucleation provides a high enough temperature for low-vapor pressure substances to condense) or by chemical reactions in the atmosphere [WHO, 2003]. These small particles are able to grow into larger particles via coagulation (two or more particles are forming into one large particle) or condensation (gas or vapor molecules condense on the surface of existing particles). There are four major classes of PM that is being formed via nucleation and later on grow into larger particles via coagulation and condensation: 1.Heavy metals vaporized during combustion; 2. Elemental carbon, generated from short C molecules during combustion; 3. Organic carbon and sulfates; 4. Nitrates. However these particles do not grow larger than 1 µm, because the efficiency of both coagulation and condensation decreases when the particles size is increasing. Another source of fine sized particles is the combustion of fossil fuels. Materials vaporized during combustion are able to condense into fine particles [Who, 2003].
Another major source of PM is the so called secondary particles. The secondary particles are a result of intermediate reactions of gasses in the atmosphere. Secondary sulphate and nitrate are usually the most dominant components of fine particles [WHO, 2003].

1.4 European limit values

In 1999 the European Union has decided to implement limit values for PM concentrations. The EU handles a limit value for average annual concentrations of PM_{10} of 40 µg m^{-3} and a 36th highest day concentration of 50 µg m^{-3}. This means the average concentration in a day may only be higher than 50 µg m^{-3} for 35 days in a year [EU, 1999]. On January the 1st of 2010 the EU introduced a target value of 25 µg m^{-3} for $PM_{2.5}$. This target value will be converted into a limit value on January the 1st of 2015 [EC, 2010].

1.5 Exposure to airborne particulate matter in Europe

There are different levels of exposure to airborne PM at different types of locations. In order to have a nuanced perspective on the exposure of airborne PM on the European population, it is sensible to distinguish the following location types [Putaud et al, 2009], see table 1.

Table 1. Different types of exposure locations. Source Putaud et al, 2009

Location	Description of location
Natural background	distance from large pollution sources > 50 km
Rural background	distance from large pollution sources 10 - 50 km
Near-city background	distance from large pollution sources 3 - 10 km
Urban background	less then 2500 vehicles/day within 50 m radius
Industrial background	located within industrial areas
Kerbsides (also referred as traffic locations)	located by traffic lanes

The European Environment Agency (EEA) has interpolated PM exposure data from urban and rural background stations into an exposure map of Europe for the year 2005. Current background concentrations of PM_{10} exceed both the annual average value and 36th highest day value in many European Regions [EEA, 2009]. See figure 1 and 2. This means parts of the European population are exposed to a concentration of PM exceeding the limit values [EEA, 2009]. See figure 3.
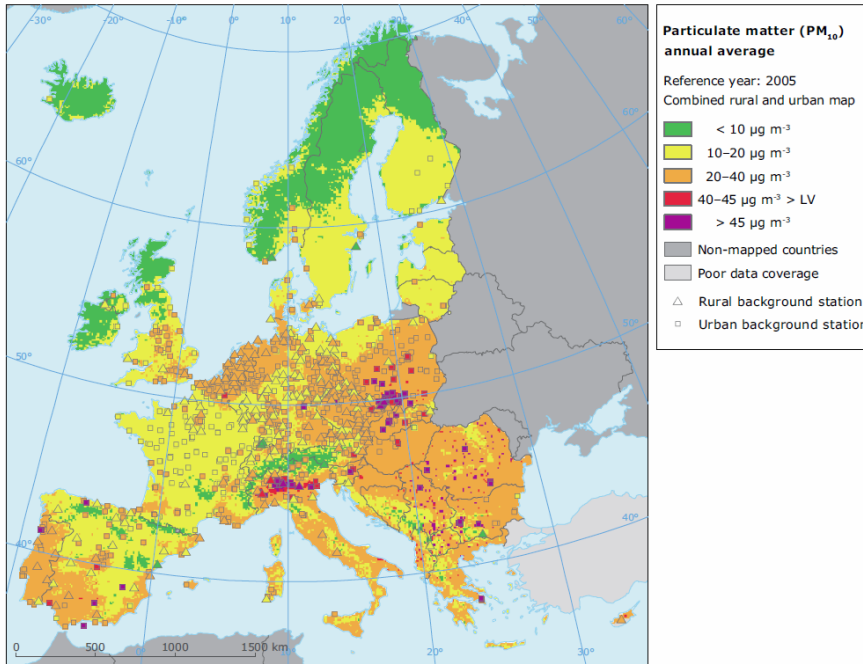
Figure 1. Combined urban and rural map for PM$_{10}$ annual average concentration in Europe 2005. Source: EEA, 2009
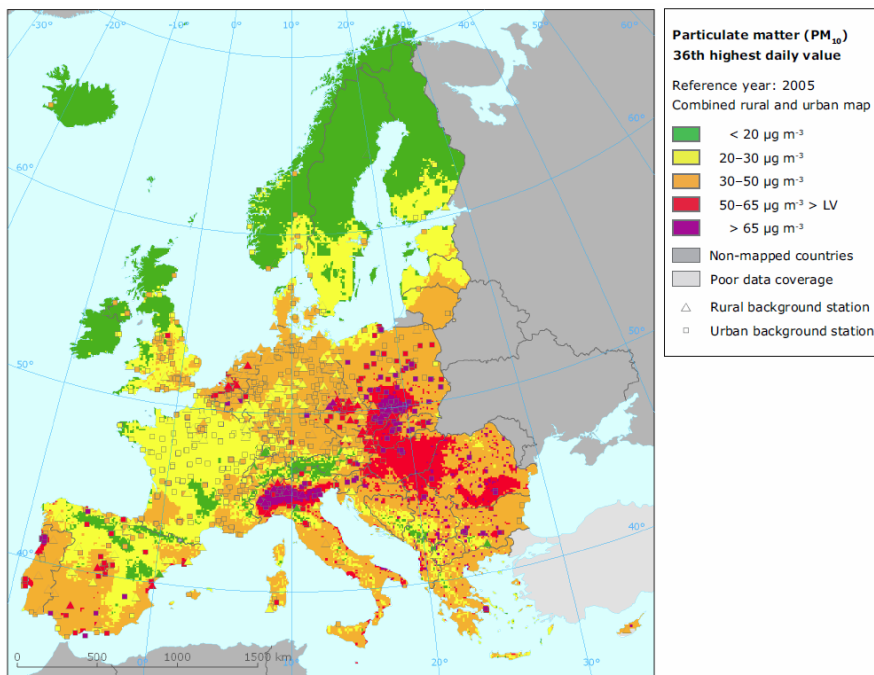
Figure 2. Combined urban and rural map for PM$_{10}$ 36th highest day concentrations in Europe. Note: in comparison to its neighboring countries, the PM$_{10}$ concentration in France is relatively low due to PM$_{10}$ values not being measured by using the recommended reference method and by applying a correction factor of (only) 1.0. Source: EEA, 2009.

The concentrations of PM$_{10}$ in the air are in many European regions exceeding the limit values. See figure 3.
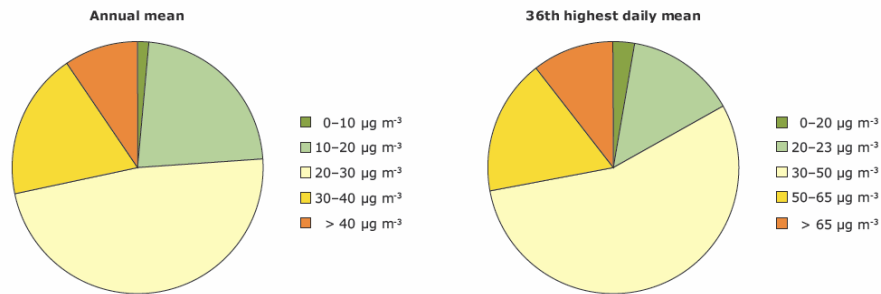
Figure 3. Exposure of the European to PM_{10} concentrations, annual mean (left) and 36th highest daily mean (right). Source: EEA, 2009.

The PM exposure at kerbsides consists of the urban background concentration added to the PM emitted by the traffic passing by. Concentrations are measured directly next to the traffic lane. These measured concentrations mainly apply for traffic participants such as cyclists and pedestrians experiencing a peak exposure of PM at traffic locations [RIVM, 2005]. The PM emission related to traffic can be divided into three groups: 1. Direct exhaust emissions; 2. Direct emissions other than exhausts; 3. Indirect or re-suspended emission from the tire and road interface [Ketzel et al, 2006]. Exposure factors related to traffic are the number of vehicles, types of vehicles, average speed, share of constant speed and non-exhaust emissions [Brizio et al, 2007].

Therefore the amount of PM exposure at kerbsides is dependable on a number of traffic related factors and local conditions at the kerbside itself. Local conditions influencing PM exposure are meteorological conditions, presence of buildings, building roof heights and presence of trees [Brizio et al, 2007].

1.6 Health effects and mortality due to particulate matter

Fine dust particles are a hazardous component of air pollution is, since there is a correlation between mortality rate and PM_{10} exposure [Dominici et al, 2003]. $PM_{2.5}$ seems to be an even more hazardous component. It is estimated that mortality rate effects are greater at a higher ratio of ($PM_{2.5}$)/PM_{10} [Levy et al, 2000]. The European Environmental Agency (EEA) has made an estimation for the mortality due to exposure to PM_{10}. See figure 4.
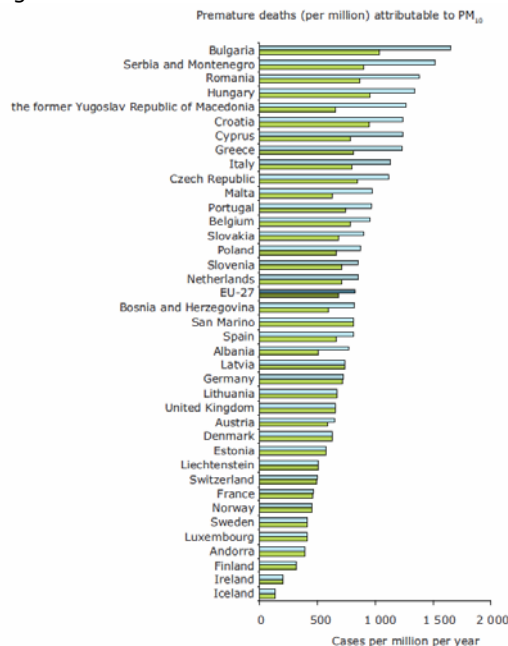
Figure 4. Mortality of PM_{10} in various European countries, presented in premature deaths per million per year. Source: EEA, 2009.

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Besides an increase in mortality rate, the presence of fine dust particles also leads to various health effects, such as chronic obstructive lung diseases and cardiovascular morbidity [Schlesinger, 2003], cancer [Roller, 2009] and health effects on pregnancy outcomes [Dejmek, 2000].

1.7 Most important proposed mechanism of PM toxicity: oxidative stress

It is proposed that different health effects due to PM may share the same toxicological mechanism. The most important mechanism that has been proposed for respiratory infections, lung cancer and chronic cardiopulmonary diseases is oxidative stress caused by reactive oxygen species (ROS) [Valavanidis et al, 2008]. All aerobic organisms have antioxidant defenses in order to protect important biological macromolecules such as proteins, carbohydrates, membrane lipids, and mitochondrial and cellular DNA. Oxidative stress occurs when the antioxidant defenses fail to protect these macromolecules from oxidizing. If the level of ROS is too high, the antioxidant defenses cannot protect the macromolecules anymore. When the antioxidant defenses are overwhelmed with ROS, mitochondria may be involved, releasing proapoptotic factors and inducing apoptosis of lung cells [Valavanidis, 2008].

1.8 ESCAPE

Since fine dust is such a threat to public health it has become an important issue in European politics. However the European policy is hampered by considerable uncertainty about the magnitude and nature of the impacts of long term exposure to air pollution on human health [Brunekreef, 2008]. Therefore the European Study of Cohorts for Air Pollution Effects (ESCAPE) has been launched in 2008. ESCAPE is a collaboration of more than 30 European cohort studies including some 900,000 subjects. The aim of ESCAPE is to quantify health impacts of air pollution and to reduce the uncertainty. Also ESCAPE tests new hypotheses on specific health effects of air pollution [Brunekreef, 2008]. The focus of ESCAPE lies on four categories of cohort studies: 1. Pregnancy and birth cohort studies; 2. Studies on respiratory diseases in adults; 3. Studies on cardiovascular disease in adults; 4. Studies on cancer incidence and mortality [Brunekreef, 2008].

1.9 Research goal of the Thesis

The ESCAPE project also wants to investigate how important the composition of elements of fine dust particles is when assessing possible health effects and mortality due to fine dust particles. Several studies have measured over 60 different elements present in a fine dust particle. Therefore it seems unachievable to perform a proper epidemiological health study for every different element. Instead the investigators of the ESCAPE project have decided to focus on a selection of elements. However they have not decided which elements to prefer in this selection. The goal of this thesis is therefore to give advice about which elements should be selected for further analysis in the epidemiological studies that ESCAPE is performing.

1.10 Main question and sub questions

With regard to the research goal, the main research question is the following:

"Which elements in airborne fine dust particles are preferred to be analyzed in the air pollution epidemiological analysis of the ESCAPE project?"

ESCAPE focuses on four end points: 1. Pregnancy and birth outcomes; 2. Respiratory diseases in adults; 3. Cardiovascular disease in adults; 4. Cancer incidence and mortality. Because oxidative stress is proposed to be the main mechanism for these effects, the sub research questions are:

1. *"Which elements in fine dust particles are associated with oxidative stress"*

2. *"Which elements in fine dust particles are associated with cancer?"*

3. *"Which elements in fine dust particles are associated with cardiovascular diseases?"*

4. *"Which elements in fine dust particles are associated with respiratory diseases?"*

5. *"Which elements in fine dust particles are associated with higher mortality?"*

6. *"Which elements in fine dust particles are associated with health effects in pregnancy and birth outcome?"*

2. Method

This thesis is based on literature research only. Therefore all the data and results that have obtained are extracted from published scientific articles or educational books.

2.1 General elemental composition of PM

In order to place study results of the various elements in the proper perspective, study results of Putaud and co-authors are presented addressing the general composition of PM in Europe. This way it can be analyzed if the most toxic elements are also the most common elements in PM.

2.2 Selection of endpoints

The selection of endpoints is based on the interests of the ESCAPE project. ESCAPE has chosen four endpoints: 1. Pregnancy and birth outcomes; 2. Respiratory diseases in adults; 3. Cardiovascular disease in adults; 4. Cancer incidence and mortality. Because it is proposed that oxidative stress is the main mechanism of these effects, 'Oxidative stress' is added as an endpoint in this report.
Therefore the potential health effects of PM elemental composition has been assessed over 6 endpoints: 1. Oxidative stress; 2. Carcinogenesis; 3. Cardiovascular disease; 4. Respiratory disease; 5. Mortality; 6. Health effects on pregnancy and birth outcome.

2.3. Scientific publications for each endpoint

The aim has been to find at least one recent scientific publication for each endpoint, but preferably two or three. All the scientific publications must address PM elemental composition in relation with a certain endpoint. A study associating cancer incidence with certain elements in PM has not been found. Instead the carcinogenesis of elements according to the IARC and an *in vitro* study performed in rats by Roller is presented.

2.4 Summary of study results

A large table has been made to summarize the results for all endpoints. In the first column a selection is presented of all the elements relevantly mentioned in the scientific publications. In the other columns study results of these elements are noted, categorized to the different endpoints. In these columns is noted what type of association a study found for each element. If there has not been found any association, the table cell remains blank.

2.5 Comparing and discussing study results for each endpoint

If two or more scientific publications are found for one endpoint, the results of these studies are compared on differences and similarities. When an endpoint has only one scientific publication available, the interpretation and validation of this publication study results has been discussed.

2.6 Concluding which elements are most appropriate for further investigation by ESCAPE

Because a study associating cancer incidence with certain PM elements has not been find, there has not been drawn any conclusion on this endpoint. Endpoint 'oxidative stress' is no endpoint in the ESCAPE project itself. Study results on oxidative stress are supposed to act as support in the findings on the other endpoints. This means that conclusions are only drawn for 'cardiovascular disease', 'respiratory disease', 'mortality' and 'pregnancy and birth outcome'. An element with significant association for every of these points is regarded as 'most advisable' for the ESCAPE project to further investigate. Elements associated with the majority (3) of these endpoints are regarded as 'appropriate' for further investigation. It is also possible that an element is associated in multiple studies with just one of the endpoints, but none of the other endpoints. In that case the element is 'specifically appropriate' for its endpoint.

3. Results

3.1 General composition of particulate matter in Europe

Putaud and co-authors have performed a study on physical and chemical characteristics of PM from 60 rural, urban and locations across Europe. The study has calculated the proportion of major contributors of PM for the Northwestern, Southern and Central regions of Europe. The outcomes of these calculations are summarized in table 2.

Table 2. Proportion of major contributors to particulate matter in Northwestern, Southern and Central Europe. Source: Putaud et al, 2009

		PM_{10}			$PM_{2.5}$			PM_{coarse}		
		Rural	Urban	Kerbside	Rural	Urban	Kerbside	Rural	Urban	Kerbside
N-western Europe	Min. dust	4%	12%			5%	1%	26%		
	Sea salt	12%	10%	7%		4%	1%	15%		
	SO_4	13%	14%	8%		21%	18%	6%		
	NO_3	16%	14%	12%		16%		20%		
	OM	15%	18%	16%		25%		14%		
	EC	4%	5%	9%		7%		1%		
	TC	14%	18%	20%		25%		12%		
Southern Europe	Min. dust	15%	21%	28%		11%	14%		42%	69%
	Sea salt	3%	12%	5%		6%	2%		22%	11%
	SO_4	16%	12%	12%		15%	15%		4%	5%
	NO_3	14%	9%	8%		7%	7%		11%	9%
	OM		26%			23%			13%	
	EC		6%			8%			2%	
	TC	13%	21%	28%		30%	38%		11%	
Central Europe	Min. dust	9%	12%	15%	3%	5%	6%	22%	25%	29%
	Sea salt	2%	2%	2%	1%	1%	1%	2%	3%	5%
	SO_4	19%	15%	9%	17%	19%	12%	5%	4%	4%
	NO_3	13%	12%	8%	6%	13%	10%	10%	7%	6%
	OM	23%	21%	21%	15%	22%	26%	5%	15%	13%
	EC	6%	10%	17%	5%	14%	21%	3%	3%	10%
	TC	32%	32%	38%	19%	31%	35%	6%	14%	19%

* OM = Organic matter. EC = Elemental Carbon. TC = Total Carbon

3.2. PM elements associated with oxidative stress

Important chemicals in particulate matter contributing to oxidative stress are organic carbon compounds and heavy metals [Henkler et al, 2010]. A strong correlation has been found between PM concentration of redox-active organic carbon compounds such as quinones and PAHs and damage in macrophages and bronchial epithelial cells. Studies showed that the carcinogenicity of quinones results from the formation of ROS [Valavanidis, 2008].

Particulate matter can contain heavy soluble metals such as *Fe, Ni, V, Co, Cu* and *Cr*. These soluble metals are associated with increase in ROS production and cellular oxidative stress [Valavanidis, 2008], because they are able to host as a catalyst in a Fenton reaction creating ROS [Hodgson, 2010]. See formula 1.

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \bullet OH + OH^-$$
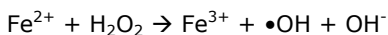
Formula 1: Iron as example for a metal acting as a catalyst in a Fenton reaction where peroxide is converted into ROS radical hydroxyl.

3.2.1 Study of Maciejczyk and co-authors on PM elements and oxidative stress

It is proposed that heavy metals and organic carbon compounds such as PAHs are able to induce oxidative stress because of they are soluble and because of their redox potential [Valavanidis, 2008]. In order to assess which metals or organic compounds can be associated with oxidative stress Maciejczyk and co-authors performed a study on the oxidant generation capacity of source-apportioned PM$_{2.5}$ [Maciejczyk et al, 2010]. Maciejczyk and co-authors collected samples in a rural New York area between March 2003 and January 2005. These samples were analyzed in a source-apportionment model. Then human epithelial cells were indirect exposed to these samples in an *in vitro* analysis by placing the cultured cells into an aqueous suspension. Maciejczyk and co-authors have used the activation of NF-kB (nuclear factor-κB) as biomarker for cellular responses related to oxidative stress [Maciejczyk et al, 2010]. They found a relatively strong association between Ni concentration and activation of NF-kB. They also found a significant but weaker correlation for Ba, Mn and Fe [Maciejczyk et al, 2010]. See table 3.

Table 3. Correlation coefficients between average elemental concentration PM and NF-kB activation. Source: Matiejczyk et al 2010

	Average (ng/m³)	SD (ng/m³)	CC *r* with NF-κB
Na	560	940	0.075
Mg	110	180	0.01
Al	350	450	−0.16
Si	940	830	−0.05
S	12000	12000	−0.14
Cl	66	260	−0.03
K	250	190	−0.07
Ca	180	140	−0.05
V	23	43	0.089
Mn	9.1	17	0.181*
Fe	500	440	0.17*
Ni	38	56	0.256*
Cu	12	19	−0.12
Zn	81	78	−0.14
Se	11	14	−0.11
Br	27	23	−0.13
Ba	13	46	0.194*
Pb	28	52	−0.12
BC	6000	4200	0.104

CC, correlation coefficient; BC, black carbon; SD, standard deviation.
*$p < 0.01$.

After source identification analysis Maciejczyk and co-authors concluded that metals are the only significant PM source contributing to the activation of NF-kB [Maciejczyk et al, 2010]. See table 4.

Table 4. Correlation coefficients (r) of the cellular response NF-kB with the sources identified by factor analysis. Source: Matiejczyk et al, 2010

Source	r-Value	p-Value
Resuspended soil	−0.0525	0.411
Metals	0.305	< 0.0001
Industrial/inciner	−0.144	0.0233
Transported	−0.090	0.161
Residual oil	0.093	0.146

3.2.2 Study of Ntziachristos and co-authors on PM elements and oxidative stress

Ntziachristos and co-authors have performed a study on the relationship between redox activity and chemical speciation of size-fractioned PM. They measured dithiothreitol (DDT) consumption in order to quantitatively determine superoxide radical anion formation, the first step in the generation of ROS. The PM samples were collected at various locations (road tunnel, freeway, background sites) so the redox activity of different PM samples could be determined and associated with their chemical characteristics [Ntziachristos et al, 2007].

Ntziachristos and co-authors have determined three fractions of PM: $PM_{0.15}$, $PM_{2.5}$ and coarse fraction. They found DDT activity the highest for $PM_{0.15}$, followed by $PM_{2.5}$ and the coarse fraction. When assessing the chemical components' DDT activity potential in a for all particle sizes univariate regression model, Ntziachristos and co-authors only found *OC* and PAHs to be significant correlation coefficients between DDT activity and different PM species. See table 5. However when specifically assessing the $PM_{0.15}$ and $PM_{2.5}$ mode they also found *NO_3, SO_4* and several metallic elements (*Cr, Mn, Fe, Cu, Zn, Ba and Pb*) to be significant correlation coefficients. See table 6.

Table 5. Correlation coefficients for DDT activity with different PM species for all PM modes. Source: Ntziachristos et al, 2007

Species	R	p
EC	0.26	0.30
OC	0.12	0.64
OC (excluding two unrealistic values)	0.87*	< 0.01
NO_3	-0.45	0.06
SO_4	-0.08	0.75
Metals and elements	-0.19	0.45
PAH 202–228 (FLU, PYR, BaA, CHR)	0.57*	0.04
PAH 252 (BkF, BbF, BaP)	0.92*	< 0.01
PAH 276–278 (BghiP, IcdP, dBahA)	0.95*	< 0.01

* indicates significance at the p = 0.05 level

Table 6. Correlation coefficients for DDT activity with different PM species for PM modes $PM_{0.15}$ and $PM_{2.5}$ in an univariate regression model. Source: Ntziachristos et al, 2007.

Species	$PM_{0.15}$		$PM_{2.5}$	
	R	p	R	p
EC	0.14	0.77	-0.18	0.70
OC[a]	0.92*	0.01	0.79*	0.05
NO3	-0.63	0.13	-0.81*	0.03
SO4	-0.75*	0.05	-0.80*	0.03
Metals and elements	0.44	0.31	-0.12	0.80
Na	-0.66	0.11	0.03	0.95
Mg	-	-	-0.52	0.29
Al	-0.10	0.83	-0.67	0.10
Si	-0.04	0.93	-0.63	0.13
Cl	0.15	0.75	0.63	0.13
K	-0.06	0.89	-0.69	0.09
Ca	0.55	0.20	-0.62	0.14
Ti	0.66	0.11	0.67	0.10
V	0.32	0.53	0.19	0.76
Cr	0.53	0.28	0.86*	0.05
Mn	0.90*	0.01	0.78	0.12
Fe	0.95*	< 0.01	0.96*	< 0.01
Ni	0.55	0.26	-0.46	0.36
Cu	0.95*	< 0.01	0.94*	< 0.01
Zn	0.93*	< 0.01	0.52	0.23
Br	-0.30	0.52	-0.54	0.21
Sr	0.74	0.09	0.70	0.12
Zr	0.80	0.10	0.86	0.06
Sn	0.71	0.18	-0.10	0.87
Ba	0.89*	0.04	0.92*	0.01
Pb	0.95*	< 0.01	0.88*	0.02

[a] Two unrealistic values have been removed from the OC samples.
* indicates significance at the p = 0.05 level

Ntziachristos and co-authors state that the univariate regressions may not be in the position to discriminate and independently quantify the impact of PAHs and transition metals. Therefore they have applied a multivariate regression analysis in order to separate their effects. *Cl* and *Cr + V* were found to be able to improve the correlation of PAH with DDT activity [Ntziachristos et al, 2007]. See table 7.

Table 7. Coefficients of significant correlation in multivariate regression analysis

Independent Variables	Unstandardized Coefficients		Standardized Coefficients	Significance level
	Value	Std. Error		
Constant	0.0152	0.0033		0.001
PAH > 252(μg per g of PM mass)	1.43×10^{-4}	8.78×10^{-6}	0.812	< 0.001
Cl (%)	-3.40×10^{-3}	7.3×10^{-4}	-0.199	0.001
Cr+V (%)	0.166	0.0386	0.214	0.002

Ntziachristos and co-authors concluded that the correlation of DDT activity with PAHs indicates that organic compounds with affinity to PAH or PAH derivatives are responsible for the redox properties of the PM samples. Inorganic species such as metals also show up in the correlations. Metals are not expected to contribute to the measured DDT consumption in a direct mechanism. Their presence in statistical associations however demonstrates that they act as surrogates of a particularly redox active PM source [Ntziachristos et al, 2007].

3.3 Association between carcinogenicity and different elements in PM

Large epidemiological studies in the United States have shown a statistical association between air concentration of the fine dust fraction $PM_{2.5}$ in the general environment and increased risk of lung cancer [Roller, 2009]. Inhalible organic compounds and heavy metals are known to be carcinogenic. However this does not clarify all the carcinogenicity of PM such as diesel exhaust particles [Roller, 2009].

3.3.1 Carcinogenicity induced by metalloid elements in PM composition

Inhalible metalloid compounds are known to be carcinogenic via oxidative stress [Henkler et al, 2010]. The International Agency for Research on Cancer (IARC) have classified *As, Cr, Ni* and *Cd* as category 1 carcinogens: "Carcinogenic to humans" [IARC, 2010]. However other metals such as *Fe, V, Pb*, and *Co* are also able to cause oxidative DNA damage, but their relevance to human carcinogenesis is much less clear [Henkler et al, 2010].

3.3.2 Carcinogenicity induced by organic compounds

An important mechanism of ROS generation is the conversion of organic compound into quinones [Henkler et al, 2010]. H_2O_2 and $O_2\bullet^-$ are generated in this process. PAHs are the main contributors of organic compound carcinogenicity, because they are able to constantly generate H_2O_2 and $O_2\bullet^-$ via futile redox-cycling as long as the reducing capacity of cells is maintained [Henkler et al, 2010].

3.3.3 Carcinogenicity of diesel particles

Several independent rat studies have shown surprisingly strong carcinogenic effects to inhaled diesel particles, even if the particles are virtually free of organic compounds. Further research of the IARC has lead to sufficient evidence of the carcinogenicity of black carbon and titanium oxide. The number of publications of *in vitro* studies researching *TiO₂* and carbon black nano particles has increased over the last years. Overall they show clear positive evidence for carcinogenicity in rats, see table 8. [Roller, 2009].

Table 8. Quantitative overview of rat study results from several studies on diesel engine emission, carbon black and TiO_2. Source: Roller, 2009.

Substance	Retained particle dose in lung After 1 year of exposure [mg]	[µl]^a	After ~2 years [mg]	Rats with lung tumor/ rats evaluated [%]	Percent risk/µl dust^b	Source
Diesel engine emissions	f/m 0.24	0.13	0.6	3/223; 1.3		Mauderly et al., 1987; Cheng et al., 1984; Wolff et al., 1987; Nikula, 2000
	f/m 2.18	1.18	11.5	8/221; 3.6^c	2.3	
	f/m 7.29	3.94	20.5	29/227; 12.8^c	3.0	
Controls (f/m)		—	—	2/230; 0.9	—	
Carbon black Printex 90	15.4	8.3		12/72; 17^c	2.0	Heinrich et al., 1994
	15.4	8.3		7/72; 9.7^c	1.2	
Controls (f)		—	—	0/72; 0	—	
Printex 90^d	38	20.5	44	39/100; 39^c	1.9	Heinrich et al., 1995
TiO₂ P 25	35	9.2	39	32/100; 32^c	3.4	
Diesel engine emissions	2.8	1.5	6.3	0/198; 0	0	
	11	5.9	24	11/200; 5.5^c	0.8	
	36	19	64	22/100; 22^c	1.1	
Controls (f)		—	—	1/217; 0.5	—	
Carbon black Elftex-12	f 6.2	3.4	17	8/107; 7.5^c	0.9	Nikula et al., 1995
	m 7.9	4.3	25	2/106; 1.9		
	f 12	6.5	37	28/105; 27^c	1.9	
	m 15	8.1	40	4/106; 3.8		
Diesel engine emissions	f 9.8	5.3	36	8/105; 7.6^c	0.8	
	m 12	6.5	45	5/105; 4.7		
	f 21	11	81	29/106; 27^c	1.3	
	m 28	15	90	9/106; 8.5		
Controls		f —	—	0/105; 0	—	
		m —	—	3/109; 2.8	—	

^aCalculated from the measured retained particle mass and density.

^bObserved percentage of rats with lung tumor (minus controls; = estimate of risk) divided by retained dust volume in lung (measure of the carcinogenic potency of a dust in the respective group for comparison with other groups and experiments). For the study of Nikula et al. (1995), the measure is given for female and male rats combined.

^cSignificantly higher than control ($p < .05$; Fisher´s exact test). In the study of Nikula et al. (1995), the tumor incidences in all dose groups are also significantly increased when females and males are combined (lowest significant tumor incidence with carbon black 10/213 = 4.7% versus 3/214 = 1.4%; $p = .043$).

^d0.04% of the particle mass could be extracted as organic substances (diesel soot for comparison: 40% with the same method). Mean values per mg Printex 90: 0.6 pg benzo[a]pyrene (diesel soot 3.9 ng), 1-nitropyrene < 0.5 ng (diesel soot 19.1 ng).

The IARC have found it necessary to critically evaluate the carcinogenic hazards of *carbon black* and *TiO₂*. Therefore the IARC committed in 2006 a working group to evaluate the hazard of inhaled *carbon black* and *TiO₂*. This working group concluded there is no adequate evidence of carcinogenicity of *carbon black* and *TiO₂* based on epidemiological studies. However the overall data from rodent cancer studies have provide sufficient evidence of carcinogenicity for both *carbon blac*k and *TiO₂*. The working group's conclusion is that *carbon black* and *TiO₂* are possibly carcinogenic to humans [Baan, 2007].

3.4 PM elements associated with cardiovascular disease

Although airborne PM is associated with cardiovascular disease, the chemical constituents that cause harm are unknown [Bell et al, 2009]. Recent studies have been able to link short-term cardiovascular effects to certain PM elements.

3.4.1 Study of Bell and co-authors on PM elements and cardiovascular disease.

The relationship between PM and health varies seasonally and regionally, as well as the composition of elements in PM [Bell et al, 2009]. Different universities in the USA have cooperated in a study performed by Bell and co-authors with measurements of $PM_{2.5}$ and administration of hospital admissions. They were able to set up two national data bases for the USA: 1. A database of long-term average concentration of $PM_{2.5}$ chemical compositions for 2000 – 2005; 2. A database of relative risks (RR) for cardiovascular and respiratory hospitalizations for persons 65 years or older associated with a 10 µg m^{-3} increase in $PM_{2.5}$ total mass on the same day for 106 U.S. counties for 1999 through 2005 [Bell et al, 2009]. By linking the two databases the universities were able to link cardiovascular hospitalizations to specific elements in PM [Bell et al, 2009]. The conclusion of the study is that *V*, Elemental Carbon (*EC*) and *Ni* are significantly linked to an increase of cardiovascular risk estimates, even when their values were adjusted for co-pollutants. *NO₃, Cl, Na, Zn, Cu* and *Pb* are also linked to an increase, but they lack statistical significance [Bell et al, 2009]. See figure 5.

Figure 5. Percent increase in health effects estimates for particulate matter with aerodynamic diameter 2.5 mm or less ($PM_{2.5}$) lag 0 and risk of
cardiovascular hospitalizations per IQR increase in the fraction of $PM_{2.5}$ total mass for each component. The points reflect the central estimate and the horizontal line represents the 95% posterior interval. Statistically significant associations are shown in bold. CVD 5 cardiovascular disease; EC = elemental carbon; IQR = interquartile range; OCM = organ carbon matter. Source: Bell et al, 2009.

3.4.2 Study of Zanobetti and co-authors on PM elements and cardiovascular disease.

Another similar study has been performed in the USA showing slightly different results. This study lead by Zanobetti was focused on the association between daily PM and emergency hospital admissions due to cardiac cause [Zanobetti et al, 2009]. The study used meta-regression to investigate the seasonal and community specific $PM_{2.5}$ composition as an effect modifier. Zanobetti has chosen three different endpoints that were related cardiovascular health effects in a study over 26 US communities, for the years 2000-2003: 1. Hospital admissions for cardiac causes (CVD); 2. Myocardial infarction (MI); Congestive heart failure (CHF). Zanobetti has found different elements to be a significant effect modifier for CVD and MI. See table 9.

Table 9: Effects modifiers cardiac events. Source: Zanobetti et al, 2009.

	P-value for modifier	%	95% CI		IQR
Cardiovascular disease					
Br	0.01	0.81	0.23	1.40	0.00010
Na$^+$	< 0.01	0.87	0.35	1.39	0.00945
Ni	< 0.01	0.90	0.46	1.35	0.00012
V	0.05	0.73	0.01	1.44	0.00017
Al	0.05	0.53	0.00	1.07	0.00193
Myocardial Infarction					
OC	0.03	1.03	0.13	1.94	0.07060
Ni	0.04	1.13	0.04	2.22	0.00012
As	< 0.01	2.35	0.84	3.85	0.00006
Cr	0.05	1.34	0.00	2.68	0.00010
Na$^+$	0.03	1.42	0.16	2.68	0.00945
Mn	0.03	0.99	0.14	1.85	0.00018
K	0.05	1.61	0.01	3.22	0.00270

3.5 PM elements associated with respiratory effects

Respiratory effects are associated with PM exposure. However it still remains uncertain which elements in PM are responsible for these effects [Bell et al, 2009]. Recent studies have been able to link PM elements with short-term respiratory effects.

3.5.1 Study of Bell and co-authors on PM elements and respiratory effects

In order to assess respiratory effects of specific elements in PM Bell and co-authors have used the same methods as for cardiovascular effects: they have linked a national USA database of long-term average concentration of $PM_{2.5}$ chemical compositions for 2000 – 2005 with a database of relative risks (RR) for cardiovascular and respiratory hospitalizations for persons 65 years or older associated with a 10 µg m^{-3} increase in $PM_{2.5}$ total mass on the same day for 106 U.S. counties for 1999 through 2005. See paragraph 3.4.1. By linking these two databases Bell and co-authors were able to associate respiratory related hospitalizations with specific elements of PM. They conclude *EC, V* and *Ni* are significantly associated with hospital admissions due to respiratory effects. Elements *Ca, Na$^+$, OC, Cu, Cl, Si, Ti, Mg, Al, NO$_3$* and *K* are insignificantly associated [Bell et al, 2009]. See figure 6.
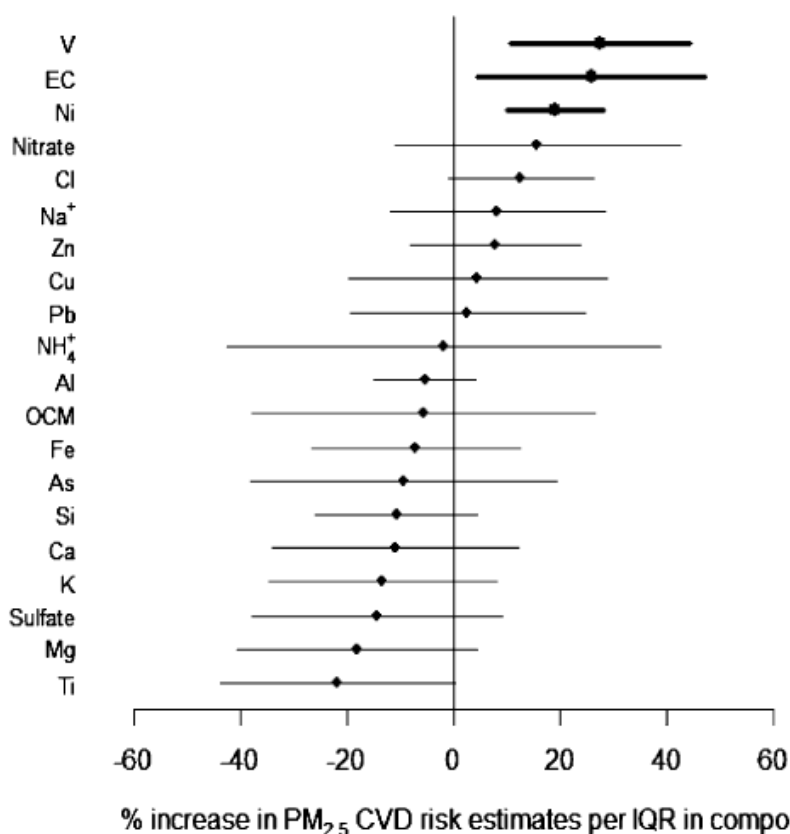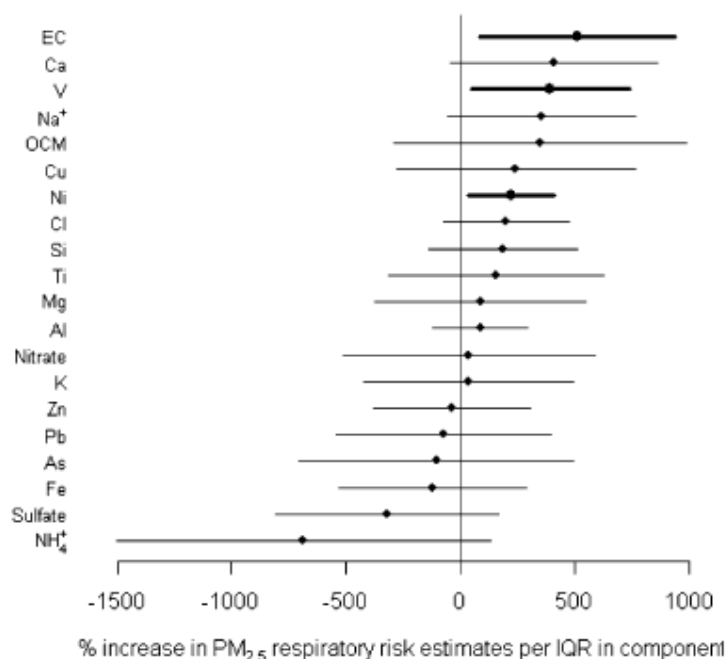

Figure 6. Percent increase in health effects estimates for particulate matter with aerodynamic diameter 2.5 mm or less ($PM_{2.5}$) lag 0 and risk of respiratory hospitalizations per IQR increase in the fraction of $PM_{2.5}$ total mass for each component. The points reflect the central estimate and the horizontal line represents the 95% posterior interval. Statistically significant associations are shown in bold. CVD 5 cardiovascular disease; EC 5 elemental carbon; IQR 5 interquartile range; OCM 5 organ carbon matter.

3.5.2 Study of Zanobetti and co-authors on PM elements and respiratory effects

Another similar study has been performed in the USA by Zanobetti and co-authors. The study was focused on the association between daily PM and emergency hospital admissions due to respiratory cause [Zanobetti et al, 2009]. The study used meta-regression to investigate the seasonal and community specific $PM_{2.5}$ composition as an effect modifier. Zanobetti and co-authors have chosen respiratory disease as endpoint in a study over 26 US communities, for the years 2000-2003. Zanobetti and co-authors did not find a specific element to be significantly correlated with respiratory diseases. Only elements *Ni* and *Na* are presented as almost significant with a p-value of 0.06.

3.5.3 Study of Happo and co-authors on PM elements and respiratory effects

Happo and co-authors conducted an experiment on mice within the framework of the project "Chemical and biological characterization of ambient air coarse, fine, and ultrafine particles for human health risk assessment in Europe" (PAMCHAR) coordinated by the National Public Health Institute of Finland. Happo and co-authors investigated the inflammatory activity and tissue damage in the mouse lung due to exposure to elements in PM. For their study they collected samples in six European cities (Duisburg, Prague, Amsterdam, Helsinki, Barcelona and Athens) in periods between October 2002 and July 2003. These size-segregated particulate samples were prepared for animal experiments. The dry particulate samples and blanks were thawed out and stabilized to room condition. Thereafter they were suspended into pathogen free water to obtain a final concentration of 5 mg/ml to be used in animal exposure. The mice were intratracheally instilled with a single particulate dose of 10 mg/kg (50цl/animal). After the mice were instilled, bronchoalveolar lavage fluid (BALF) was collected from the mice at 4h, 12h, and 24h after exposure. The BALF samples were analyzed for inflammatory and tissue damage indicators: Tumor necrosis factor alpha (TNF-α), interleukin-6 (Il-6), and keratinocyte-derived chemokine (KC). Happo and co-authors regarded a p-value < 0.05 to be significant and p-value < 0.2 to be nearly significant. They found significant correlations for Mg^{2+}, Ca^{2+}, Al, Cu and Fe with certain indicators. They also found nearly significant correlations for NO_3^-, NH_4^+, K^+, Ca^{2+}, As, Ni, V, Al and Fe. See table 10.

Table 10. Correlation between elements in PM fine fraction and coarse fraction with inflammatory and tissue damage indicators. Source: Happo et al, 2008.

	$PM_{2.5-0.2}$					$PM_{10-2.5}$				
	Total cells	Protein	TNF-α	IL-6	KC	Total cells	Protein	TNF-α	IL-6	KC
Inorganic water-soluble										
Cl^-	−0.600	−0.371	−0.143	−0.257	−0.314	0.771	0.600	0.086	−0.257	0.257
NO_3^-	**−0.886***	−0.771	−0.486	−0.600	−0.714	**0.886***	0.657	0.029	−0.143	0.029
SO_4^{2-}	−0.314	−0.086	0.257	0.143	−0.029	0.600	0.143	−0.029	−0.543	−0.314
Na^+	0.029	0.086	−0.086	0.143	−0.029	0.714	0.657	−0.200	−0.200	0.029
NH_4^+	**−0.886***	−0.771	−0.486	−0.600	−0.714	0.257	−0.086	−0.429	−0.771	−0.600
K^+	**−0.886***	−0.771	−0.486	−0.600	−0.714	**0.886***	0.657	0.029	−0.143	0.029
Mg^{2+}	−0.029	0.200	0.371	0.257	0.257	**0.943****	0.771	0.143	0.143	0.257
Ca^{2+}	**0.829***	**0.943****	**0.943****	**0.829***	**1.000****	0.600	0.429	0.771	0.600	0.771
Al	0.486	0.314	−0.029	0.429	0.086	**−0.943****	−0.771	−0.371	−0.200	−0.600
As	−0.771	**−0.886***	**−0.829***	−0.714	**−0.943****	0.143	−0.029	−0.314	−0.314	−0.657
Cd	−0.086	−0.257	−0.429	0.029	−0.486	0.143	−0.029	−0.314	−0.314	−0.657
Co	−0.143	−0.257	−0.543	−0.086	−0.486	0.200	0.371	−0.771	−0.257	−0.543
Cr	0.486	0.600	0.543	0.771	0.486	0.257	0.600	−0.314	0.714	0.086
Cu	0.429	0.543	0.771	0.657	0.600	**0.943****	0.771	0.143	0.143	0.257
Fe	0.486	0.543	0.143	0.486	0.371	0.486	0.486	−0.429	−0.257	−0.143
Mn	0.543	0.600	0.314	0.771	0.371	0.600	0.543	−0.314	−0.143	−0.371
Ni	0.771	**0.829***	0.600	0.714	0.771	0.657	**0.829***	−0.143	0.543	0.200
Pb	0.086	−0.029	−0.200	0.257	−0.257	0.314	0.429	−0.257	−0.086	−0.429
V	0.657	0.771	0.714	0.600	**0.829***	0.714	0.200	0.771	−0.257	0.486
Zn	0.086	−0.029	−0.200	0.257	−0.257	0.657	0.714	−0.314	−0.143	−0.200
Inorganic insoluble										
Al	**0.829***	0.714	0.486	**0.829***	0.543	**−0.941****	**−0.880***	−0.273	−0.273	−0.395
Fe	0.657	0.714	0.486	**0.829***	0.543	0.771	**0.943****	−0.086	0.429	0.257
Ca	0.143	0.314	0.257	0.143	0.371	−0.257	0.086	0.429	0.771	0.600
K	−0.507	−0.270	0.034	−0.439	−0.034	**−0.829***	−0.657	−0.086	−0.257	−0.200
Si	0.714	0.771	0.486	0.600	0.714	−0.600	−0.429	−0.371	−0.543	−0.429

Note. The values in this table are Spearman correlation coefficients (ρ). Boldfaced values indicate statistically significant or nearly significant correlations: ** $p < .05$, * $p < .2$.

They also found nearly significant association for general organic compound and significant associations for some specific organic compounds. See table 11.

Table 11. Association between organic compounds and inflammatory markers. Source: Happo et al, 2008

	$PM_{2.5-0.2}$					$PM_{10-2.5}$				
	Total cells	Protein	TNF-a	IL-6	KC	Total cells	Protein	TNF-a	IL-6	KC
Organic compounds										
Sum of dicarboxylic acids	**0.886***	**0.943****	0.714	**0.829***	**0.886***	0.600	0.429	0.771	0.600	0.771
Oxalate	**1.000****	**0.943****	0.657	**0.886***	**0.829***	0.543	0.086	0.771	0.257	0.600
Succinate	**0.886***	**0.943****	0.714	**0.829***	**0.886***	0.486	0.543	0.600	0.771	0.657
Malonate	**0.943****	**0.886***	0.600	**0.943****	0.714	0.600	0.771	0.029	0.029	0.257
Monosaccharide anhydrides	**−0.829***	**−0.943****	**−0.943****	**−0.829***	**−1.000****	n.a	n.a	n.a	n.a	n.a
Endotoxins	−0.086	−0.257	−0.257	−0.486	−0.143	0.486	0.543	0.600	0.771	0.657
Benzo[a]pyrene	−0.657	**−0.829***	**−1.000****	−0.771	**−0.943****	−0.086	−0.143	−0.657	−0.657	**−0.886***
Benzo[a]anthracene	−0.657	**−0.829***	**−1.000****	−0.771	**−0.943****	0.257	0.086	−0.257	−0.429	0.600
Benzo[b]fluoranthene	**−0.829***	**−0.943****	**−0.943****	**−0.829***	**−1.000****	−0.145	−0.203	−0.696	−0.609	**−0.928****
Benzo[k]fluoranthene	−0.657	**−0.829***	**−1.000****	−0.771	**−0.943****	−0.086	−0.143	−0.657	−0.657	**−0.886***
Indeno[1,2,3-cd]pyrene	−0.657	**−0.829***	**−1.000****	−0.771	**−0.943****	−0.200	−0.300	−0.500	−0.400	**−0.900***
Dibenzo[a,h]anthracene	0.000	−0.300	−0.300	−0.100	−0.400	−0.600	−0.600	0.400	0.300	0.100
Total sum of PAHs	−0.657	**−0.829***	**−1.000****	−0.771	**−0.943****	−0.086	−0.143	−0.657	−0.657	**−0.886***
Sum of genotoxic PAHs	−0.657	**−0.829***	**−1.000****	−0.771	**−0.943****	0.029	−0.058	−0.551	−0.638	**−0.812***

Note. The values in this table are Spearman correlation coefficients (ρ). Boldfaced values indicate statistically significant or nearly significant correlations: ** $p < .05$, * $p < .2$.

Happo and co-authors also performed a regression analysis between elements in PM and inflammatory response. They found a negative curve linear association for PAHs, a positive close to linear association for dicarboxylic acids and a consistent close-to-linear positive association for transition metals *Ni* and *V*. See figure 7.
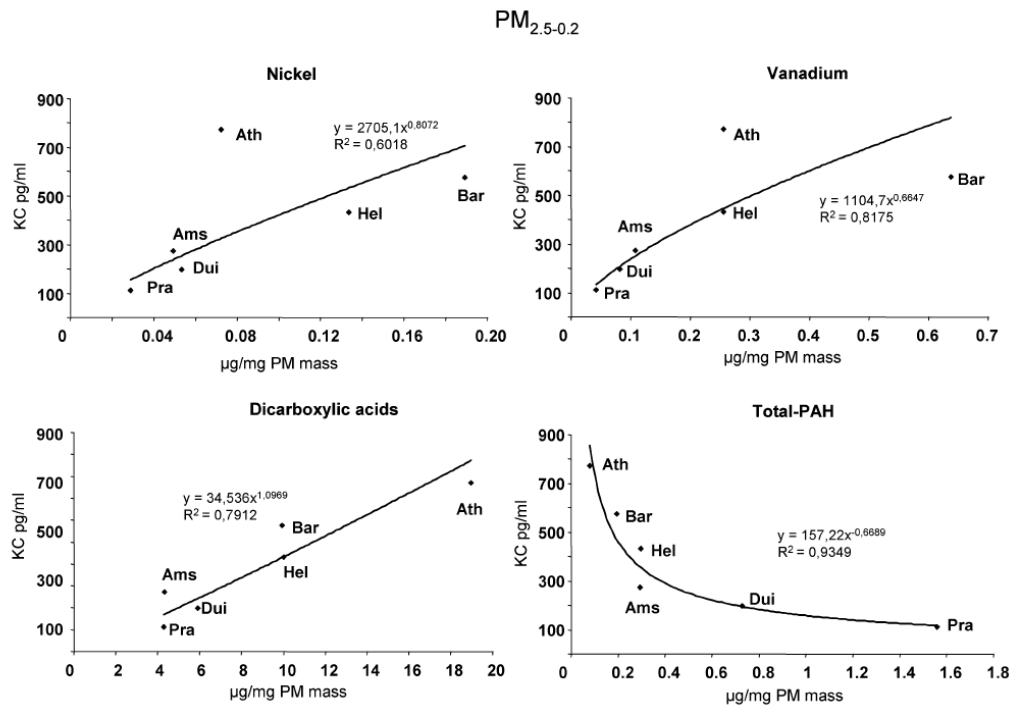
Figure 7. Regression between dose of Ni, V, dicarboxylic acids and PAH.

Happo and co-authors conclude that their study results suggest that oxidized organic compound and transition metals, most consistently Ni and V, contribute to the inflammatory activity of fine particulate samples in the mouse respiratory tract. Soil derived particulate constituents (Ca^{2+}, Al, Fe, Si) show similar contributions, however their role in coarse particulate samples is not obvious. Regionally and long-transported inorganic ions (NO_3^-, NH_4^+, SO_4^{2-}) have either negative or inconsistent associations with inflammatory activity [Happo et al, 2008].

3.6 PM elements associated with mortality

Although the association between PM mass and mortality is well established, there remains uncertainty about which chemical components of PM are most harmful to human health [Franklin et al, 2008].

3.6.1. Study of Franklin and co-authors on PM elements and mortality

Franklin and co-authors used a hierarchical approach in order to determine how the association between daily $PM_{2.5}$ mass and mortality is modified by $PM_{2.5}$ composition. They selected 25 communities in the USA based on availability of $PM_{2.5}$ mass concentrations and daily mortality records between the years 2000 and 2005. The study combined $PM_{2.5}$ mass and species concentration data recorded by the U.S. Environmental Protection Agency (EPA) with mortality data recorded by the U.S. National Center of Health Statistics and meteorological data from the U.S. National Climate Data Center. Then Franklin and co-authors performed a seasonal analysis. In order to determine season-specific associations between daily $PM_{2.5}$ mass concentration and mortality for each community, they used Poisson regression. In the next stage Poisson regression effect estimates and standard errors were combined using random effects meta-analysis to obtain an overall effect across the study domain. Mean seasonal concentration ratios of species to the total $PM_{2.5}$ mass were determined for each community. These proportions were then used in meta-regression to quantify the extent of the association between $PM_{2.5}$ mass and mortality modified by particle composition [Franklin et al, 2008]. Franklin and co-authors found significant effect modification to $PM_{2.5}$ mass proportion for elements *Al, As, Ni, S* and *Si* and nearly significant effect modification by *Br, Cr*, *NO₃* and *Zn*. See table 12.

Table 12. Effect modification by species to $PM_{2.5}$ mass proportion. Source: Franklin et al, 2008.

Model	Species	P for Effect Modification by Species to $PM_{2.5}$ Mass Proportion	% Increase in Nonaccidental Mortality Per 10-μg/m^3 Increase in $PM_{2.5}$ for an Interquartile Increase in Species to $PM_{2.5}$ Mass Proportion[a]	Heterogeneity Explained (%)[b]
Univariate	Aluminum	<0.001	0.58	45
	Arsenic	0.02	0.55	35
	Bromine	0.11	0.38	5
	Chromium	0.12	0.33	16
	Elemental carbon	0.79	0.06	0
	Iron	0.43	0.12	3
	Potassium	0.10	0.41	28
	Manganese	0.42	0.14	10
	Sodium ion	0.22	0.20	14
	Nickel	0.01	0.37	41
	Nitrate	0.07	−0.49	28
	Ammonium ion	0.84	0.04	3
	Organic carbon	0.59	−0.02	4
	Lead	0.31	0.17	11
	Silicon	0.03	0.41	25
	Sulfate	0.01	0.51	33
	Vanadium	0.28	0.30	3
	Zinc	0.19	0.23	15

[a] Adjusted for temperature.
[b] Includes heterogeneity explained by temperature.

3.7 PM elements associated with health effects in pregnancy and birth outcomes

Little is known about the influence of PM elemental composition and its influence on birth outcome. Bell and co-authors are one of the first to conduct a study on this subject. Their study also provides on of the first investigations of $PM_{2.5}$ and pregnancy outcomes. Their research was aimed to identify which $PM_{2.5}$ constituents or sources are most strongly associated with loss of birth weight. Therefore they have identified which constituents were most associated with specific sources to assist interpretation of estimates for constituents [Bell et al, 2010]. This means the study does not present a spectrum of different PM elements, but a small selection of elements representing their source. See table 13.

Table 13. Elements representing sources in Bell and co-authors study on PM elements and pregnancy and birth outcomes. Source: Bell et al, 2010

Source	Representing elements
Motor Vehicles	Zn, EC
Road dust	Si, Al
Oil Combustion	V, Ni
Salt	Cl
Other regional sources	S

This means the study only presents results for small number of PM elements. Elements *Zn, EC, Si, Al, V* and *Ni* are significantly associated with an increase in risk of Small-at-term Birth, only *Cl* and *S* are not significantly associated. However only *Zn, V* and *Ni* show significant association with actual loss of birth weight. See table 14.

Table 14. Elements and constituents associated with change in birth weight and risk increase Small-at-term Birth. Source: Bell et al, 2010

Constituent	IQR ($\mu g/m^3$)	Change in Birthweight (95% CI)	Percent Increase in Risk of Small-at-term Birth (95% CI)
Motor vehicles	1.4	−2 (−7 to 4)	8 (−1 to 18)
Zinc	0.006	−7 (−13 to −2)	12 (3 to 21)
Elemental carbon	1.1	−6 (−11 to 0)	13 (3 to 24)
Road dust	1.6	−4 (−10 to 1)	10 (1 to 19)
Silicon	0.05	−5 (−10 to 0)	10 (3 to 19)
Aluminum	0.03	−5 (−10 to 0)	11 (3 to 20)
Oil combustion	0.74	−4 (−10 to 1)	−3 (−11 to 6)
Vanadium	0.004	−5 (−8 to −1)	8 (2 to 15)
Nickel	0.002	−7 (−12 to −3)	11 (3 to 19)
Salt	0.17	−3 (−7 to 1)	5 (−2 to 12)
Chloride	0.009	−2 (−4 to 1)	3 (−1 to 7)
Regional sources	1.5	−3 (−8 to 2)	7 (−1 to 16)
Sulfur	0.3	−3 (−10 to 4)	7 (−5 to 20)
$PM_{2.5}$ mass	3.6	−3 (−9 to 2)	7 (−1 to 17)

Chemical constituents are divided into key sources, although all constituents listed result from multiple sources. Data were restricted to term births. Models were adjusted for apparent temperature, infant's sex, parity, nature of delivery, prenatal care, length of gestation, year of birth, tobacco and alcohol use during pregnancy, and mother's age, race, and education.

3.8 Summary of endpoint study results

Table 15. Summary of study results on all endpoints

Element	Oxidative stress		Carcinogenisis	Cardiovascular disease		Respiratory effects			Mortality	Pregnancy and birth outcome	
	Association to NF-kB activity*1	Association to DDT activity*2	Proposed as carcinogenic to human*3	Association with increase of risk estimate*4	Effect modifier of PM*5	Association with risk estimate increase*4	Effect modifier of PM*5	BALF response in mice lung*6	Effect modification to $PM_{2.5}$ mass*7	Actual loss of birth weight*8	Increase of risk estimate for small-at-term birth*8
Al	.	.	.	.	Significant effect modifier	Insignificant association	.	Significantly associated	Significant effect modifier	Insignificantly associated	Signifanctly associated
As	.	.	Carcinogenic to human	.	.	.	.	Nearly significant associated	Significant effect modifier	.	.
Ba	Significant but weaker association	Significant association in fine PM fraction	.	.	.	.	.	.	.	.	.
Br	.	.	.	.	Significant effect modifier	.	.	.	Nearly significant effect modifier	.	.
Ca	.	.	.	.	.	Insignificant association	.	Significantly associated	.	.	.
Carbon black	.	.	Possibly carcinogenic to human			.	.	.	.	.	.
Cd	.	.	Carcinogenic to human			.	.	.	.	.	.
Cl	.	Improves PAH correlation	.	Insignicant association		Insignificant association	.	.	.	Insignificantly associated	Insignificantly associated
Co	.	.	Possibly carcinogenic to human			.	.	.	.	.	.
Cr	.	Significant association in fine PM fraction	Carcinogenic to human			.	.	.	Nearly significant effect modifier	.	.
Cu	.	Significant association in fine PM fraction and improves PAH correlation		Insignicant association		Insignificant association	.	Significantly associated	.	.	.
EC	.	.	.	Significant association	Difficult to assess	Significant association	.	.	.	Insignificantly associated	Signifanctly associated
Fe	Significant but weaker association	Significant association in fine PM fraction	Possibly carcinogenic to human	.	.	.	.	Significantly associated	.	.	.
K	.	.	.	.	.	Insignificant association	.	Nearly significant associated	.	.	.

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Resume table 15

Element	Oxidative stress		Carcinogenisis	Cardiovascular disease		Respiratory effects			Mortality	Pregnancy and birth outcome	
	Association to NF-kB activity*1	Association to DDT activity*2	Proposed as carcinogenic to human*3	Association with increase of risk estimate*4	Effect modifier of PM*5	Association with risk estimate increase*4	Effect modifier of PM*5	BALF response in mice lung*6	Effect modification to $PM_{2.5}$ mass*7	Actual loss of birth weight*8	Increase of risk estimate for small-at-term birth*8
Mg	.	.	.	.	.	Insignificant association	.	Significantly associated	.	.	.
Mn	Significant but weaker association	Significant association in fine PM fraction	.	.	.	.	.	.	.	.	.
Na	.	.	.	Insignicant association	Significant effect modifier	Insignificant association	Nearly significant effect modifier	.	.	.	.
NH_4	.	.	.	.	.	.	.	Nearly significant associated	.	.	.
Ni	Strong significant association	.	Carcinogenic to human	Significant association	Significant effect modifier	Significant association	Nearly significant effect modifier	Consistent nearly linear regression	Significant effect modifier	Signifanctly associated	Signifanctly associated
NO_3	.	Significant association in fine PM fraction	.	Insignicant association		Insignificant association	.	Nearly significant associated	Nearly significant effect modifier	.	.
OC	.	Significant association in all PM modes	Carcinogenic to human		Difficult to assess	Insignificant association	.	.	.	.	.
Pb	.	Significant association in fine PM fraction	Possibly carcinogenic to human	Insignicant association	.	.	.	.	.	.	.
S	.	.	.	.	.	.	.	.	Significant effect modifier	Insignificantly associated	Insignificantly associated
Si	.	.	.	.	.	Insignificant association	.	.	Significant effect modifier	Insignificantly associated	Signifanctly associated
SO_4	.	Significant association in fine PM fraction				.	.	.	.	.	.
Ti	.	.	Possibly carcinogenic to human	.	.	Insignificant association	.	.	.	.	.
V	.	Improves PAH correlation	Possibly carcinogenic to human	Significant association	Significant effect modifier	Significant association	.	Consistent nearly linear regression	.	Signifanctly associated	Signifanctly associated
Zn	.	Significant association in fine PM fraction		Insignicant association		.	.	.	Nearly significant effect modifier	Signifanctly associated	Signifanctly associated

*1 According to Maciejczyk et al, 2010. *2 According to Ntziachristos et al, 2007. *3 According to Baan, 2007, Roller 2009, IARC 2010. *4 According to Bell et al, 2009. *5 According to Zanobetti et al, 2009. *6 According to Happo et al, 2008. *7 According to Franklin et al, 2008. *8 According to Bell et al, 2010.

4. Discussion

4.1 Limitations

4.1.1 Number of studies

The effects of PM elemental composition on human health have been assessed over 6 different endpoints. It was preferred to find two or three recent studies associating PM elemental composition with the endpoint. This goal has not been succeeded. See table 16.

Table 16. Number of studies associating PM elemental composition with each endpoint

Endpoint	Number of studies found
Oxidative stress	2
Carcinogenesis	0
Cardiovascular disease	2
Respiratory disease	3
Mortality	1
Pregnancy and birth outcome	1

This means the study results for 'Mortality' by Franklin and co-authors and 'Pregnancy and birth outcome' by Bell and co-authors is not checked by comparing them with other studies. As a consequence the consistency of found associations between PM elements and 'Mortality' and 'Pregnancy and birth outcome' is unclear. A study associating carcinogenesis with elements in PM has not been found. Instead the carcinogenesis of elements according to IARC and an *in vitro* study performed by Roller is assessed. This assessment shows which elements present in PM are carcinogenic or possibly carcinogenic to human. However it is still unclear if these elements are also carcinogenic in the exposure pathway of PM.

4.1.2 Studies do not address long-term effects

The focus of the ESCAPE project lies on the long-term effects of exposure to PM [Brunekreef, 2008], whereas the found study results for each endpoints are mainly focusing on short-term effects. See table 17.

Table 17. Summary of studies for each endpoint, description of studied effects and whether they are long or short term effects.

Endpoint	Study	Description of studied effect	Short or long term
Oxidative stress	Maciejczyk et al, 2010	NF-kB activity	Short
	Ntziachristos et al, 2007	DDT-activity	Short
Carcinogenesis	Baan, 2007	Proposed as carcinogenic to human by IARC	Long
	Roller, 2009	Rats with lung tumors	Short
Cardiovascular disease	Bell et al, 2009	Hospital admissions	Short
	Zanobetti et al, 2009	Hospital admissions	Short
	Happo et al, 2008	BALF response in mice lung	Short
Respiratory	Bell et al, 2009	Hospital admissions	Short
	Zanobetti et al, 2009	Hospital admissions	Short
Mortality	Franklin et al, 2008	Effect modification to $PM_{2.5}$ mass on mortality	.
Pregnancy and birth outcome	Bell et al, 2010	Actual loss of birth weight and increase risk estimate small-at-term birth	Short

There are various studies performed on long-term exposure to PM associated with adverse health effects and mortality [Lippman, 2009]. However these studies do not address PM elemental composition. Since long-term effects contributed by PM elemental composition is

still unavailable, the short-term effects associated with PM components found in the recent studies must act as an indicator for possible long-term effects of these components.

4.1.3 Correlation between components

PM is a complex mixture of various components. Therefore it is difficult to associate individual elements in PM with health effects, because the inevitable association between species originating from the same source confounds the ability to assess the degree to which they are individually responsible for toxic effects attributable to PM [Ntziachristos et al, 2007]. However the described studies do not present quantitative data related to this issue, except for Ntziachristos and co-authors study on DDT-activity, Bell and co-authors study on cardiovascular and respiratory disease and Happo and co-authors study on inflammation and tissue damage in mice lung.
Ntziachristos and co-authors performed a multivariate regression analysis in order to tackle this issue. They found *Cl* and *Cr + V* to significantly improve the effect of PAH on DDT-activity. However they also state transition metals *Mn, Fe, Cu*, and *Zn* could also improve the effect, but because of their high correlation with PAH they offer no additional explanation of DDT-activity [Ntziachristos et al, 2007].
Bell and co-authors have found *EC, Ni* and *V* to be elements that significantly increase the risk estimates for both cardiovascular and respiratory related hospital admissions. They have made estimations for adjustments for *EC, Ni* and *V* acting as a co-pollutant on each other [Bell et al, 2009]. See appendix 1, table 18. These estimations show that *EC, Ni* and *V* possibly influence on each others effects.
Happo and co-authors have presented a matrix showing the correlations of each component with the other elements. See appendix 1, table 19 and 20. They have found several significant and nearly significant correlations between components.
The quantitative results of Ntziachristos and co-authors, Bell and co-authors and Happo and co-authors prove that correlation between components needs to be taken into account when assessing the effects of components individually. Correlation between components is a confounding factor because the presence of a certain component is related to the outcome and exposure of another component. Therefore results of individual elements could best be regarded as indicative for an effect rather than actual effects.

4.1.4 Outdoor concentration measurements and indoor and personal exposure

The described studies have related outdoor measurements with mortality and adverse health effects. However outdoor monitors are likely to underestimate exposure to many of the elements present in PM [Adgate et al, 2007]. Adgate and co-authors have performed a study measuring trace elements of PM concentration outdoor, indoor and personally. They often found personal concentrations to be the highest, except for trace elements such as Ca and Al originating from crustal material [Adgate et al, 2007]. See appendix 2, table 21.

4.1.5 Described epidemiological studies were performed in the U.S.A.

There are four different studies discussed linking the endpoints to epidemiological data. All of these studies have been performed in the U.S.A., whereas ESCAPE is performing its studies in Europe. The results found on the U.S. population may not be totally applicable on Europe, because of possible difference in PM characteristics and population characteristics.

4.2 Comparison between the study results of Maciejczyk and co-authors and Ntziachristos and co-authors on oxidative stress

Maciejczyk and co-authors and Ntziachristos and co-authors have used different methods in order to explain the potential of different PM elements to induce oxidative stress. A major difference is that Maciejczyk only have measured OC and nitrates in their 1st stage of their 3-stage measurement campaign. In the 2nd and 3rd stage the measurements for OC and nitrates were unavailable [Maciejczyk et al, 2010]. Maciejczyk and co-authors found Ni to have the most significant correlation with NF-kB response, whereas Ntziachristos did not find a significant correlation for Ni and DDT activity. This may be the result of the relative low contribution of Ni in the total PM mass (< 0.1%) in Ntziachristos and co-authors samples [Ntziachristos et al, 2007] in comparison to the Maciejczyk samples (0.18%) [Maciejczyk et al, 2010].

When comparing the results of Maciejczyk and co-authors with Ntziachristos and co-authors it is clear that Ba, Fe and Mn have significant correlation with an indication for oxidative stress inducement. There is disagreement on Cu, Ni, Pb and Zn being significantly correlated. OC, NO_3, SO_4 and Cr are significant in Ntziachristos and co-authors' study but not measured in Maciejczyk and co-authors' study.

4.3 Comparison between study results on carcinogenesis by Roller, Baan and IARC

The publications of Baan, Roller and the IARC are not typical epidemiological researches linking PM elemental composition to carcinogenesis. Roller has performed a study on rats, concluding TiO_2 and carbon black induce lung tumors in rats [Roller, 2009]. The evaluation by the IARC working group published by Baan agrees TiO_2 and carbon black are 'possibly carcinogenic to human' [Baan, 2007]. The 'list of agents classified by the IARC monographs' show elements As, Cd, Ni and OC are considered to be carcinogenic [IARC, 2010]. However it is not clear if they are also carcinogenic in the PM exposure pathway, because an epidemiological study linking PM elemental composition to cancer incidence is lacking.

4.4 Comparison between study results on cardiovascular disease by Bell and co-authors and Zanobetti and co-authors

Zanobetti and Bell have chosen both for cardiovascular disease related hospital admissions as one of the endpoints. However their results are slightly different. See table 15. It must be noted that the study of Bell and co-authors probably is not very informative, for they present risk estimate increase on a very large scale (>1000%). See figure 5.

Zanobetti and Bell both agree that high composition of Ni and V are significant effect modifiers. Bell and co-authors found EC to be a significant effect modifier, whereas Zanobetti and co-authors found EC to be not. EC and OC are often highly correlated with $PM_{2.5}$ mass, making it very difficult to distinguish EC or OC effect from mass effect [Zanobetti et al, 2009].

Zanobetti and co-authors have discussed the results of Bell in their publications. They refer to a small difference between their study design and Bell's study design: Bell and co-authors did not take indoor infiltration into account, where Zanobetti and co-authors did. This may be confounder, since temperature is an important predictor PM composition. Bell and co-authors have performed a study over 106 communities, whereas Zanobetti and co-authors on 26, meaning Bell and co-authors' study probably has more power.

4.5 Comparison between study results on respiratory disease by Bell and co-authors, Zanobetti and co-authors and Happo and co-authors.

Despite the different study designs, the study results of Happo and co-authors can be compared with the study results of Bell and co-authors and Zanobetti and co-authors. However the study of Happo and co-authors shows little power, because only 6 effect points are compared. Most of the presented components show relatively high (> |0.75|) correlation with one of the effect points, but these correlations are still insignificant. Only components SO_4^{2-}, Na^+, Cd, Fe, Pb, Zn and insoluble Al and K did not show such a correlation, see table 11. The study of Bell and co-authors on respiratory disease is also not very informative. They present risk estimate increases on a very large scale (> 1000%).

When comparing the study results of Bell and co-authors, Zanobetti and co-authors and Happo and co-authors it is clear that V and Ni are most associated with respiratory health effects. Furthermore *EC, OC, Ca, Na$^+$, Cu, Cl, Si, Ti, Mg, Al, NO$_3$* and *K* have a possible association with respiratory health effects. See table 15.

4.6. Discussion on study of Franklin and co-authors on PM elements and mortality

Franklin and co-authors discuss there was too little variability in the species proportions among the communities, making it difficult to detect effect modification of the PM$_{2.5}$-mortalitity association. The proportion of *EC* and *OC* had small variability across the different communities. Their small coefficients of variation may explain why no effect modification was seen [Franklin et al, 2008]. Franklin and co-authors did not assess within-community variability, because their monitoring and availability of health data was limited. However they were able to reduce measurement error by averaging the species proportions over each season and multiple years. They also analyzed sub seasonal temporal patterns and correlations between seasonally averaged and unaveraged species ratios. These analyses indicate that their approach adequately represented the predominant temporal variability of species ratio [Franklin et al, 2008].

Furthermore Franklin and co-authors observed a lower effect estimate for PM$_{2.5}$ mass mortality in the west than in the east, despite the higher PM$_{2.5}$ mass concentrations. This may be due to the amount of indoor exposure and ventilation. Homes in the west are generally newer and better ventilated. Therefore the difference in relationship between population exposure and outdoor concentrations needs to be taken into account [Franklin et al, 2008].

The results of the study of Franklin and co-authors do not agree with the results of the early study of Mar on PM composition and mortality. Mar and co-authors have conducted a study on the association between PM composition and mortality for the region of Phoenix, Arizona in the U.S.A. over the period of 1995 to 1997. They concluded *K, EC* and *TC* can be significantly associated with cardiovascular mortality. They also found a negative association for soil (the summing of the oxides *Al, Si, Ca, Fe* and *Ti*), *S* and *Pb* [Mar et al, 2000]. Franklin and co-authors have stated they there was to little variability in the proportion of *EC* and *OC* across the different communities for a significant association. Mar and co-authors did find an association for *EC* and *TC*, however they only performed a study over 1 community. Furthermore it is surprising that Franklin and co-authors found *Al, S* and *Si* to be significant effect modifiers of PM, whereas Mar and co-authors found a negative association for soil (including *Al* and *Si*) and *S*.

The results of Franklin and co-authors are more agreeable with the results of the early study on PM composition and mortality performed by Laden and co-authors. Laden and co-authors investigated the elemental composition of size-fractioned particles in order to identify several distinct source-related fractions of fine particles. They examined the association of these fractions with daily mortality for six U.S. cities. The conclusion of this study was that particles from mobile and coal combustion contribute to mortality and crustal particles do not [Laden et al, 2000]. Laden and co-authors also evaluated specific elements in PM$_{2.5}$. They found *Ni, Pb* and *S* to be significantly associated with an increase in mortality. Elements *Fe* and *V* are significant predictors for mortality when they are evaluated separately, however when *Ni, Pb* and *S* were included in the model they were not significant anymore [Laden et al, 2000]. Franklin and co-authors study results agree with the significant association with *Ni* and *S*, however they also found *Al, As* and *Si* to be significant effect modifiers. Laden and co-authors did not include these elements in their study because they were not routinely found above the limit of detection.

4.7 Discussion on study of Bell and co-authors on PM elements and pregnancy and birth outcome

Bell and co-authors have discussed various limitations of their study in their publication. They have used a source-apportionment method with a selection of indicator constituents that are characteristic for individual sources. Bell and co-authors state the indicator constituents are not unique for their sources and the results should be interpreted with an understanding that they are not exclusive source markers. Additional research is needed to further illuminate the health effects of PM characteristics and sources [Bell et al, 2010]. The study also suffers on a lack of spatial variation data. Bell and co-authors have used county-wide exposure estimates, whereas spatial heterogeneity of PM$_{2.5}$ constituents and sources may vary within the county, introducing potential misclassification. Because the

spatial variation is larger for some constituents and sources than others, the degree of misclassification could differ per constituent or source. This within-community variation may have affected the results, possibly leading to an underestimation of effects [Bell et al, 2010].

The exposure estimates were based on residence at delivery. Studies of residential mobility during pregnancy are limited, but research suggests that most mothers only move short distances during pregnancy, suggesting that PM_{10} and ozone exposure is similar on the address during delivery and the addresses during pregnancy [Bell et al, 2010].

Bell and co-authors also state future work is needed to investigate other model structures and variables for which they did not have sufficient data. For example body mass index (BMI) of the mother. A 1 kg/m increase in mothers' BMI has been associated with a 20-g increase in birth weight [Fleten et al, 2010]. BMI may be associated with pollutant exposures, since it can follow community patterns [Bell et al, 2010].

5. Conclusion

ESCAPE has chosen four different endpoints for their cohort studies: 1. Pregnancy and birth cohort studies; 2. Studies on respiratory diseases in adults; 3. Studies on cardiovascular disease in adults; 4. Studies on cancer incidence and mortality. A study associating cancer incidence with certain elements in PM has not been found. Instead the carcinogenesis of elements according to the IARC and an *in vitro* study in rats have been discussed. Because a study associating cancer incidence with certain PM elements lacks in this report, a conclusion on this endpoint has not been drawn.

Oxidative stress has not been chosen as an endpoint in the ESCAPE project. Because oxidative stress is the main proposed mechanism for the other endpoints, the findings about certain elements in PM influencing oxidative stress serve to support the findings on the other endpoints. Therefore pregnancy and birth outcome, respiratory disease, cardiovascular disease, and mortality are the endpoints for which a conclusion has been drawn. Nickel and Vanadium have been significantly associated with al of these endpoints, supported by a respectively strong association and a PAH improving association with oxidative stress. There are no other elements with such strong associations for every endpoint. See table 15. Therefore it is advisable for ESCAPE to investigate the health impacts and uncertainties of elements Nickel and Vanadium in PM. Aluminum and Elemental Carbon show significant association for 3 endpoints. See table 15. From these elements, only Elemental Carbon is an element with a relative large proportion in PM in Europe. See table 2. Surprisingly none of these elements seem to have a significant association with oxidative stress. However, because these elements show significant association for the majority of the endpoints, they seem to be appropriate for an ESCAPE study that does not focus on one endpoint. There is no element significantly associated to a certain endpoint in more than one study, and show no significant associations to the other endpoints. However this may be still the case for elements Arsine, Sulfur and Silicon in association with mortality and for Zinc in association with pregnancy and birth outcome, because these endpoints only have been discussed with a single study. See table 15.

Overall it is most advisable for the ESCAPE project to select element Nickel and Vanadium for further investigation. Aluminum and Elemental Carbon seem to be appropriate for further investigation. There are no elements specifically appropriate for just one endpoint.

6. Literature

Adgate, J.L., Mongin, S.J., Pratt, G.C., Zhang, J., Field, M.P., Ramachandran, G., Sexton, K. 2007. Relationships between personal, indoor, and outdoor exposures to trace elements in $PM_{2.5}$. Science of the Total Environment: Volume 386, pp 21-32, 2007

Baan, R.A., 2007. Carcinogenic hazards from inhaled carbon black, titanium dioxide, and talc not containing asbestos or asbestiform fibers: recent evaluations by an IARC monographs working group. Inhalation Toxicology: Volume 19 (Supplement 1.), pp 213-228, 2007

Bell M.L., Ebisu, K., Peng, R.D., Samet, J.M., Dominici, F. 2009. Hospital admissions of fine particle air pollution. American Journal of Respiratory and Critical Care Medicine: Volume 179, pp 1115-1120, 2009.

Bell, M.L., Belanger, K., Ebisu, K., Gent, J.F., Lee, H.J., Koutrakis, P. Leaderer, B.P. 2010. Prenatal exposure to fine particulate matter and birth weight. Epidemiology: Volume 21, Number 6, November 2010.

Brizio, E., Genon, G., Borsarelli, S. 2007. PM emissions in a urban context. American Journal of Environmental Sciences: Volume 3 (3), pp 166-174, 2007

Brunekreef, B. 2008. ESCAPE European study of cohorts for air pollution effects, desciption of work for collaborative project. University of Utrecht. Utrecht. 2008.

Dejmek, J., Solansky, I., Benes, I., Lenicek, J., Sram, R.J. 2000. The impact polyciclic aromatic hydrocarbons and fine particles on pregnancy outcome. Environmental Health Perspectives: Volume 108, Number 12, December 2000

Dominici, F., McDermott, A., Zeger, S.L., Samet, J.L. 2003. National maps of the effects of particulate matter on mortality: exploring geographical variation. Environmental Health Perspectives: Volume 111, Number 1, January 2003

European Comission (EC). 2010. Air quality standards. Available online: http://ec.europa.eu/environment/air/quality/standards.htm. Consulted October 5th 2010.

European Environment Agency (EEA). 2009. Spatial assessment of PM_{10} and ozone concentrations in Europe (2005). EEA. Copenhagen. 2009

European Union (EU). 1999. Richtlijn 1999/30/EG van de Raad van 22 april 1999 betreffende grenswaarden voor zwaveldioxide, stikstofdioxide en stikstofoxiden, zwevende deeltjes en lood in de lucht; L 163/41. Publicatieblad van de Europese Gemeenschappen. 1999

Fleten, C., Stigum, H., Magnus, P., Nystad, W. 2010. Exercise during pregnancy, maternal pregnancy body mass index, and birht weight. Obstet Gynecology: Volume 115, pp 331-337, 2010

Franklin, M., Koutrakis, P., Schwartz, J. 2008. The role of particle composition on the association between $PM_{2.5}$ and mortality. Epidemiology: Volume 19. pp 680-689, 2008

Happo, M.S., Hälinen, A.I., Jalava, P.I., Pennanen, A.S., Sillanpaä, Hillamo R., Salonen, R.O. 2008. Chemical compositions responsible for inflammation and tissue damage in the mouse lung by coarse and fine particulate samples from contrasting air pollution in Europe. Inhalation Toxicology: Volume 20, pp 1215-1231, 2008

Henkler, F., Brinkmann, J., Luch, A. 2010. The role of oxidative stress in carcinogenesis induced by metals and xenobiotics. Cancers: Volume 2, pp 376-396, 2010

Hodgson, E. 2010. A textbook of modern toxicology. John Wiley & Sons. Hoboken, New Jersey. 2010

International Agency for Research on Cancer (IARC). 2010. Agents classified by IARC monographs. IARC. Available online: http://www.iarc.fr/en/publications/list/ Consulted Octerber the 5th, 2010

Ketzel, M., Omstedt, G., Johansson, C., Dűring, I., Pohjola, M., Oettl, D., Gidhagen, L., Wåhlin, P., Lohmeyer, A., Haakana, M., Berkowicz, R. 2006. Estimation and validation of $PM_{2.5}/PM_{10}$ exhaust and non-exhaust emission factors for practical street pollution modeling. Atmospheric Environment: Volume 41, pp 9370-9385, 2007

Laden, F., Neas, L.M., Dockery, D.W., Schwartz, J. 2000 Association of fine particulate matter from different sources with daily mortality in six U.S. cities. Environmental Health Perspectives: Volume 108, Number 10, October 2000

Levy, J.I., Hammit, J.K., Spengler, J.D. 2000. Estimating the mortality impacts of particulate matter: What can be learned from between-study variability? Environmental Health Perspectives. 2000

Lipmann, M. 2009. Environmental toxicants, human exposure and their health effects 3rd edition. John Whiley & Sons. Hobokemn, New Jersy. 2009

Maciejczyk , P., Zhong, M., Lippman, M. Chen, L.C. 2010. Oxidant generation capacity of source-apportioned $PM_{2.5}$. Inhalation Toxicology, early online, pp 1-8 2010

Mar, T.F., Norris, G.A., Koenig, J.Q., Larson, T.V. 2000. Associations between air pollution and mortality in Phoenix, 199-1997. Environmental Health Perspectives: Volume 108, Number 4, April 2000

Ntziachristos, L., Froines, J.R., Cho, A.K., Sioutas, C. 2007. Relationship between redox activity and chemical speciation of size-fractioned particulate matter. Particle and Fibre Toxicology: Volume 4, Number 5, 2007 .

Putaud, J.-P., Van Dingenen, R., Alastuey A., Bauer, H., Birmili, W., Cyrys, J., Flentje, H., Fuzzi, S., Gehrig, R., Hansson, H.C., Harrison R.M., Herrmann H., Hitzenberger R., Hüglin, C., Jones, A.M., Kasper-Giebl A., Kiss, G., Kousa, A., Kuhlbusch T.A.J., Löschau G., Maenhaut, W., Molnar A., Moreno, T., Pekkanen, J., Perrino, C., Pitz, M., Puxbaum, H., Querol, X., Rodriguez, S., Salma, I., Schwarz, J., Smolik, J., Schneider, J., Spindler, G., ten Brink, H., Tursic, J., Viana, M., Wiedensohler, A., Raes, F. 2009. A European aerosol phenomenology - 3: Physical and chemical characteristics of particulate matter from 60 rural, urban, and sites across Europe. Atmospheric Environment: Volume 44, pp 1308-1320, 2010

Rijksinstituut Volkgezondheid en Milieu (RIVM). 2005. Fijn stof nader bekeken. Milieu- en Natuurplanbureau: Report 500037008, 2005

Roller, M. 2009. Carcinogenicity of inhaled nanoparticles. Inhalation Toxicology: Volume 21, pp 144-157, 2009

Schlesinger, R.B. 2000. Properties of ambient PM responsible for human health effects: coherence between epidemiology and toxicology. Inhalation Toxicology: Volume 12 (Supplement 1), pp 23-25, 2000

Valavanidis A., Fiotakis, K., Vlachogianni, T. 2008. Airborne particulate matter and human health: Toxicological assessment and importance of size and composition of particles for oxidative damage and carcinogenic mechanisms. Journal of Environmental Science and Health Part C: Volume 26, pp 339-362, 2008.

World Health Organization (WHO). 2003. Health aspect of air pollution with particulate matter, ozone and nitrogen dioxide. Report on a WHO working group. Bonn, Germany. 2003

Zanobetti, A., Franklin, M., Koutrakis, P., Schwartz, J. 2009. Fine particulate air pollution and its components in association with cause-specific emergency admissions. Environmental Health: Volume 8, Number 58, 2009

List of PM component abbreviations

Abbreviation	PM Component
Al	Aluminum
As	Arsenic
Ba	Barium
Br	Bromine
Ca	Calcium
Carbon black	Carbon black
Cd	Cadmium
Cl	Chlorine
Co	Cobalt
Cr	Chromium
Cu	Copper
EC	Elemental Carbon
Fe	Iron
K	Potassium
Mg	Magnesium
Mn	Manganese
Na	Sodium
NH_4	Ammonium
Ni	Nickel
NO_3	Nitrate
OC	Organic Carbon
PAH	Polycyclic Aromatic Hydrocarbon
Pb	Lead
S	Sulfur
Si	Silicon
SO_4	Sulfate
TC	Total Carbon
Ti	Titanium
V	Vanadium
Zn	Zinc

Appendix

Appendix 1. Quantitative data on correlation between components in PM

Table 18. Adjustment for co-pollutants in PM in Bell and co-authors study on cardiovascular and respiratory disease. Source Bell et al, 2009

	Co-pollutant Adjustment	$PM_{2.5}$ and CVD Hospital Admissions*	$PM_{2.5}$ and Respiratory Hospital Admissions
Elemental carbon (EC)	None	25.8 (4.4 to 47.2)[†]	511 (80.7 to 941)
	Nickel	14.0 (−7.6 to 35.5)	399 (−45.1 to 843)
	Vanadium	14.9 (−7.8 to 37.6)	386 (−74.8 to 846)
	Nickel and vanadium	11.9 (−10.4 to 43.2)	362 (−98.0 to 823)
Nickel	None	19.0 (9.9 to 28.2)	223 (36.9 to 410)
	EC	17.3 (7.7 to 26.9)	176 (−18.7 to 370)
	Vanadium	15.5 (4.1 to 26.9)	151 (−78.4 to 381)
	EC and vanadium	14.9 (3.4 to 26.4)	136 (−94.9 to 368)
Vanadium	None	27.5 (10.6 to 44.4)	392 (46.3 to 738)
	EC	23.1 (4.9 to 41.4)	279 (−93.2 to 651)
	Nickel	10.9 (−9.6 to 31.5)	230 (−193.7 to 653)
	EC and nickel	8.1 (−13.3 to 29.5)	140 (−300 to 579)

Definition of abbreviations: CVD = cardiovascular disease; EC = elemental carbon; $PM_{2.5}$ = particulate matter with aerodynamic diameter ≤ 2.5 μm.
* The correlation between the fractions of $PM_{2.5}$ for each pair of components is 0.48 for nickel and vanadium, 0.33 for vanadium and EC, and 0.30 for nickel and EC.
[†] Values in parentheses are interquartile ranges.

Table 19. Correlation between elements in PM in the study of Happo and co-authors on respiratory disease. Source: Happo et al, 2008

	$Nss\text{-}SO_4^{2-}$	NO_3^-	NH_4^+	SS	WSS	WIS	OE	EC	POM	UM
$PM_{2.5-0.2}$										
$Nss\text{-}SO_4^{2-}$	1									
NO_3^-	0.657	1								
NH_4^+	0.657	**1.000****	1							
SS	−0.257	0.257	0.257	1						
WSS	0.086	−0.486	−0.486	0.086	1					
WIS	−0.543	−0.771	−0.771	0.143	0.600	1				
OE	0.200	0.257	0.257	0.429	0.314	−0.371	1			
EC	−0.371	−0.257	−0.257	0.600	0.543	0.543	0.371	1		
POM	−0.314	−0.314	−0.314	−0.600	−0.314	−0.029	−0.314	−0.029	1	
UM	−0.029	−0.522	−0.522	−0.174	0.493	0.493	−0.261	−0.261	−0.464	1
$PM_{10-2.5}$										
$Nss\text{-}SO_4^{2-}$	1									
$NO_3\text{-}$	0.657	1								
NH_4^+	0.771	0.600	1							
SS	0.543	**0.886***	0.600	1						
WSS	0.029	0.143	−0.429	0.029	1					
WIS	−0.600	**−0.943****	−0.714	**−0.943****	0.143	1				
OE	0.600	**0.943****	0.486	0.771	0.029	**−0.886***	1			
EC	**0.841***	0.464	**0.812***	0.406	−0.493	−0.551	0.522	1		
POM	0.493	−0.058	0.290	−0.377	−0.232	0.145	0.087	0.603	1	
UM	**−0.943****	**−0.829***	**−0.829***	−0.714	−0.086	0.771	−0.714	−0.725	−0.290	1

* p < 0.2 **p < 0.05

Table 20. Abbreviations Happo and co-authors for describing PM components . Source: Happo et al, 2008

Parameter	Abbreviation	Formula
Non-sea-salt sulfate	$nss\text{-}SO_4^{2-}$	$[Nss\text{-}SO_4^{2-}] = [SO_4^{2-}] - 0.246 \times [Na^+]$
Nitrate[a]	NO_3^-	
Ammonium[a]	NH_4^+	
Sea salt[a]	SS	$[SS] = 3.248 \times [Na^+]$
Water-soluble soil[a]	WSS	$[WSS] = [Fe_2O_3] + [Al_2O_3] + [CaO] + [K_2O]$
Water-insoluble soil[b]	WIS	$[WIS] = [Fe_2O_3] + [SiO_2] + [Al_2O_3] + [CaO] + [CaCO_3] + [K_2O] - [WSS]$
Other elements[a]	OE	$[OE] = [As]+[Cd]+[Co]+[Cr]+[Cu]+[Ni]+[V]+[Mn]+[Pb]+[Zn]$
Elemental carbon[c]	EC	
Particulate organic matter[c]	POM	$[POM] = 1.4 * OC$
Unidentified matter	UM	$[UM] = [gravimetric\ PM_x] - [sum\ of\ identified\ components\ of\ PM_x]$

Table 21. Outdoor, indoor and person exposure of PM elements. Source: Adgate et al, 2007.

Element	Outdoor						Indoor						Personal					
	N[a]	% >0[b]	Mean	Median	Q10[c]	Q90[d]	N[a]	% >0	Mean	Median	Q10	Q90	N[a]	% >0	Mean	Median	Q10	Q90
S	140	100.0	472.1	334.4	185.7	860.2	235	98.7	398.2	272.1	109.8	786.8	234	98.7	486.6	351.6	115.3	935.1
Ca	140	96.4	253.6	232.2	80.4	436.5	235	69.4	410.6	85.0	−116.5	349.5	234	67.2	835.6	174.1	−273.6	1324.2
Al	140	99.3	142.3	96.3	39.4	209.0	235	63.8	181.0	23.3	−63.5	83.5	234	63.4	359.3	58.6	−113.3	404.1
Na	140	83.6	83.7	33.1	−6.9	206.5	235	82.1	73.6	20.6	−7.3	126.3	234	71.1	149.2	31.9	−78.1	407.8
Fe	140	72.9	23.6	12.6	−11.0	59.4	235	96.2	63.5	43.1	11.9	115.6	234	93.2	124.0	78.6	11.8	215.0
Mg	140	81.4	28.8	10.9	−2.3	39.0	235	86.4	29.0	16.3	−3.3	57.8	234	77.9	52.7	27.5	−17.3	116.4
K	140	54.3	11.9	3.2	−29.9	54.5	235	89.4	69.4	38.4	−1.9	132.1	210	71.9	77.8	47.5	−57.7	198.5
Ti	140	82.1	3.8	3.0	−0.5	8.3	235	97.4	1.5	0.8	0.2	3.7	234	94.5	3.8	1.4	0.3	12.3
Zn	140	58.6	6.1	2.7	−6.3	20.1	235	85.1	10.8	6.5	−1.4	23.9	234	76.2	24.1	9.6	−13.9	75.4
Cu	140	91.4	3.7	2.4	0.1	8.2	235	84.7	4.5	1.5	−0.3	9.9	234	80.9	12.6	4.9	−1.2	27.5
Ni	NA	NA	NA	NA	NA	NA	235	48.5	12.0	−0.1	−1.2	6.3	234	66.0	13.2	1.8	−2.6	18.4
Pb	140	85.7	2.0	1.5	−0.2	4.4	234	97.9	3.4	2.4	0.66	6.8	234	94.9	6.2	3.2	0.67	9.3
Mn	140	85.0	1.0	0.6	−0.1	2.6	235	98.3	2.1	1.5	0.46	4.2	234	98.3	4.6	2.3	0.71	6.5
Sb	140	86.4	0.11	0.08	0.00	0.24	235	97.9	0.29	0.21	0.05	0.57	234	97.4	0.67	0.30	0.07	0.85
Cd	140	84.3	0.08	0.05	−0.01	0.18	235	99.1	0.30	0.12	0.04	0.33	234	96.6	0.40	0.14	0.04	0.56
V	140	82.9	0.10	0.05	−0.02	0.23	235	97.0	0.21	0.12	0.04	0.49	234	94.9	0.28	0.16	0.03	0.60
La	140	87.9	0.04	0.02	0.00	0.09	235	94.9	0.20	0.05	0.01	0.36	234	92.3	0.28	0.11	0.01	0.68
Cs	140	96.4	0.01	0.00	0.00	0.01	235	86.4	0.01	0.00	0.00	0.01	234	72.3	0.01	0.00	0.00	0.03
Th	140	94.3	0.00	0.00	0.00	0.01	235	99.6	0.01	0.00	0.00	0.01	234	95.7	0.01	0.00	0.00	0.01
Sc	140	59.3	0.00	0.00	0.00	0.01	151	45.5	0.00	0.00	0.00	0.01	175	48.1	0.02	0.01	−0.02	0.04
Ag	140	48.6	0.01	0.00	−0.01	0.05	151	60.9	0.11	0.07	0.01	0.27	175	64.3	0.13	0.08	−0.01	0.30
Co	NA	NA	NA	NA	NA	NA	235	66.0	0.11	0.02	−0.03	0.45	234	65.5	0.35	0.07	−0.08	1.5
Cr	140	45.7	0.03	−0.09	−0.58	0.76	235	91.5	1.4	1.2	0.1	3.0	234	91.9	3.4	2.6	0.18	7.8

Elements sorted by median outdoor concentration.
[a] N=number of O, I and P samples vary depending on the number of valid analytical results.
[b] %>0=percentage of samples with instrument readings above zero after field blank subtraction.
[c] Q10=10th percentile.
[d] Q90=90th percentile.