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**Health risks in relation to air quality, especially particulate matter**

Interim report

P.J.A. Rombout, H.J.Th Bloemen, L.van Bree, E. Buringh, F.R. Cassee, P.H. Fischer, J.I.Freijer, H.Kruize, M. Marra, A.Opperhuizen

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RIVM, P.O. Box 1, 3720 BA Bilthoven, telephone: 31 - 30 - 274 91 11; telefax: 31 - 30 - 274 29 71

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The evaluations presented in this interim report are to be considered as prelimanary as they are based only on part of the research results and occasionally are not yet validated. Conclusions directly or indirectly are to be treated accordingly.

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# ABSTRACT

A quantitative risk assessment of health effects associated with particulate matter (PM), especially ambient PM10 levels, for the Netherlands has indicated premature mortality among approximately 1000 persons. Local information, including air pollution mix and health status of the population, has proven to be essential in such a risk assessment. One of the questions not answered yet is if smaller particles (PM2.5) are more toxic than PM10. According to the particle dosimetry models developed for the project, the local dose in the lungs of groups with a less than optimal health status may differ substantially when compared to healthy adults; this may partly explain differences in susceptibility.

Modelling the Dutch and European emissions of PM and precursor gasses with an air pollution dispersion model has indicated that part (nearly half) of the Dutch yearly PM10 averages are still unaccounted for. A monitoring programme has been started to determine the composition of the missing PM10 and its sources.

An extensive programme of experimental inhalation toxicology using a mobile particle concentrator has also been developed to conform to epidemiological associations and more specifically to the discovery of causative fractions (and their sources). In vitro tests with lung tissue taken from a variety of individuals demonstrated great variability between these individuals in their susceptibility to collected ambient PM of different-sized fractions at the different locations.

A scientific workshop, envisaged for mid-2001, will allow a wider application of the results, with answers to the questions of the Ministry of Housing, Spatial Planning and Environment possibly expected by the beginning of 2002.

# SAMENVATTING

Een kwantitatieve risicoschatting leverde op dat een voortijdige strefte van duizend mensen in Nederland geassocieerd is met de huidige $PM_{10}$ niveaus. Lokale informatie (over het mengsel aan luchtverontreiniging en gegevens over de gezondheidstoestand van de bevolking) blijken essentieel te zijn voor het uitvoeren van een adequate risicoschatting. Een van de overblijvende vragen is bijvoorbeeld of kleinere deeltjes ($PM_{2.5}$) nu gevaarlijker zijn dan $PM_{10}$. Longdosimetrie modellen voor deeltjes die voor het programma zijn ontwikkeld, laten zien dat de lokale depositie en dosis in de longen van een COPD patiënt behoorlijk kunnen verschillen met die van een gezonde volwassene.

Bij het modelleren van de jaargemiddelde concentraties luchtverontreiniging op grond van de Nederlandse en buitenlandse emissies van $PM_{10}$ en precursor gassen bleek dat een deel (bijna de helft) van de Nederlandse jaargemiddelde niveaus vooralsnog niet verklaard wordt. Er is een meetprogramma gestart om de samenstelling van de ontbrekende massa en bronnen op te sporen.

Er is een experimenteel inhalatie toxicologisch programma met een mobiele fijn stof concentrator ontwikkeld om de epidemiologische associaties te bevestigd te krijgen en zo meer aan de weet te komen over de causale stof fracties en hun bronnen. In-vitro testen van deeltjes op longweefsel van humane patiënten laat zien dat er een grote inter-individuele variatie is in de reactie op deeltjes verzameld in verschillende groottefracties en op verschillende plaatsen in Nederland.

Om de resultaten een wijdere verspreiding te geven is in het midden van 2001 een wetenschappelijke workshop gepland. De verwachte antwoorden kunnen begin 2002 tegemoet worden gezien.

# CONTENTS

# 1. Introduction

Epidemiological scientific evidence has signalled the existence of air pollution related health effects in populations all over the world of a severity and to an extent that has not been imagined at the start of this decade. These health effects seem to take place at concentrations, which are well below the existing limit values. Therefore in 1997 the US EPA promulgated new National Ambient Air Quality Standards (NAAQS) for ambient particulate matter. In the USA the current air quality standard $PM_{10}$ was retained and a new standard for $PM_{2.5}$ was added, based on the available evidence on health effects and on the need for a nation-wide monitoring program on $PM_{2.5}$ air quality. In 1998, new Air Quality Limit Values for $PM_{10}$ were adopted in the EU. All these standards and values apply to the mass concentrations of particles with aerodynamic diameters lower than the 50% cut-off limits of 2.5 µm ($PM_{2.5}$) and 10 µm ($PM_{10}$). Table 1 summarises in a simplified scheme the various new annual and daily mean standards and limit values and the limitations for exceeding the daily standards (24-h mean).

*Table 1 Particulate Matter National Ambient Air Quality Standards (USA) and Air Quality Limit Values (EU) to Protect Public Health (simplified)*

| | | Annual mean | | Daily mean | |
|---|---|---|---|---|---|
| USA | $PM_{10}$ | 50 | 3-y average of annual mean concentrations (2012*) | 150 | 3-y average of the 99$^{th}$-percentile of 24-h mean concentrations (2012) |
| | $PM_{2.5}$ | 15 | 3-y average of annual mean concentrations (2012) | 65 | 3-y average of the 98$^{th}$-percentile of 24-h mean concentrations (2012) |
| EU | $PM_{10}$ | 40<br>20 | (2005)<br>(2010, preliminary) | 50 | Exceeding ≤ 35/year (2005)<br>Exceeding ≤ 7/year (2010, preliminary) |

* Years in which standards and limit values have to be effective.

Mean values expressed as mass concentrations in µg/m$^3$.

The EU air quality objectives for $PM_{10}$ are stricter than the USA air quality standards, resulting in the need in the EU for reductions in emissions from various sources to a much greater extent than formerly anticipated. The new PM standards will be revised in 2002 (USA) and 2003 (EU) following a critical review of new scientific data from studies on exposure, air quality, emission and source apportionment, PM toxicity and adverse health effects. In particular, in 2003 the EU will also consider whether the PM Daughter Directive should be adjusted to control for fine fraction of $PM_{10,}$ i.e. $PM_{2.5,}$ or an important source-related PM fraction like automobile exhaust. The EU, the Dutch Ministry of Environment, and the RIVM all called for new research on fine particles to determine whether these PM

fractions are of more importance than $PM_{10}$ and whether or not $PM_{2.5}$ should be regulated separately.

These directives of the EU necessitate extensive policy measures in the Netherlands in order to meet these values. To be able to effectively and efficiently reach those limits and to get the necessary commitment in society for these policy measures the Dutch Government wants to have a report at the end of 2001 for which they have formulated five questions, which they want to have answered:

1. How do the various indicators of PM compare as relevant for the causation of health effects?
2. What is the relationship between concentrations of ambient PM and health effects in order to make a substantiated choice for a PM standard?
3. What are the actual PM concentrations in the Netherlands and how big are the contributions of the different source categories to those concentrations?
4. Which indicator of PM is preferable, if next to health relevance also risk management considerations are taken into account?
5. What is the quantification of the total source risk chain now and in the foreseeable future?

For this answer the ministry of VROM has asked RIVM to devise a project and a plan of action. This report describes a second interim state of affairs after a first mid term review in Dutch (Bloemen et al., 1998) and gives some view of the research venues that have been chosen to present an answer in 2001 to the Ministry.

The framework of the project is comparable to the risk assessment paradigm of the National Research Council of the USA (1995). It centres on the total source effect chain as a causal and deterministic chain that can be used to develop policy options and evaluate the effect of certain policy measures before they have been really taken and can used to evaluate the future development of this causal chain. In Figure 1 a more general conceptual framework for the risk assessment and risk management is presented, that is used during this project (Buringh et al., 1998). During the project the different links of the total chain will be filled in and eventually a quantitative risk assessment will be presented, that will enable the questions above to be answered.

# Integrated Risk Assesment Paradigm

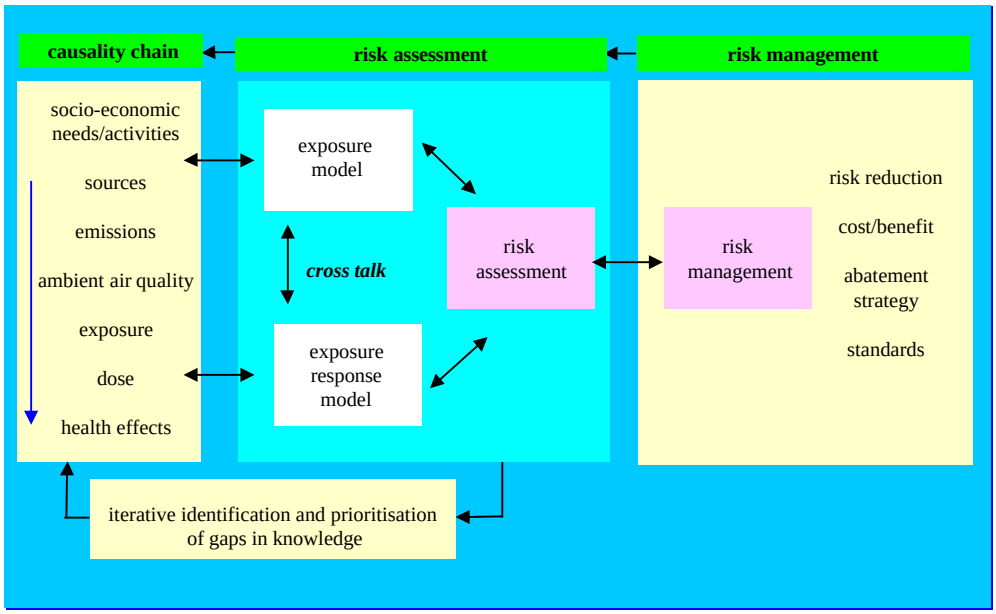


*Figure 1. Conceptual framework for risk assessment and risk management.*

Figure 1 presents the conceptual framework of a general PM Decision Support System (DSS). The PM associated health effects can be thought to occur according to the so-called causality chain. Sources emit primary PM of certain sizes and gaseous precursors of secondary PM. During their stay in the ambient atmosphere the original particle size distributions are transformed, gases are converted into particles, particles disappear due to wet and dry deposition, PM concentrations get lower due to dispersion and finally PM is transported to various parts of our ambient environment. Indoor/outdoor ratios and reactivity of the PM drive the dynamics of concentrations in various micro environments. Human activities eventually lead to the inhalation of PM (and other environmental pollutants). Part of the inhaled dose is retained in the respiratory tract and may be the cause of an effect in the target tissues, eventually culminating in (adverse) health effects.

The part from emissions to exposure can be characterised as the exposure assessment. To quantify this part, expertise is necessary of engineers, air quality modellers and experts in aerosol sampling and measurement. The part relating PM exposures to health effects can be characterised as the exposure-response assessment. To quantify this part, expertise of exposure-response modellers, social scientists, (inhalation) toxicologists and epidemiologists is vital. In the final step of the heath impact analysis and risk characterisation and estimation the expertise of both domains is combined into a quantitative risk assessment (QRA). The risk managers may use this risk estimate as a basis for the Risk Management (RM).

Parallel or after the risk quantification, various policy options can be devised. In consultation with the various experts from the different domains a number of abatement options or scenarios may be formulated. With a DSS these alternatives can be used in an iterative cycle as a basis for new risk and possibly also cost estimates. On the basis of various options the effectiveness or cost-effectiveness of different strategies may be quantified and subsequently be used by the risk managers in the policy process.

The explanation given above concerns the long-term goal (2001) of the programme, as it does not allow any advise until a PM DSS is constructed and validated.

In 1995 a so-called ‘pentagon’ model of five fractions of PM has been proposed for the Netherlands. These five fractions have been studied in more detail in this project, as the elusive ‘causative factor’ was assumed to be contained in one or more of these. Those fractions are: $PM_{10}$, $PM_{2.5}$, $PM_{0.1}$ (as a proxy for the number of particles), secondary aerosol (sum of sulphate, nitrate and ammonium; $PM_{sec}$) and carbonaceous aerosol ($PM_{carb}$) originally only from combustion sources, now comprising all carbonaceous (OC + EC). This mental model with five fractions, based on chemistry and physics, helps to understand the complex process of mutual influences. Targeting one of these parameters with abatement policies will have repercussions for the other four. For the risk assessment paradigm these five fractions should therefore be considered in their mutual relations. This ‘pentagon’ model is a practical way making reality more transparent.

The role of gaseous components, which together with PM make up the ambient mixture of air pollution to which the population is exposed, has been wilfully neglected in the ‘pentagon’ in order not to make matters even more complicated. Also free $H^+$ is not included in the ‘pentagon’, as there is an excess of neutralising ammonia in the Netherlands, contraru to the situation in the Eastern US. PM may be transported over long distances, for instance on a yearly average basis 75% of the secondary aerosol in the Netherlands is of foreign origin. Therefore PM has to be viewed on a European scale. Primary aerosols of non combustion origin are generally speaking larger in particle size than secondary aerosols and therefore are not transported over much more than 200 km. This still means such aerosols are an international problem for the Netherlands, because our country is of approximately the same dimensions (Janssen et al., 1999).

For this report a uniform terminology will be used, which is in accordance with the terminology used in English speaking countries but differs from a literal translation of Dutch terminology. For $PM_{10}$ a definition is presented in European Standard EN 12341, other often used terminology as coarse or fine is less clear. Therefore some specific definitions are at its place in this introductory paragraph in order to avoid confusion and ambiguity. $PM_{10}$ is in accordance with the term thoracic particulate mass (ACGIH, 1996). The aerosol fraction with an aerodynamic diameter between the two 50% cut-off points of 2.5 and 10 µm will be called “**coarse**” or the coarse fraction of $PM_{10}$ ($PM_{coarse}$). The fraction of the aerosol with an aerodynamic diameter under the 50% cut-off point of 2.5 µm and above the physical limits of concentrators (approximately 0.15 µm) is called “**fine**”, or $PM_{fine}$. The fraction with aerodynamic diameters under approximately 0.15 µm is called “**ultra fine**”, or $PM_{ultrafine}$.

All three fractions together: ultra fine + fine + coarse form the $PM_{10}$. And $PM_{2.5}$ is composed of ultra fine and fine PM. These above definitions clarify the original size concepts in the ‘pentagon model’.

# 2. Associations of health effects and air quality

## 2.1 Studies on short term effects of $PM_{10}$ on mortality and morbidity

Within the framework of the project an epidemiological study was conducted to investigate the association between short-term variations in mortality and ambient air concentrations in the Netherlands (Hoek et al., 1997). One of the purposes of that study was to evaluate whether the magnitude of the air pollution effects as reported in studies from other countries was valid for the Netherlands for quantifying health effects in the Dutch population. The results of the study would be applied to estimate the actual number of premature deaths in the Netherlands based on current air pollution levels. Daily total mortality counts, mortality counts for respiratory, cardiovascular and mortality data from several other causes were collected from the Central Bureau of Statistics (CBS). Daily air pollution concentrations of the pollutants $PM_{10}$, BS, $O_3$, $SO_2$, $NO_2$, and CO were collected from the National Air Quality Monitoring Network (RIVM). At that time data for $PM_{10}$ were only available for 1992, 1993 and 1994. After taking into account several confounders (like season, influenza and temperature), short-term fluctuations of daily mortality were associated with short-term fluctuations in previous day concentrations of all air pollutants. In table 2 a recapitulation of the main results of the study are shown. Results are presented as Relative Risks (RR) per 100 $\mu g/m^3$ $PM_{10}$.

*Table 2. Relative Risk for total and cause specific mortality in the Netherlands per 100$\mu g/m^3$ $PM_{10}$ at lag1. Source: Hoek et al., (1997)*

| Cause of death | Relative Risk per 100 $\mu g/m^3$ $PM_{10}$ | 95% CI |
|---|---|---|
| Total daily mortality | **1.020** | **1.004 – 1.037** |
| COPD | 1.068 | 0.996 – 1.144 |
| Pneumonia | 1.076 | 0.987 – 1.172 |
| Cardiovascular | 1.011 | 0.986 – 1.036 |

**Bold numbers** indicate a statistically significant effect

For the entire Netherlands, an increase of the $PM_{10}$ concentration with 100 $\mu g/m^3$ was statistically significant associated with a relative risk of 1.02 for total mortality. Such a figure indicates that mortality after a day with high levels of $PM_{10}$ (100 $\mu g/m^3$ higher than on the previous day) will be increased with 2%. For the other causes of deaths relative risks were all positively associated with $PM_{10}$, although these associations were not statistically significant.

The relative risk of 1.02 from the Dutch study is smaller than reported in a number of studies in the USA. Compared with the results of a large European study, in which the acute health effects of air pollution in a number of European cities was investigated (APHEA study), the relative risk is in the lower range of the relative risks in the APHEA study (Katsouyanni et al., 1997). Overall, the estimates from studies from the USA are slightly higher than those from Europe. Until now no conclusive explanation for this difference has been given. A possible explanation for the relatively low relative risks in the Dutch and the APHEA study is that in studies in the USA particle concentrations typically peak in the summer and in Europe

in the winter. Thus, the RR's for $PM_{10}$ in Europe are less influenced by summer data. In the summer period however, the RR in the Dutch study was 1.10 and in the APHEA study 1.09. However, other factors as differences in exposure measurements and sampler location, differences in pollution toxicity or mix, differences in proportion of sensitive sub-population, and model fit could also explain part of these differences.

A limitation of the Dutch study is that at that time only three years of data were available for $PM_{10}$. Therefore in the remainder of the project a longer time series of $PM_{10}$ will be analyzed. By that time the first $PM_{2.5}$ measurements will be available, which makes a comparison between effects of $PM_{10}$ and $PM_{2.5}$ feasible. A second improvement from a longer time series is that it will be possible to explore the differences that currently seem to exist between the seasons in the Netherlands. For those three years that are available the yearly RR for total mortality is 1.02, while the winter RR is 1.03 and the summer RR is 1.10. A separate analysis by Hoek et al., (1999), only on the three available years of PM data, indicated that high air pollution effect estimates in the summer are not an artifact of insufficient adjustment to high temperatures. This study also indicated that the air pollution effect estimates in the summer season were unchanged when pollen counts were entered as additional confounders. The high air pollution effect estimates in the summer season for pollutants that have their highest concentration in the winter season ($PM_{10}$, $SO_2$, $NO_2$, CO) are not due to interaction between those pollutants and ozone.

Based on the relative risks for $PM_{10}$ and on the average $PM_{10}$ concentration in the Netherlands, estimations can be made of the number of deaths in Netherlands attributable to $PM_{10}$. The results are presented in table 3.

*Table 3. Estimated yearly number of deaths in the Netherlands associated with exposure to $PM_{10}$*

| Cause of death | Number of deaths per year | 95% Confidence Interval |
|---|---|---|
| Total | **1000** | **200 – 1900** |
| COPD | 150 | 0 – 350 |
| Pneumonia | 110 | 0 – 250 |
| Cardiovascular | 350 | 0 – 900 |

**Bold numbers** indicate a statistically significant effect

As can be seen from Table 3, we have estimated that on average per year the death of approximately 1000 people in the Netherlands is associated with exposure to air pollution, ($PM_{10}$). In a previous estimation of the health effects of $PM_{10}$ in the Dutch population (Bloemen et al., 1998) the calculated number of total deaths was approximately four times higher. However, that estimate was based on the overall average Relative Risks based on the available scientific literature at that moment, which included only one limited Dutch study on the health effects of $PM_{10}$ (Verhoeff, et al., 1996). Therefore the magnitude of the overall Relative Risk for PM was dominated by American studies. As has been mentioned previously, effect estimates in US studies are higher than in European studies, this explains the higher effect estimate presented previously in Bloemen et al., (1998). We think that for describing $PM_{10}$ effects in the Dutch population the use of the Relative Risks stemming from a Dutch study covering the total population of the Netherlands will deliver the most accurate

results, because it is based on the local pollution mix, meteorology and susceptibility of the population.

In Table 4 the associations for other air pollutants are shown. The relative risks (RR) are expressed per relevant concentration range. Statistically significant associations are highlighted.

*Table 4. Relative Risk for total and cause specific mortality in the Netherlands for other air pollutants. Source: Hoek et al., (1997).*

| Cause of death | $O_3$ RR per 150 µg/m$^3$ | BS RR per 50 µg/m$^3$ | $SO_2$ RR per 50 µg/m$^3$ | $NO_2$ RR per 50 µg/m$^3$ | CO RR per 1500 µg/m$^3$ |
|---|---|---|---|---|---|
| Total daily mortality | **1.039** | **1.021** | **1.024** | **1.027** | **1.030** |
| COPD | 1.006 | 1.016 | 0.989 | **1.052** | **1.084** |
| Pneumonia | **1.146** | 1.042 | 1.050 | **1.088** | 1.100 |
| Cardiovascular | **1.055** | **1.018** | **1.024** | **1.016** | 1.015 |

**Bold numbers** indicate a statistically significant effect

Table 4 shows that other major air pollutants (both particulate and gaseous) are, like $PM_{10}$, associated with mortality in the Netherlands. This is due to the moderate to high correlation between the separate air pollution components. Of course meteorology is the driving force in this correlation, resulting in a simultaneous daily increase or decrease of pollutants in the mixture of air pollution. Due to this interdependency of the various pollutants it remains questionable whether the mortality effects as found in relation with $PM_{10}$ can be attributed specifically to ambient $PM_{10}$. The generally moderate to high correlation among air pollutants makes it problematic in statistical analyses to separate effects from specific components of the air pollution mixture. Despite these difficulties some efforts were made to analyse the independent effects of single pollutants by using models in which two air pollutants were analysed simultaneously. The results of these analyses showed that $PM_{10}$ associations were influenced when gaseous components were added in the model. It was concluded that particles were not more consistently associated with mortality than the gaseous pollutants.

Because of the difficulties due to correlation between pollutants, we have chosen for an approach in which the separate air pollutants will be evaluated in terms of plausibility of causality. This will be based on the temporal and spatial correlation and different indoor/outdoor ratio's of the various gaseous and particulate components of $PM_{10}$. An example of such an approach has recently presented by Buringh et al., (1999). This study investigated associations between $SO_2$ and daily mortality at different levels of exposure and found the effects to be stronger (per unit concentration) at lower levels. Then the study showed that in geographic areas with low levels, the effects were in fact smaller (per unit) than in areas with high levels, suggesting that $SO_2$ in this case is a surrogate rather than an active ingredient. Such analyses circumvent the above described co-linearity that often exits between PM and gaseous co-pollutants.

In a continuation of the mortality study, Hoek et al., (1999) examined interactions between pollutants (ozone and $PM_{10}$ in summer), confounding by airborne pollen in the summer, and the associations between secondary aerosol components sulfate and nitrate with daily mortality. It was concluded that there was no interaction between ozone and other pollutants, pollen did not confound the associations between air pollution and mortality, and that significant associations were found between aerosol sulfate and nitrate and daily mortality.

Parallel to the mortality analyses, associations between hospital admissions in the entire Netherlands and air pollution were analyzed by the University of Groningen (Vonk et al., 1998). Statistical models were comparable with the models used in the mortality analyses. Based on the relative risks, the number of hospital admissions for respiratory causes were calculated; results are presented in table 5.

*Table 5. Estimated yearly number of hospital admissions in the Netherlands associated with exposure to $PM_{10}$. Based on data from Vonk et al., (1998)*

| Cause of admission | Number of admissions per year | 95% CI |
|---|---|---|
| Respiratory | **650** | **130 – 1100** |
| Cardiovascular | **950** | **250 – 1700** |

**Bold numbers** indicate a statistically significant effect

It was estimated that yearly in the Netherlands about 1600 hospital admissions for respiratory or cardiovascular causes are associated with exposure of the Dutch population to $PM_{10}$.

In general the results of these two Dutch studies are in concordance with studies reported in the international literature. Recently a large number of studies has been published on the relationship between particulate air pollution and mortality or morbidity. In summary, relative risks estimated for hospital admissions and daily mortality were generally positive, statistical significant, and consistent with previously reported associations. However, like in the Dutch studies, several studies also showed significant associations between mortality and gaseous pollutants, such as CO and $O_3$.

### 2.1.1 Pilot study on acute respiratory cardiopulmonary effects in the elderly

Recently new epidemiological evidence appeared on the underlying mechanism leading to associations between ambient particulate matter and cardiovascular effects. In a panel of elderly subjects three studies found decreases in heart rate variability in association with particulate matter (Pope, et al., 1999; Liao, et al., 1999; Gold, et al., 1998). Decreased hart rate variability indicates decreased vitality and increased vulnerability of the person for external triggers (for instance air pollution). More insight in the underlying mechanisms is considered to be valuable information, necessary to explain the statistical associations found in epidemiological studies. In the framework of the project in 1998 therefore plans were developed to conduct an epidemiological study to assess the effects of air pollution on heart rate variability in a panel of elderly people. A pilot study was started at the beginning of the

year 1999 to test the feasibility of the field protocol to investigate the cardiopulmonary effects in a panel of elderly persons with existing cardiopulmonary symptoms. For the study non-smoking elderly patients with existing cardiovascular or pulmonary symptoms, living in an elderly peoples' home were selected through a doctor's practice. The doctor invited the eligible persons to participate in the study. In total 16 persons were included in the pilot study. During a period of 3 months, every second week measurements were made of ECG and heart rate variability using Holter recorders for 2 hours. Per person maximally 6 measurements were performed. During 2 days Holter measurements were recorded during 24 hours. At the same day that Holter measurements were taken, lung function was measured by using spirometry. No personal or ambient exposure measurements were done during this pilot study, because the purpose of the study was only testing the feasibility of the Holter and lung function protocol.

The results of the pilot show that recruiting the subjects is difficult. In our case only a dozen subjects were needed, however for a "full" study it is estimated that at least 50 subjects are needed to get sufficient power and significant results. Without a doctor's practice, recruiting will be very inefficient and it will probably take several weeks to months to get enough participants to end up with 50 complete data sets.

At the end of the pilot, an evaluation form was distributed among the participants. The protocol as it has been used is acceptable by the study participants. Only 3 of 16 participants dropped out of the study; two of which at the beginning (one because she was admitted to hospital for other reasons and one because the lung function testing was too hard to perform) and one during the study because of lack of time. On average per person 4.5 measurements were obtained (out of a maximum of 6). First analyses of the ECG-recordings show qualitative good recordings. Statistical analyses of the data were started at the end of 1999. Experiences with the lung function measurements indicate some problems with this specific group of subjects. Most of the study participants were not able to perform lung function measurements according to ATS-standards. In addition, some persons indicated that they found the test very strenuous and hard for them to perform. Data processing on Holter recordings is currently ongoing.

## 2.2 Studies on long term effects of PM in the Netherlands

### 2.2.1 Traffic related effects from two Dutch studies

Brunekreef et al. (1997) and Van Vliet et al. (1997) reported a study carried out in 1995 among primary school children living in sub-urban areas, located near major highways in the Province of South Holland in the Netherlands. The associations between lung function parameters and respiratory symptoms collected through parent-completed questionnaires and the distance from the children's schools and residences to the nearest highway, truck traffic flow at these highways, and the ambient and indoor (schools) concentration of particulate matter were investigated. Among the children living within 300 m of a highway a lower lung function (PEF, FVC, and $FEV_1$) was associated with increased truck traffic density on that highway and with measured black smoke concentrations in the children's schools. Furthermore, a higher prevalence of cough and upper respiratory symptoms was associated with distance from the children's residences to the nearest highway and with truck traffic density on that highway. No significant associations were observed for wheeze, shortness of breath with wheezing, bronchitis, asthma, or allergy.

In a replicate Dutch study among primary school children the associations between traffic related exposure variables and parent-reported respiratory symptoms and measured lung function parameters were investigated again (Van Vliet et al., 1999). The results with reported symptoms showed more or less similar associations between exposure variables and upper and lower respiratory symptoms as were found in the 1997 study. However, the results of the 1999 study with respect to the measured lung function parameters were not consistent with the results found in 1997. In this study Van Vliet et al., (1999) reported associations of the density of heavy traffic with health effects (however, not with light traffic), and of the air pollution concentrations with health effects. They did not find a relation with the distance of the road and health effects. Logically speaking such a result would have been expected, as the traffic related air pollution concentrations decrease with the distance to a road.

### 2.2.2 Exposure indicators for traffic related air pollution

Several studies have reported chronic health effects related to living near major roads. Generally speaking exposure to traffic related air pollution has not been well characterised in these studies. Therefore in Amsterdam a study was performed to evaluate differences in concentrations of air pollutants outside and inside homes in streets with low and high traffic intensity. The study was done in the framework of the Small Area Variation in Air quality and Health (SAVIAH) study (Fischer et al., 2000). Pollutants measured were particulate matter ($PM_{10}$ and $PM_{2.5}$), the reflectance ("blackness") of the $PM_{10}$ and $PM_{2.5}$ filters, Polycyclic Aromatic Hydrocarbons (PAH) and Volatile Organic Compounds (VOC). Measurements were performed during 19 days in the winter and spring of 1995. Per day two to four homes were measured. In total 36 homes without major indoor sources of air pollution such as smoking were included in the study, 18 in major streets and 18 in quiet streets.

Outdoor $PM_{10}$ and $PM_{2.5}$ concentrations were 15-20% higher at homes located in high traffic intensity streets compared to low traffic homes. A substantially larger contrast (of approximately a factor two) was found for outdoor concentrations of the particulate components BaP, total PAH and absorption coefficient ('soot'). This contrast was also found for the gas phase components benzene and total VOC. With the exception of the VOC's, differences of a similar magnitude were also found in indoor air in these homes. It was concluded that $PM_{10}$ and $PM_{2.5}$ are not specific indicators of exposure to traffic related air pollution. In the study the (outdoor) contrasts of BaP, total PAH, absorption coefficient, benzene and total VOC were highly correlated, suggesting that any of these could have been selected to represent exposure to traffic air pollution. No conclusions could been drawn on the unmeasured components like $NO_x$ and CO, which are probably also good indicators for traffic related air pollution.

## 2.3 New epidemiological insights

Recently a large number of new epidemiological studies have been published. Most of these studies confirmed earlier studies on the associations between exposure to particulate air pollution and morbidity and mortality. It would be beyond the scope of this report to discuss these studies extensively. However, a limited number of studies are worthy to be described in detail because they are helpful for a better understanding of the PM associated health effects.

### 2.3.1 Cardiovascular effects associated with PM

Although epidemiological studies have linked particulate air pollution with cardiopulmonary mortality, underlying biological mechanisms remain largely unknown. Unexplored pathophysiological pathways include transient declines in blood oxygenation and/or changes in cardiac rhythm following particulate exposure. Although the number of literature references still is relatively small, new data emerge that illuminates some of the physiological changes that may occur on the mechanistic pathway leading from PM exposure to adverse cardiac outcomes. Pope et al. (1999) made daily measurements of pulse rate and blood oxygen saturation using pulse oximetry on a panel of 90 elderly subjects during the winter of 1995-1996 in Utah Valley. Blood oxygen saturation was not consistently associated with $PM_{10}$. A 100 $\mu g/m^3$ increase in the previous-day $PM_{10}$ concentration was associated with an average increase of 0.8 beats/min. The odds of the pulse rate being elevated by 5 or 10 beats/min were increased by and 29 and 95%, respectively. Although there was little evidence of pollution-related hypoxia, alterations in pulse rate could reflect cardiac rhythm changes and may be part of the pathophysiology linking PM exposure to cardiopulmonary mortality. Liao et al. (1999) studied 26 elderly subjects at a retirement centre in Baltimore. Over three consecutive weeks daily six-minute resting heart rate data were collected during which the time between sequential R-R intervals was recorded. Statistical significant associations were observed between decreases in heart rate variations and $PM_{2.5}$ concentrations measured indoors or outdoors. Associations were stronger for subjects with comprised cardiovascular health.

Gold et al. (1998) reported decreases in heart rate variability among 21 active elderly subjects in association with $PM_{2.5}$ measured in the two hours prior to a physical examination.

### 2.3.2 Harvesting or mortality displacement

In the public health interpretation of the results from time series analysis, a key issue is whether the increased mortality associated with higher pollution levels is restricted to very frail persons for whom life expectancy is short in the absence of pollution. This possibility has been termed the “harvesting hypothesis.” Zeger et al. (1999) presented an approach to estimating the association between pollution and mortality from times series data that is resistant to short term harvesting. The method is based in the concept that harvesting alone creates associations only at shorter time scales. They used frequency domain log-linear regression to decompose the information about the pollution-mortality association into distinct time scales, and then created harvesting resistant estimates by excluding the short-term information that is affected by harvesting (Kelsall et al., 1999). They showed that the association between TSP and mortality counts from Philadelphia (1974-1988) is inconsistent with the harvesting-only hypothesis, and the harvesting-resistant estimates of the total suspended particles relative risk are actually **larger** -and not smaller- than the ordinary estimates. It is assumed that acute effects of particulate air pollution may shorten life from a few days to a few months.

### 2.3.3 Association between air pollution and post-neonatal infant mortality

Much of the evidence from epidemiological studies involves effects on the elderly population; there is less evidence about the effects of PM on children, especially those under 2 years of age. Air pollution episodes in the 1950s (at much higher levels than are currently observed) led to acute increases in infant mortality, and some recent epidemiological studies suggest that infant or child mortality may still result from air pollution, even at current levels. The results indicate that the effects of air pollution on infant mortality are specific for respiratory causes in the post-neonatal period. In a recent editorial in "Epidemiology" concern is expressed about a number of recently published studies that indicate to a relationship between air pollution and infant mortality and morbidity (Brunekreef, 1999).

Bobak and Leon (1992) carried out an ecological study of infant mortality and air pollution in the Czech Republic. Weak positive associations were found between neonatal mortality and quintiles of TSP and $SO_2$. Stronger effects were seen for post-neonatal mortality, with a consistent increase in risk from the lowest to the highest TSP quintile. The strongest effects were seen for post-neonatal respiratory mortality, which increased consistently from lowest to highest TSP quintile. The highest to lowest quintile risk ratios for post-neonatal respiratory mortality were 2.41 (1.10-5.28).

Woodruff et al., (1997) studied the relationship between post-neonatal infant mortality and particulate matter in the US in cohorts consisting of approximately 4 million infants born between 1989 and 1991. The odds ratio (OR) and 95% CI for total post-neonatal mortality for the high exposure versus the low exposure group was 1.10 (1.04 -1.16). In normal birth weight infants, high $PM_{10}$ exposure was associated with respiratory causes [OR = 1.40, (1.05, 1.85)] and sudden infant death syndrome [OR = 1.26, (1.14, 1.39)]. This study suggests that particulate matter is associated with a risk of post-neonatal mortality.

Bobak and Leon (1999) investigated the association between exposure to air pollution and post-neonatal respiratory deaths. They conducted a case-control study covering all births registered in the Czech Republic from 1989 to 1991. Exposure was assigned as the arithmetic mean of all 24-hour air pollution (TSP, $SO_2$ and $NO_X$) measurements in the district of residence of each case and control for the period between the birth and death of the index case. The effects were strongest in the post-neonatal period and were specific for respiratory causes. For these, rate ratios for a 50 $\mu g/m^3$ increase in TSP, $SO_2$, and $NO_X$ were 1.95 [95% confidence interval = 1.09-3.50], 1.74 (1.01 - 2.98), and 1.66 (0.98 - 2.81), respectively. TSP only showed a consistent association when all pollutants were entered in one model. No evidence was found of a relation between any pollutant and mortality from other causes.

Loomis et al. (1999a) conducted a time-series study of infant mortality in the south-western part of Mexico City in the years 1993 to 1995. Excess infant mortality was associated with the level of PM in the days before death, with the strongest association observed for the average concentration of fine particles during the period 3 to 5 days previously. A 10 $\mu g/m^3$ increase in the mean level of PM during these 3 days was associated with a 6.9% (2.0-11.3%) excess of infant deaths. Infant mortality was also associated with the levels of nitrogen dioxide and ozone 3 to 5 days before death, but not as consistently as with particles.

### 2.3.4 Studies of doctors' visits

Medina et al. (1997) examined short-term relationships between doctors' house calls and urban air pollution in Greater Paris. They found associations between asthma house calls and air pollution, especially in children. Risks for 24-hour sulphur dioxide, nitrogen dioxide and PM were all in the same range. Another published study looking at effects of air pollution on health in the primary care setting was conducted by Hajat et al., (1999), who evaluated the relationship in London between daily General Practice doctor consultations for asthma and other lower respiratory diseases and air pollution. Positive associations, weakly significant and consistent across lags, were observed between asthma consultations and $NO_2$ and CO in children, and $PM_{10}$ in adults, and between other lower respiratory disease consultations and $SO_2$ in children. The results of these two studies suggest that the widely documented air pollutant associations noted for visits of hospital emergency departments and hospital admissions are also applicable to a wider population consulting their physician, rather than an emergency department or hospital.

Thus, these two studies support the hypothesis that looking at only hospital admissions and emergency hospital visits probably underestimates the numbers of morbidity events in a population due to acute ambient PM exposure.

## 2.4 Future activities

The future activities on the relationship between health effects and air quality are instrumental for a better and more quantitative process of risk assessment. It is important to get a more substantiated risk assessment of the PM related health effects by analysing a longer time series than could be used for the past QRA. Especially some of the more puzzling points in the current RA as the differences between seasons (a higher risk in summer) and the differences in potency between the USA, Western and Eastern Europe need to be studied in somewhat more detail. With these activities it is tried to reduce the currently long list of suspects for the causative factor for the health effects. Future activities will address questions of the magnitude of the PM-problem in the Netherlands, the role of $PM_{10}$, $PM_{2.5}$ and gases in the association between mortality and air pollution, and the heterogeneity in results from international epidemiological studies from different geographic areas

- An extension of the time series analyses on mortality and air pollution will be conducted in 2000. In comparison to earlier analyses on the relationship between air pollution and mortality, a larger $PM_{10}$ data set (4-5 additional years, resulting in a seven/eight year time series) will be analysed. The results of these analyses will be compared with earlier analyses, and due to the larger data set relative risk estimates for $PM_{10}$ health effects in the Netherlands will become more reliable and applicable in QRA. Additionally the possibilities for the analysis of the first $PM_{2.5}$ data will be explored. If feasible, these exposure data will also be analysed in relation to the mortality data.
- Causes for heterogeneity in results of epidemiological studies are until now unsolved. Studies from the USA show a higher relative risk per unit pollution than European studies. Generally speaking, the yearly average $PM_{10}$ levels are somewhat lower in the USA than in Europe. Within Europe, differences in relative risks were seen between

Western-European and Eastern-European study centres, with higher relative risks in Western European areas. Again generally speaking, concentrations are lower in Western Europe than in Eastern Europe. Although it has been speculated that differences in exposure measurements, differences in pollution toxicity or mix, differences in proportions of sensitive sub-populations between studies might be reasons for differences in risk estimates, no appropriate studies have been conducted to address this phenomenon. A contrast analysis is foreseen to explore these issues in 2000/2001. Based on statistical analyses of contrasts in exposure situations in space and time that were reported in epidemiological studies, new insight might be gained in the causes of these differences. Especially the role of different co-pollutants in the relation between air pollution and mortality and the process of data analysis will be addressed. Identification of the most important causes of health effects is essential for the development of effective abatement strategies.

- Although the pilot study on the acute respiratory cardiopulmonary effects in the elderly showed that such a study is feasible, no efforts will be made in 2000 to conduct a large study. For this, time schedules from now on will be too short and regular RIVM capacity will be not available in 2000. Therefore a decision whether or not to execute such a study is postponed to the year 2000.

# 3. Air Quality

## 3.1 RIVM PM research

The first integrated assessment of particulate matter in the Netherlands (Bloemen et al, 1998) has resulted in the identification of uncertainties that need to be clarified to improve the understanding of the causality chain of sources – concentrations – health effects and subsequently assessing the impact of existing and foreseen abatement measures. The uncertainties in the air quality domain were considered relevant as the EU directives stipulate annual and daily averaged levels that might be hard to comply with. Therefore a research programme was anticipated that is partly executed by RIVM (3.1) and partly by other research institutes in the Netherlands (3.2), with active co-ordination by the Ministry of VROM and RIVM.

### 3.1.1 Air quality assessment by modelling

To enable the assessment the air quality based on emission inventories and dispersion modelling an approach was developed and completed in 1999 named Sigma (Σ). It allows the fast calculation of concentration fields (Netherlands) for the assigned emission categories for primary and secondary PM both for the current years and projections in the (near) future and is analogue to a source-receptor matrix. It assumes linear behaviour of primary and secondary PM which hold for compositions similar to the current one. In general this approach was followed for the first integrated assessment but two essential improvements were identified:

The particle size distribution (PSD) of emissions plays an important role in the dispersion modelling. The default PSD used in the first integrated assessment could both over- and underestimate the concentrations, depending on the source-receptor distance and the PSD of the source category. Research in the field of emission inventory knowledge is needed to arrive at mode defined PSD for each source category.
Emission inventories tend to improve continuously as more data and knowledge becomes available. Including this would call for lengthy and extensive recalculations of the concentration fields. Assuming linear behaviour of the PM constituents a fast linear combination of the concentration fields gives the total concentration of PM in a substantial reduced time.

The Sigma approach allows the incorporation of newly obtained data and knowledge on the emissions and natural source contributions without repeating the dispersion calculation. It further enables the calculation of the annual averaged concentration levels for the other parameters of the ‘pentagon’ (secondary aerosol- $PM_{sec}$, carbonaceous aerosol $PM_{carb}$ and the fine mode - $PM_{2.5}$ and $PM_{ultrafine}$). Figure 2 gives the assessment of the PM levels in 1995 based on current knowledge of the anthropogenic emissions and their default PSD (based on research in NOKLUK programme in 1980’s) and the discrepancy between the measurements and model calculations. An increase of 5% (2 $\mu g/m^3$) at major urban sites is assumed.

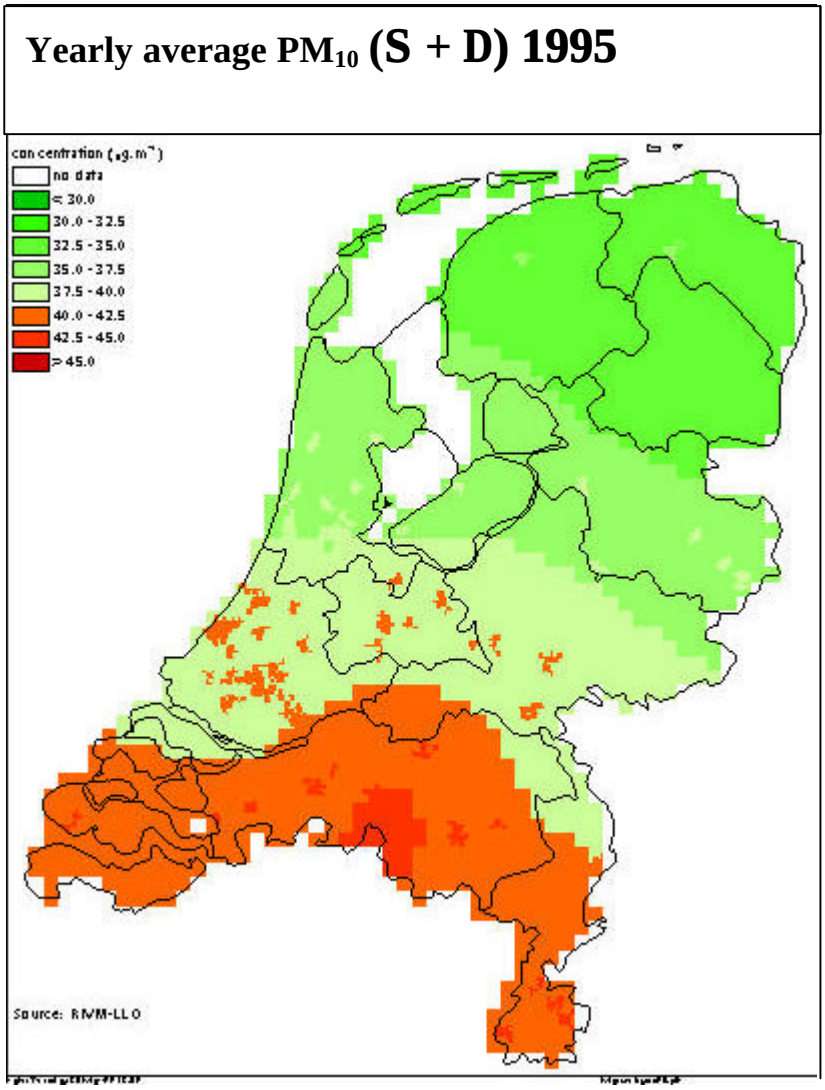


*Figure 2: Concentration field based on model calculation (S) and assessment of the discrepancy between model and measurements (D). At major urban locations a 5% increase is assumed.*

It is expected that the discrepancy will be reduced by information both on the modelling (emissions and PSD) and the quality of the measurements obtained from ongoing or planned research (see later).

### 3.1.2 Occurrence and behaviour – phenomenology of $PM_{10}$

As part of the additional actions a project was defined to describe the phenomenology of PM based on the observations of the National Air Quality Monitoring network. The project commenced May 1999 and will be concluded in February 2000. The scope of the project is to analyse the data of the single stations and regionally. The objective is to identify the relevant phenomena emerging from these descriptions. Additionally a number of special cases are analysed in more depth including other measured air pollutants.

The database consists of hourly averaged $PM_{10}$ concentrations measured since 1992/1993 at 19 monitoring stations located at various types of sites throughout the country. Although the geographical coverage of the stations is limited the information embedded in the database was thought to be useful in improving the understanding of the various relevant aspects.

### 3.1.3 Quality of measurements

Studies conducted in the early nineties showed that automatically operating PM monitors systematically underestimated the occurring PM levels when compared with reference methods. Initially this was corrected for by a factor (for the Netherlands a factor of 1.33 was used). Recent studies conducted in the Netherlands and elsewhere showed that the deficit of collection efficiency might not (mainly) be caused by the size selective head but the effect of losses of specific components of PM, mainly ammonium nitrate and organic aerosol. As the composition of PM will differ with respect to these specific components in time and space, a season and site dependent correction factor might have to be applied. The relevance of this is made clear by the notion that overestimating the correction factor in rural areas and underestimating it urban areas will reduce the discrepancy between measurements and model calculations in rural areas and increase it in urban areas.

Moisture plays an important role in the measurement of PM. Firstly, at high relative humidity particles will grow due to adsorption of water and might even grow beyond sizes excluded by the size selective inlet device. Secondly, as moisture is potentially only partly removed by the heating of the inlet (which is also the cause of the losses of ammonium nitrate and organic aerosol) its mass will be detected by the monitor and counted as PM mass.

To evaluate the impact of the above mentioned processes on the quality of the National Air Quality Monitoring network measurements a project was defined – *Quality of measurements, (in Dutch: Kwaliteit Stofmetingen)*- aiming at the underpinning of the correction factor. In a number of laboratory experiments and experiments at two sites (one rural and one urban influenced by traffic) the discrepancy between the National Air Quality Monitoring network monitor and others (including a reference method) was investigated. The project was supported by Bureau Blauw and started in November 1998. The laboratory experiments and the field experiments at the rural site have been concluded. The measurements at the urban site will be concluded at the end of 1999.

The preliminary results indicate that moisture is adsorbed on the filter and on the collected material of the monitor proportional to the relative humidity even with a heated inlet (50$^{o}$C as well as 80 $^{o}$C). Some of the moisture will be lost again at lower relative humidity, the impact of which depends on the change of the relative humidity during the integration period. Furthermore, losses of ammonium nitrate occur in the National Air Quality Monitoring network monitor under test conditions. The extent of underestimating of ammonium nitrate under field conditions cannot yet be assessed. No losses of ammonium sulphate were found in the National Air Quality Monitoring network monitor even when the inlet was heated to 80 $^{o}$C. For the losses of semi-volatile organic material no data is yet available. Comparison of mass data collected in the *Origin of Particulate Matter, (in Dutch: BronStof* project suggest that the part of the semi-volatile material (including the organic fraction) lost in automatically operating systems might be substantial. Relevant to the interpretation of these results is the difference of the monitoring systems used in the ‘Origin of Particulate Matter’ project (mainly TEOMs) and in the National Air Quality Monitoring network (FAG-β-dust).

At the end of 1998 the directive EN 12341 for the $PM_{10}$ reference method was published by CEN under mandate of the DG XI as part of the Daughter Directive. One of the proposed reference methods is used in the project described above.

Furthermore, research is started to formulate a $PM_{2.5}$ reference method to be completed in 2003/2004. The research takes in to account the above mentioned artefacts and is conducted in a number of Member states at various types of sites (Berlin, London (Atlantic urban) and Vienna (continental urban); Stockholm (Nordic suburban); Vredepeel (Rural – ammonium impacted); Rome, Madrid and Athens (Mediterranean urban).

The information and insights obtained in the Dutch project as well as preliminary results of the various European initiatives will enable an extended founded description of the PM levels by mid 2000.

### 3.1.4 Origin of Particulate Matter

The scope of the project was to measure and speciate PM during one year at four locations,

Figure 3 gives the composition of $PM_{2.5}$.

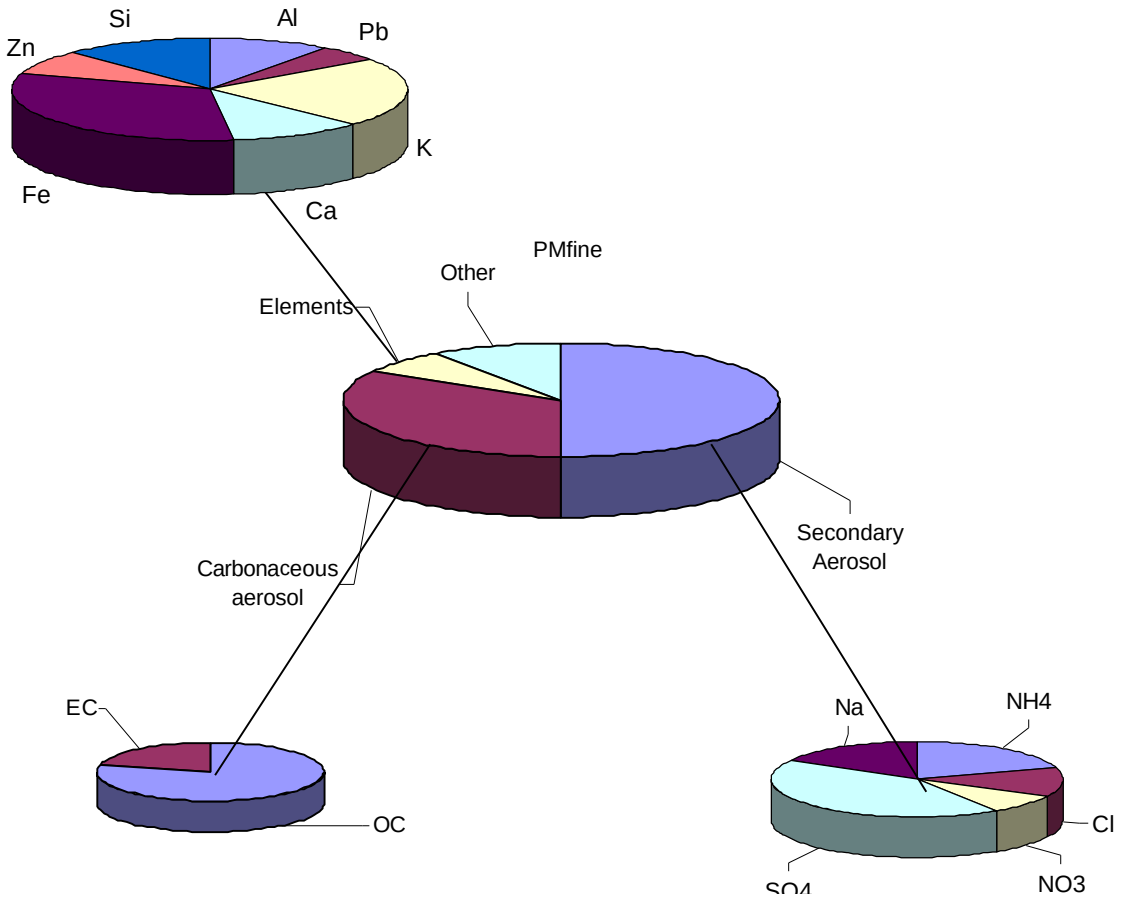


*Figure 3: Composition of $PM_{2.5}$ at an urban site (based on a limited data set – winter 1998-1999)*

different in assumed impact of sources and characterised as street, suburban and regional background (either agricultural or marine impacted).

These four locations were extended with another suburban and industrial site financed and operated by DCMR and the Province of Gelderland. The field operation is carried out OMEGAM, Amsterdam, supported by several analytical laboratories (RIVM-LAC, RIVM-LOC, SunSet Laboratories and Mitac UIA). The project started in august 1998, the field measurements and sample analyses will be completed in February 2000. The evaluation is planned to be completed and reported in June 2000.

The first preliminary results, based on measurement mainly during the winter period, show that the continuous automatic measurements of the PM mass are lower than the integrated mass collected on filters and that this discrepancy varies with the site. This outcome underlines the importance of the evaluation of the monitoring method used in the National Air Quality Monitoring network. A further result is the high contribution of the fine mode ($PM_{2.5}$) in the $PM_{10}$ mass – 0.8 to 0.9 measured with the filter method. Until now the average ratio was assumed to be 0.5 to 0.6, Van Putten et al., (1998). The discrepancy between both methods (filter and automatic) is in agreement with the high $PM_{2.5}$/ $PM_{10}$ ratio assuming that the losses occur preferably in the fine mode, of which ammonium nitrate and organic aerosol (OC) are the main constituents.

The overall average composition is made up of inorganic secondary aerosol (40%), carbonaceous aerosol - elemental and organic carbon – (25%), sea salt aerosol (30%) and remaining, including soil particles and elements from various sources (5%). For traffic and/or industrial laden sites the contribution of carbonaceous aerosol is higher. A slight west-east gradient exists for sea salt aerosol (negative gradient) and secondary aerosol (positive gradient).

The results from the projects on the “Quality of Measurements” and “Origin of Particulate Matter” are relevant to the discussion on selection of $PM_{2.5}$ and $PM_{10}$ standards. The preliminary results indicate at a relatively high loss of the constituents of $PM_{2.5}$ compared to $PM_{10}$ resulting in a higher ratio of $PM_{2.5}/PM_{10}$ of the real concentrations than used until now at urban and industrial sites and a lower ratio at rural stations. This implies that the $PM_{2.5}$ levels could be underestimated and that the PM problem is mainly a $PM_{2.5}$ issue. It is stressed here again that the results are just preliminary and that further evaluation of the results is mandatory to confirm this finding.

Based on the complete data set (one year of samples) a more detailed description of the composition of PM will be given and the concentrations will be apportioned to the relevant sources. Comparing these results with model calculations of the concentration contributions will give the answers for the objectives of the project.

## 3.2 Additional PM research

### 3.2.1 Reported research

In addition to the projects done at RIVM and due to the tight time schedule a number of identified blank spaces is filled in by other reserch institutes. These projects, that the ministry of VROM has commissioned, are jointly coordinated by RIVM and VROM. Two studies

were completed in 1999 that address the PM emissions of source categories that are considered to be highly uncertain. These include:

- Emissions of the category handling, services and storage (Dutch code HDO) was the subject of a study using existing data to arrive at improved emission factors. (Vrins, 1999). Based on four different approaches it concluded that the total emission of handing and storage as part of the category HDO is 2.3 kton (current value 1.0 kton). Vrins (1999) presents a range of 1.5 to 3.1 kton for this emission category. Based on Bloemen et al, (1997) such an emission will lead to a negligible increase in the yearly average $PM_{10}$ levels in the rural areas of the Netherlands (approximately 0.1 $\mu g/m^3$). However the local influence in the Rijnmond area of the HDO emissions will be larger. Based on Bloemen et al., (1997) a increase in yearly average concentrations of 6 $\mu g/m^3$ can be estimated for Rijnmond by HDO, if these emissions of Vrins (1999) would have been included in the current emissions inventory in the Netherlands.
- The agricultural emissions other than stable emissions and combustion emissions were investigated in a literature study (Chardon, 1999). It was concluded that agricultural emissions in the Netherlands are approximately 8 kton per year, with a range from 3.7 to 12.5 kton per year. Based on Bloemen et al., (1997) such an emission would increase the yearly average $PM_{10}$ concentrations in rural areas with approximately 1 $\mu g/m^3$, if these emissions of Chardon (1999) would have been included in the current emissions inventory.

Emission inventories for the Netherlands and in particular the European countries (as compiled in the TNO database) used in the first integrated assessment of particulate matter in the Netherlands (Bloemen et al, 1998) has attracted the interest of European assessment groups. The data set originally compiled for this programme, is now used in a number of assessments. It is acknowledged that a number of improvements are needed and feasible. In a recent EMEP/WMO workshop (Emissions, Sources and Models, Interlaken, Switzerland 1999) proposals were discussed to incorporate this initiative in the EMEP work program using all available data and knowledge in the member states. The timetable of this initiative acknowledges the need for a complete (interim) result by mid 2001.

### 3.2.2 Ongoing additional research

In addition to the recently concluded and reported additional research a number of activities were initiated to fill in other remaining blank spaces. These include:

- Wind driven dust: Occasionally extremely high $PM_{10}$ concentrations are measured, which coincides with high wind speeds and dry atmospheric conditions. During less extreme conditions a contribution of this natural phenomenon can be expected as well. As wind driven dust is not included in the model calculations this is a component of the discrepancy between the measurements and the model calculations. To assess the relevance of this contribution a short study is initiated (to be carried out by Vrins Luchtonderzoek) using a wide range of measurements and specific statistical analyses. Results will become available by early 2000.
- Traffic driven dust. Emission of $PM_{10}$ generated by the turbulence of traffic, and not by road or tire wear, is not included in the emission factors used for emission estimates. Recent studies in the Netherlands and elsewhere indicate that the emission of (road-) dust by the motion of (mainly heavy) traffic might be largely underestimated. To assess the

impact of this phenomenon a short study is initiated (to be carried out by TNO-MEP) aiming at quantitative estimates in time (season) and space (nature of the location)

- Secondary organic aerosol (SOA). The formation of particles through atmospheric reactions form organic precursors (both antropogenic and biogenic) is only partially understood. SOA is not included in the models applied for the PM assessments and consequently might contribute to the discrepancy. Simple measurements of organic aerosol do not easily reveal the origin as either primary or secondary and hence both measurement and process information needs to be applied to estimate the maximum concentration of SOA in the Netherlands. To this end a literature study is initiated (carried out by ECN) of which the results will become available early 2000.
- Northern Hemisphere background PM. The background level at the Northern Hemisphere is to be considered as the level caused by emissions beyond the model area used for the calculation of concentrations in the Netherlands. Although it is not expected to be high it is uncertainty-ridden. In another short study the range is to be estimated based on measurements and model calculations published in the literature. This study (conducted by ECN) will be concluded by early 2000.
- Dispersion of fine particles. The comparison of the dispersion and measurement of fine soot particles emitted by traffic show discrepancies that need to be resolved to enable estimating the exposure of these particles near roads with heavy traffic. Both the physical and chemical reactions just after the particles leave the exhaust and the linearity of the measurements are subjected to debate. To clarify the existing uncertainties a short study is initiated (carried out by ECN) to be concluded by early 2000.
- Diffusive emissions from Industrial sources. Kimmel et al., (2000) from Haskoning in Nijmegen are currently working on a project to make a very first estimate of the diffusive PM emissions from workplaces in industrial complexes. The project will be completed in the beginning of 2000. Some preliminary results indicate that in the Netherlands, due to the high level of abatement of air pollution from regular sources, these diffusive emissions are by no means negligible, and probably amount to about one third to half of the regular industrial PM emissions.

## 3.3 Future activities

The information on the ongoing activities at RIVM and at a number of other Dutch research institutes will lead to a more complete mass balance of $PM_{10}$ and $PM_{2.5}$ in the Netherlands. With this information indications can be given on the chemical composition and sources of $PM_{10}$ or fractions of PM in the Netherlands. A number of other issues still remain open though. These issues are all connected with the process of QRA. In order to arrive at a risk assessment at the end of the programme in 2001 they will therefore be addressed in future activities. They cover the particle size distribution, which is essential in establishing the dispersion and half-life of PM. The carbonaceous content may be very health relevant, as it seems to be tied up with traffic emissions. Due to the current low ambient concentrations of secondary aerosol the modelled concentrations of $PM_{sec}$ start to diverge from the measured concentrations, because the conversion process now becomes non-linear. Originally this process was satisfactorily included linearly in the models. Due to the success of the abatement policies this simplification now presents some problems. As $PM_{sec}$ is an important part of $PM_{10}$ adequate modelling of this fraction seems essential. For the future EU 24-h PM standard adequate deterministic modelling tools are essential to evaluate the influence of planned policy measures on the meeting of those limit values. And last but not least an evaluation of the influence of the whole package of modelling on the results that are used for

QRA seems an essential step in the process. At this moment a number of questions are still open. The questions that will be addressed by the various research initiatives are:

- The particle size distribution of PM emissions. As mentioned in the paragraph on Sigma PSD are relevant for a proper dispersion modelling. The currently used PSD is based on dated measurements at a rather limited number of source categories. It is anticipated that this is a potential source for the discrepancy. Data on the PSD of emissions are scarce and prone to a number of artefacts during measurement. A review of the available data (some databases on physical and chemical composition of individual processes exist) and judgement of some emission experts might improve the currently used distributions substantially.
- The current modelling of secondary aerosol. The original relations that used to exist between levels of the precursor gases and secondary aerosol nowadays seem to have changed because of the lower concentrations and the non-linearity of the process of conversion of precusor gasses into PM. This is an issue that most probably will have to be looked into.
- The carbonaceous aerosol content of emissions. As carbonaceous aerosol ($PM_{carb}$: elemental and organic carbon) – one of the pentagon parameters - gain more attention a proper estimate of the carbon content of emissions is considered increasingly more relevant both from a health perspective as well as from a model/emission validation perspective. Measuring $PM_{carb}$ is currently part of the projects on the “Quality of Measurements” and “Origin of Particulate Matter” and a desk study has been started to assess the levels of secondary organic aerosol. A missing link is still the flux of carbonaceous aerosol emitted. This information could be obtained through an approach similar to the one used for the PSD data.
- The short-term assessment of PM levels. To enable the deterministic assessment of health risks associated with episodical air pollution and the impact of short-term abatement measures a deterministic short-term dispersion model, seasonal and diurnal flux profiles of emissions are required. The EUROS-PM model development is in progress but it is not yet clear whether it can be applied in 2000. The information on seasonal and diurnal flux profiles for the major emissions is still rather poor and needs substantial improvement.
- Propagation of uncertainties in emissions. The uncertainty of the emissions is in itself not relevant; the corresponding uncertainty in the concentration contribution of the source categories is though. A rough indication of the (quantified) quality of the source emissions (as part of the TNO-database) exists. This could be used, applying the Sigma approach, to assess the overall uncertainty in the calculated concentration fields and will shed light on the significance of the remaining discrepancy between measurements and model calculation.

# 4. Exposure and dosimetry

## 4.1 PM Exposure distribution in the Dutch population

In the epidemiological literature health effects associated with $PM_{10}$ have been found with air quality data based on ambient concentrations measured at a central site monitor. However, people spend most of their time (about 80-90%) indoors. To take indoor exposure to air pollution into account micro-environmental models can be used. There are two micro-environmental models available at the RIVM: EXPOLIS (Jantunen et al., 1999) and Airpex (Freijer et al., 1998). These models use the paradigm that the exposure of people is determined by where people spend their time (so called 'micro-environments'), and the concentration of air pollutants in the different micro-environments. They therefore give a more accurate estimate of personal exposure, not only from ambient air, but also because it is possible to take indoor sources into account. With these models it is possible to calculate total exposure in different subgroups (e.g. smokers versus non-smokers, different age groups) and different micro-environments (e.g. indoor, outdoor, traffic). They can therefore be used for the evaluation of policy scenarios, for example the effect of a ban on smoking in public buildings or of traffic emission regulations.
Using EXPOLIS, a population exposure distribution of $PM_{10}$ for the Dutch population is determined for the Dutch Ministry of Health, Welfare and Sport (SPARC-project, V/263610). Most input data for this study are based on the Dutch situation. The results and methods this study will be described in the RIVM report 'Verdeling van blootstelling aan fijn stof in de Nederlandse bevolking' (Kruize, H. et al., forthcoming).

## 4.2 Doses in airways and lungs

The biological effects of ambient $PM_{10}$ particles may be dependent of their dose to critical target sites and organs. Estimating or measuring this (deposited) dose of particles is called dosimetry and it forms the link between the external exposure concentration (mostly mass) and health effects. Health effects of $PM_{10}$ and its constituting fraction in the airways and lungs may depend on a specific dose metric, usually expressed as particle mass, particle number, or surface area and reactivity. It is important to estimate particle dose and dose metric and its relationship to health effects for at least three reasons. One is that inhalation of ambient $PM_{10}$ fractions of different particle size and reactivity may result in different doses. Two is that different dose metrics, also with respect to time (peak dose, cumulative dose) may be important to specific health effects. And three is that deposition and dosimetry may be influenced by the disease state of airways and lungs because different tissue structure and geometry may influence air flow and deposition characteristics. When performed also in experimental animals exposed by inhalation to $PM_{10}$ and relevant fractions or components, dosimetry between experimental animals and humans may be compared and used for extrapolation purposes.

Dose assessment and dosimetry are essential in PM risk assessment, therefore it is important to know:

- What the deposited dose of the particles is,
- Which of the $PM_{10}$ fractions results in the highest deposited dose

- Which particle dose metrics has the closest link with health effects, and
- Whether certain human subpopulations may be more at risk partly because of an enhanced deposition and dose.

The framework of research at the RIVM is targeted to determine which $PM_{10}$ fractions and particle compositions are most likely responsible for health effects in human populations, and, which sources and emissions are contributing to these. Dosimetry studies have focused on the following specific important issues. The 'pentagon' approach for PM risk assessment including five main PM fractions was thereby taken as a basis.

The state of knowledge of available particle deposition models have been reviewed and reported recently (Freijer et al., 1997). This study resulted in some preliminary calculations and data with PM, e.g. with the frequently used human ICRP model. The study shows that the deposition of $PM_{coarse}$, $PM_{fine}$, and $PM_{ultrafine}$ is different in various airway and lung sections, The upper (extrathoracic) airways (mouth, nose, larynx), the tracheobronchial airways, and the alveolar region all receive different doses depending on the particle size. Remarkably, besides the fine and ultrafine fractions, also the coarse fraction of PM deposited to a substantial extent in both lower and upper airways. This indicates that from the perspective of deposition and dose, the coarse fractions might in principal play a role in causing adverse health effects. In addition, the study showed that in lower airways and lungs of COPD patients, an important risk group for $PM_{10}$ and $PM_{2.5}$, deposition of particles is greatly enhanced by a factor of approximately 3-5. On completing the study it was felt that none of these models could be used in the proposed risk assessment, because of a serious lack of more detailed and adequate lung morphology data and of an adequate description of air flow and particle deposition characteristics. In addition, none of these models was able to extrapolate between animals and humans.

Therefore, a collaborative project between the RIVM and the Chemical Industry Institute of Toxicology (CIIT) was set up, to complete state of the art particle deposition models in both animals and humans and to develop an user-friendly computer software program for application of these models in risk assessment studies. The MPPDep (Multiple Pathway Particle Deposition) model for airway particle deposition was developed and reported (Subramanian et al., 1999; Freijer et al., 1999; Cassee et al., 1999a). The model can be used to investigate the differences in doses and deposition between humans and experimental animals for extrapolation purposes and risk assessment. Also, the effect of the breathing pattern on the deposition of particles (resting versus exercise, old versus young, healthy versus diseased) or the impact of the size (distribution) of particulate matter on the deposited dose (rate) can be mapped. The model also shows that despite an overall low deposited dose in the lower respiratory tract (~lungs), a relatively high dose can be achieved for individual lung lobes.

An outline of the model is described in report RIVM 650010-018 (Cassee et al., 1999a) and the software is available on a CD-ROM (Freijer et al., 1999). The current software programme is only able to predict the initial deposited dose of particles in the lung. While this is the first critical step in dosimetry modeling of particulate matter, establishing PM dose-effect relationships for any human exposure scenarios lasting longer than 24 hours, requires an adequate calculation of dose over time. In order to do so, the MPPDepV1.1 model must be extended to include the influence of particle clearance and retention as well as the influence of particle hygroscopicity.

Current particle deposition models use airway and lung geometry data of a healthy, normal adult. However, COPD patients have about three fourths of the inhaled air going over only about one fourth of their lung surface. Thus, even greater differences in lobar-specific deposition of particles can be expected to occur in individuals with COPD. This means that the kind of multiple path approach to particulate deposition used in the current project for the animal model the rat needs to be extended to multiple path human data.

Previously reported RIVM and TNO studies (Cassee et al., 1999 a-d; Arts et al., 1997, 1998, 1999a, b) using different particle sizes (~0.03 – 1.5 µm CMD) of model PM constituents for the carbonaceous fraction (carbon) and the secondary fraction (ferrosulfate, (bi)sulfate, nitrate) of PM have indicated that these aerosols have a relatively low toxic potency in rats. To study the role of the size of a particle in the toxicity of inhaled PM, studies with the highly toxic chemical cadmium chloride ($CdCl_2$) were conducted. Subsequently the MPPDep model was applied to explain the differences in toxicity in rats that have been exposed to cadmium chloride aerosols at equal mass concentrations but with differences in particle diameter. The preliminary results of these studies show that particle diameter is an important determinant of the toxicity of this type of aerosol. However, adjustments for particle deposition efficiency alone do not fully explain the obeserved differences in toxicity indicating that some other dose metric of the particle may also be important. The preliminary results of these studies have been presented at the 7$^{th}$ Particle Toxicology Symposium (October 13-15, 1999, Maastricht) and will be reported after the inclusion of the data of an additional study to be performed by TNO in 1999.

Unlike $PM_{10}$, the choice for $PM_{2.5}$ as a form of a standard has not been primarily dictated by dosimetric considerations. Deposition models predict that particle deposition in airways and lungs depends to a large extent on the particle size. Figure 4 shows that two deposition modes can be distinguished around a cut point of about 0.8 µm. The larger fraction between 0.8 and 10 µm is very efficiently captured in the upper airways. However, still a significant portion of this fraction will also be deposited in the lower airways and lungs (depending on breathing parameters and particle characteristics). The finer particle fraction (0.1 and 0.8 µm), with a low overall deposition rate, is almost exclusively deposited in the lower airways and gas exchange regions. These data suggest that, from a deposition point of view, both larger and smaller particles may play a role in lower airway effects, and that larger particles may also contribute to upper airway effects. In contrasts with other views frequently presented, coarse particles may thereby still serve as important candidates for part of the health effects occurring in upper airways, lower airways and lungs. It is not known yet which type of PM-associated health effects may be linked with this, but part of the asthma and infection responses might be a possibility. Broncho-constriction is a clear symptom in people with COPD, including asthma. As shown in Figure 5, the tracheobronchial airways are also target for PM deposition of particles > 0.8 µm.

The Chemical Substances Treshold Limit Values Committee of the American Conference of Govermental Industrial Hygienists (ACGIH, 1996) and the Organization for Standardization/European Standardization Committee (ISO/CEN) use a medain cut point of 10 µm aerodynamic diameter for thoracic (lung airways plus gas-exchange region) and 4 µm for respirable (gas-exchange region) particulate mass. If the potential health effects are predominantly caused by fine PM, as some tend to believe, biologically speaking one would expect a $PM_4$ rather than a $PM_{2.5}$ standard. With such a standard the potential hazard of suspensions of solid particles and droplets in this region of the lungs would be more taken into account than with a cut point of 2.5 µm.

These considerations are the one of reasons why RIVM research activities are not solely focussed on particles with an aerodynamic diameter less than 2.5 µm, but are also directed to the coarse fraction between 2.5 and 10 µm. Apart from these dosimetry predictions, recent data from a small number of epidemiological studies indicate that, apart from the fine PM fraction, health effects are also associated the coarse PM fraction and sometimes even to a larger extent (Loomis et al.,1999b).

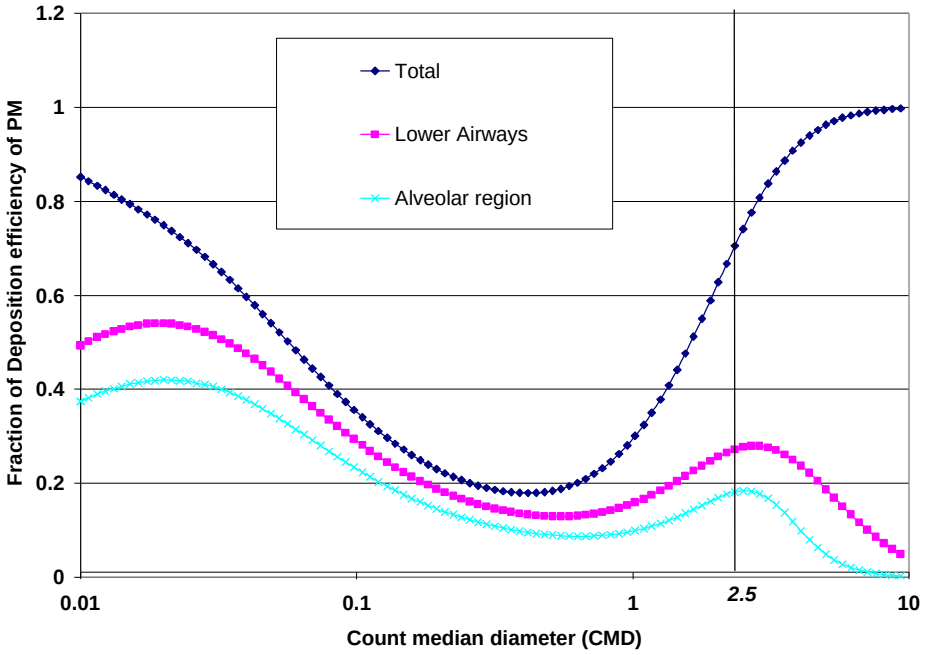


*Figure 4. The relationship between particle diameter and human airway PM deposition efficiency based on the application of MPPDepV1.1 using the defaults: breathing frequency = 12; tidal volume = 625 ml, nasal breather). The studies upon which these calculations are based, are presented in the RIVM reports 650010 018 and 650010 019.*

## 4.3 Future activities

For the calculation of the exposure of various subpopulations in the Netherlands to $PM_{10}$ the existing modelling tools will be kept up to date and operational. With a better description of the process of deposition and the calculation of dose a link will be possible between the experimental animal inhalation toxicology work and the risk assessment for the human population. Two main avenues of future activities can be discerned:

- Future activities on deposition and dosimetry modelling of PM will focus on the completion of the model with the clearance, retention and particle hygroscopicity modules and on inclusion of the multiple path morphology of the human airways and lungs (like it is now present for the rat). The MPPDep model will be used to interpret the animal toxicity data with respect to the role of particle size and deposition, and to better design animal toxicity studies. Whether or not marked adverse effects will be observed,

the results of inhalation studies in experimental animal will be used for risk assessment for ambient PM.

- Deposition and dosimetry modelling will thereby provide important data to help to understand which particle fraction is more important than others are and what the effect-relevant dose is under specific, ambient PM exposure conditions. In addition, the model will be used to predict the deposition and dose in humans when exposed to known, typically occurring ambient PM size distributions, also in susceptible human subpopulations. Furthermore dosimetry could even be used in the future to extrapolate negative results from animal models to a comparable dose in humans.

# 5. Critical $PM_{10}$ fractions

## 5.1 Toxicity and possible mechanisms

Epidemiology data on health effects associated with PM seem to be rather consistent. Whether or not these associations have to be considered as causal and which of possible PM size fractions ($PM_{10}$, $PM_{2.5}$, $PM_{ultrafine}$) and chemical or biological components ($PM_{sec}$ or $PM_{carb}$) as well as their respective emission sources are responsible for health effects, is unclear and subject of intense dispute. The biological hypotheses for mechanisms underlying these adverse health effects are just beginning to develop.

One of the first major tasks in PM toxicity evaluations at the RIVM was to prepare a state of the art report on current views on responsible PM fractions and possible mechanisms explaining health effects in risk groups. This extensive overview is provided in RIVM report 650010 015 (Van Bree and Cassee, 1999).

The report indicates that at this moment only a limited number of toxicity studies on respiratory and cardiac effects following exposure to sampled or concentrated ambient PM fractions (coarse, fine, or ultrafine) have been conducted and reported. These studies, performed in healthy human volunteers or laboratory animals (both healthy and diseased)), have not yet resulted in sufficient evidence to conclude that ambient PM levels may play a causal and biologically plausible role in PM-associated adverse effects. Specific conclusions from this report on the toxicological evidence for various PM fractions and components and on plausible mechanisms are as follows:
Current toxicity data from inhalation studies do not yet strongly favour a particular PM size fraction or chemical composition explaining PM-associated health effects. This is in general also corroborated by epidemiological studies.
Particles of different sizes might be preferentially involved in different health effects because of their size-dependent deposition in airways and lungs. Although the available information is very limited and the precise role of various PM fractions is unclear, it might be suggested that e.g. aggravation of asthma and upper respiratory illness are associated with deposition of $PM_{coarse}$ in tracheobronchial and upper airway regions and lower airway illness are more related to $PM_{fine}$.
People with compromised airways (asthma, COPD) seem to receive a considerable higher local dose of PM (depending on the applied dosemetrics).
A limited number of mechanistic studies (*in vivo* and *in vitro*) using much higher PM exposures than ambient air concentrations show that TSP, $PM_{10}$, $PM_{coarse}$, and $PM_{2.5}$ are able to induce acute injury to the pulmonary and cardiovascular system and related adverse effects (Godleski *et al*, 1996, 1997; Gordon *et al.*, 1998a-c, Costa *et al. 1997;* Pritchard *et al*., 1996; Dreher *et al*., 1996, 1997; Killingsworth *et al.* 1997). Hereby, toxicity does not seem not correlate with the PM mass concentration but with the PM content of soluble, transition metals (ROFA) and maybe also with organic constituents (endotoxins (LPS), PAHs). This suggests an important role for anthropogenic (combustion), carbonaceous mode of ambient PM and for chemical composition and surface area reactivity. These studies also suggest that fine mode particles might be more relevant than the generic, physical nature of ultrafine particles or the non-soluble components of coarse particles. However, none of these studies used inhalation exposures and near ambient air concentrations. The human relevance of the

results of *in vitro* systems always is difficult to interpret. Especially as no causal fractions have been clearly identified yet, caution is to be used with this extrapolation.
The toxicological evidence for adverse health effects caused by traffic-derived PM from acute studies is still only marginal, although recent short-term inhalation studies with diluted diesel exhaust in healthy humans show respiratory and even systemic effects at relatively low exposure levels (~100-300 $\mu g/m^3$) (Salvi et al. 1999a; Blomberg et al. 1998a). Diesel exhaust is also able to augment the response to antigens, suggesting a mechanism for the exacerbation of asthma. (Frew and Salvi, 1997 and Salvi et al., 1999b). The term diesel exhaust is used here deliberately as it is not yet clear whether it are the gases or PM, or both, which deserve the blame. Remarkably, the use of a ceramic particle trap, at the end of a diesel engine tail pipe, did not (completely) abolish the effects induced by diesel exhaust compared to unfiltered diesel exhaust, although the number of particles was reduced by the trap by ~50%. The data suggest that the gaseous part of the diesel exhaust mixture may also play a role in health effects (Rudell et al. 1999).
The few toxicity studies performed with ultrafine (carbon) particles have not yet revealed an important role for this PM fraction. Many studies were done with mass concentration much higher than ambient air levels and sometimes also with environmentally non-relevant particles (Arts et al., 1999a, b; Roth et al., 1998; Ziesanis et al., 1998; Oberdörster et al., 1995; Adamson and Prieditis, 1995; Donaldson et al., 1998; MacNee et al., 1997; Stone et al., 1998). Although in a number of these studies the size of the primary particles in the starting material was smaller than 0.1 μm, the aerodynamic diameters of the actual animal exposures problably have been larger because of aggregation of particles. The experimental design of these studies was such that even when ultra fine particles were used as a starting material, the created exposures could have been fine instead of ultra fine, Arts et al., (1999b) Therefore, the interpretation of these studies may be more complex than suggested by the original authors.
A few animal toxicity studies have shown significant positive interactions between PM (urban PM, sulfate aerosol, ultrafine carbon) and gaseous pollutants like $O_3$ in inducing pulmonary toxicity and inflammation. This suggests that the mixture of air pollution (and oxidants) may be more important than PM alone (Bolarin et al., 1997; Churg et al., 1996; Kleinman et al., 1996; Last et al, 1987). The levels of ozone exposure during these animal toxicity studies have been considerably higher than those normally encountered in the ambient atmosphere in the Netherlands. As to date there is no clear evidence form epidemiologiocal studies to support the interaction between PM and gases. Hoek and Brunekreef (1999) reported that they did not find an interaction effect between ozone and $PM_{10}$ in the Netherlands during summer, when PM associated health risks are higher.
Based on their cardiopulmonary toxic potency and the stimulation of inflammatory processes, the data from toxicological studies suggest that the primary (carbonaceous) combustion-related fractions of $PM_{10}$ and $PM_{2.5}$ may be more relevant compared to the secondary fractions for adverse human health effects in airways, lungs, and the heart Godleski et al., 1996, 1997; Gordon et al., 1998a,b; Watkinson et al., 1998; Killingsworth et al., 1997). Due to the high mutual correlation of air pollution the secondary PM components like acids, sulphates and nitrates might still serve as a proxy for the carbonaceous fraction of PM in epidemiological studies.
Data from limited PM mechanism studies have suggested various pathophysiological mechanisms like 1) inflammation, oxygen radical production, and immunotoxicity in airways, lungs, and heart, and 2) impairment of respiratory and cardiac neurological functions. Since these processes play an important role in various diseases related to $PM_{10}$-associated acute excess morbidity and (premature) mortality, an exacerbation mechanism of ambient PM for pulmonary and cardiovascular effects in susceptible human populations might be biologically plausible if substantiated in more studies. A current hypothesis on one

of the possible biological mechanisms underlying PM-associated health effects is presented in figure 5.

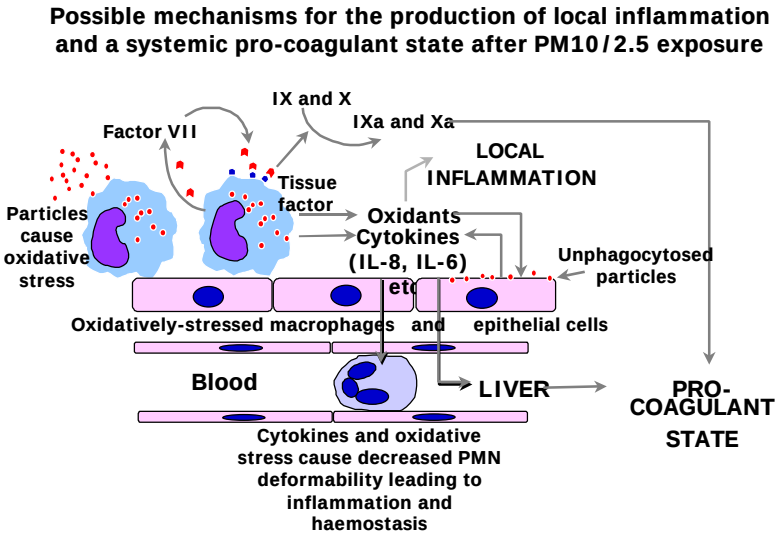


*Figure 5. Possible mechanisms for the production of local inflammation and a systemic pro-coagulant state after $PM_{10/2.5}$ exposure. Scheme was kindly supplied by Dr. Kenneth Donaldson, Napier University, Edinburgh.*

The general conclusion on the current lack of toxicological evidence for responsible PM fractions, composition, and mechanisms, is subjected to discussion in an international forum of toxicologists and epidemiologists. The report is being transformed into a manuscript for peer-reviewed publication in the international scientific literature. Other experts, also from the US EPA, will participate in this to increase its broad scientific support.

In considering the need for a fine particle standard, the US EPA concluded that from epidemiological and toxicological studies the weight of the available evidence suggests that ambient coarse particles are either less potent or a poorer surrogate for community effects of particulate air pollution than are fine particles (OAQPS Staff Paper 1996). The 1996 Staff Paper also states that “While it is difficult to distinguish the effects of fine or coarse particles from those of $PM_{10}$, consideration of comparisons between fine and coarse fraction particles suggests that fine particles are a better surrogate for those particle components linked to mortality and morbidity effects at levels below the current standards. Coarse fraction particles are most clearly linked with certain effects at levels above those allowed by the current standards. This latter situation is frequently met where the coarse fraction of particles are the dominant fraction of $PM_{10}$, like at high fugitive dust conditions.” To force a nation-wide air-monitoring programme and to deal with wind-blown dust locations, which are out of control, EPA decided to promulgate a fine particle standard in addition to the current $PM_{10}$ standard.

Different from the motivation for EU policy, which concentrates on health effects, the EPA used several arguments as a basis for its the decision and the choice for selecting a particle size cut point for fine particles ($PM_1$ or $PM_{2.5}$). They considered that, from a public health perspective, $PM_{2.5}$ is better than $PM_1$ to capture all of the potential agents and characteristics of concern like sulphates, acids, metals, organics, as well as particle surface area and particle number. In addition, $PM_{2.5}$ has been used in a number epidemiological studies as the exposure index, while no data exist on $PM_1$. Furthermore, EPA stated that there is a growing air monitoring data base on $PM_{2.5}$, based on the availability of measurement technology,

whereas data or techniques for $PM_1$ are only very limited. Moreover, with respect to sources, the EPA stated that in the $PM_{2.5}$ fraction the intrusion of soil-type, coarse mode derived particles is only 5-15%, maybe even smaller in urban areas. So, $PM_{2.5}$, instead of $PM_1$, contains almost the complete set of anthropogenic components. The EU policy is targeted to extend the $PM_{2.5}$ data base by additional research first and subsequently decide in 2003 whether there is an additional need for a fine particle standard, or that the fine fraction are sufficiently covered by a $PM_{10}$ standard in Europe.

## 5.2 Overview of toxicity study activities

Toxicity studies on ambient PM fractions were designed and performed to answer important questions in PM risk assessment and risk management:

Can ambient PM cause health effects and toxicity?
Are these effects mechanistically understandable at low PM levels?
Do effects depend on composition of specific PM fractions?
Do effects depend on specific pollution situations and typical PM mixtures and sources?

In accordance with the PM risk assessment Pentagon approach, toxicological studies focused therefore on the following aspects:

- Animal inhalation studies with (concentrated) ambient $PM_{fine}$, at discrete locations different in air pollution and source contributions.
- Intratracheal instillation studies with animals and *in vitro* studies with rat and human cells with PM fractions ($PM_{10}$, $PM_{2.5}$, $PM_{coarse}$, $PM_{fine}$ and $PM_{ultrafine}$) sampled from ambient air at distinct locations.
- Inhalation studies with primary and secondary PM constituents.
- Use of animal models in toxicity studies to mimic cardiorespiratory diseases in human subpopulations, which seem to be at higher risk for ambient PM.

RIVM has set up a PM toxicity program to address these issues as adequately as possible within the next few years, in which the following subprojects can be identified.

### 5.2.1 Ambient PM inhalation toxicity studies with the mobile AFPC

Ambient fine particle concentrators (AFPC) for conducting human and animal exposure studies have been developed by Harvard University, Boston (Sioutas et al., 1997). Such a concentrator increases particle concentration in the range 0.15-2.5 μm by a factor of approximately 20. This allows researchers to test the toxicological potential of ambient, real world PM in animal inhalation studies. Preliminary AFPC data reported so far show that concentrated $PM_{fine}$ causes substantial adverse health effects in animal models of human cardio-respiratory diseases (Godleski et al., 1996, 1997; Gordon et al., 1997). Would similar effects have occurred in (aged) humans, it would form a plausible explanation for the increased morbidity and mortality rates observed in epidemiological studies.

In January 1998 RIVM has installed an AFPC in a mobile laboratory, to be able to test the toxicological potential of ambient $PM_{fine}$ at various locations within the Netherlands. Pilot studies in experimental animals that mimic asthma or pulmonary hypertension and heart failure have been performed in 1998 on the premises of the RIVM in Bilthoven. These results have been reported in a letter to DGM in December 1998.

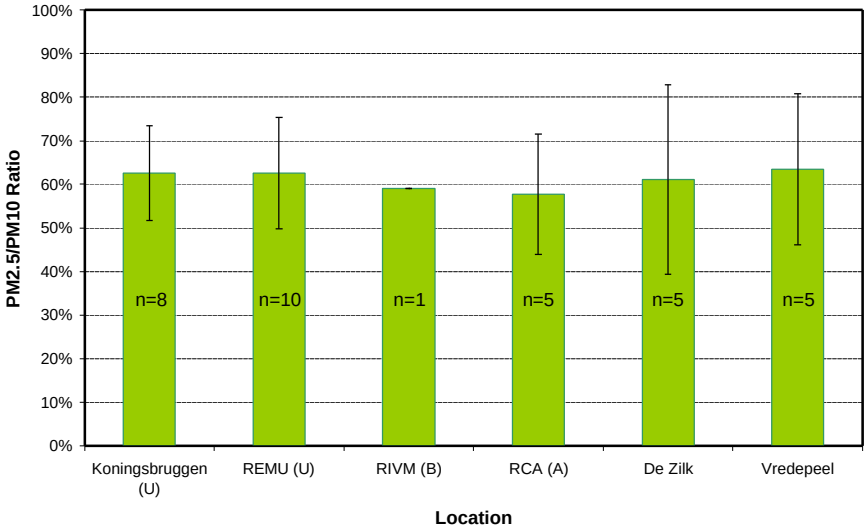


*Figure 6. The ratio of $PM_{2.5}$ and $PM_{10}$ for 5 location in the Netherlands. The number of measurements are indicated in each bar. U = Utrecht, B = Bilthoven; A = Amsterdam. De Zilk and Vredepeel are considered as rural areas.*

Early 1999, the mobile laboratory has been moved to an area in Utrecht that is dominated by heavy traffic on a busy highway (A1: Utrecht - Amsterdam) and industry. The studies comprised one to three day exposures (4-6 hr/day) to concentrated $PM_{fine}$ (CAPs) in healthy and compromised animals and were focused on acute effects. A total of 9 independent studies were performed (16 exposure days). Although mass concentrations up to 1 $mg/m^3$ were achieved, preliminary data revealed no evidence for marked or severe effects. The studies indicate that ambient $PM_{fine}$ can affect lung function and may result in inflammatory responses.

During September and October 1999, 8 additional studies were performed in non-compromised animals. In these studies concentrations up to 2 $mg/m^3$ CAPs were achieved. However, at the start of these studies the health status of the experimental animals obtained from a commercial breeder appeared to be such that these animals had to be categorised as ill in most cases. The Central Animal Laboratory of the RIVM is now performing additional analyses to look at possible interfering factors. When a clear view is provided on the health status of the animals, it will be decided whether or not the results of these studies can be used for identifying toxic effects of CAPs.

Although the conditions have been standardised as much as possible, other uncontrollable factors besides PM concentrations can greatly affect the outcome of the studies. For this reason, it is inevitable that such studies with ambient PM have to be repeated as much as possible within a short time frame. The test atmospheres have been characterised in detail during these exposures. Statistical meta-analysis of exposure parameters and with the health indicators should ultimately lead to answers to the question which PM characteristics (size,

mass, number, chemical composition) can be causally related and most strongly linked to human health effects.

### 5.2.2 Composition and toxicity of PM fractions sampled from ambient air

The current mobile AFPC only concentrates the PM fraction between 0.15-2.5 μm ($PM_{fine}$). Therefore comparisons between $PM_{2.5}$ and the coarse fraction ($PM_{coarse}$) cannot yet made. To partly overcome this disadvantage, RIVM started a large sampling campaign via the OMEGAM institute in Amsterdam collecting $PM_{10}$ and $PM_{2.5}$ fractions. This campaign completely matches the sites which are used in the project on the "Origin of Particulate Matter" in a way to link PM toxicity and composition to major sources. Because of a serious delay the campaign was finished just recently. Samples are now subjected to chemical analyses and used for toxicity screening.

RIVM has purchased a High-Volume Particle Sampler (HVPS, Sioutas *et al.*, 1997). This system segregates particles into three modes: coarse (10.0-2.5 μm), fine (2.5-0.1 μm) and ultrafine (less than 0.1 μm). The system does not heat or pretreat the PM. Collection of fine and coarse particles uses impaction substrates rather than filtering of PM. Losses of PM are therefore substantially lower compared to the more conventional filter systems. To gain knowledge on the physico-chemical composition of Dutch ambient PM, as well as to obtain PM samples that can be used to test their toxicological potency

PM fractions were collected by the HVPS in a field study at various locations dominated by different sources of emissions in a 3-month period. The first results of the physicochemical characterisation of these various PM fractions will be reported by the University of Southern California (Dr. C. Sioutas) at the end of this year. As shown in Figure 7, the study indicates that on average 60% of the $PM_{10}$ mass concentration consists of $PM_{2.5}$. This finding was observed for all 6 sites across the Netherlands, including urban, rural, traffic, and industrial zones. As has been indicated in chapter 3 on air quality the seemingly contradictory results of this study have to be studied ion more detail.

A selection of the fine and coarse fraction samples have been used to study their toxic potential in an *in vitro* system using freshly isolated macrophages This was done in a collaborative project with the University of California, Irvine (Dr. M.T. Kleinman) at the RIVM in August 1999. The first results, presented in figure 8, seem to indicate that the coarse fraction of $PM_{10}$ is more potent in inducing effects than the fine mode fraction. The results demonstrated that there were dose-dependent decreases in macrophage production of superoxide radicals as measured by the chemiluminescent method.

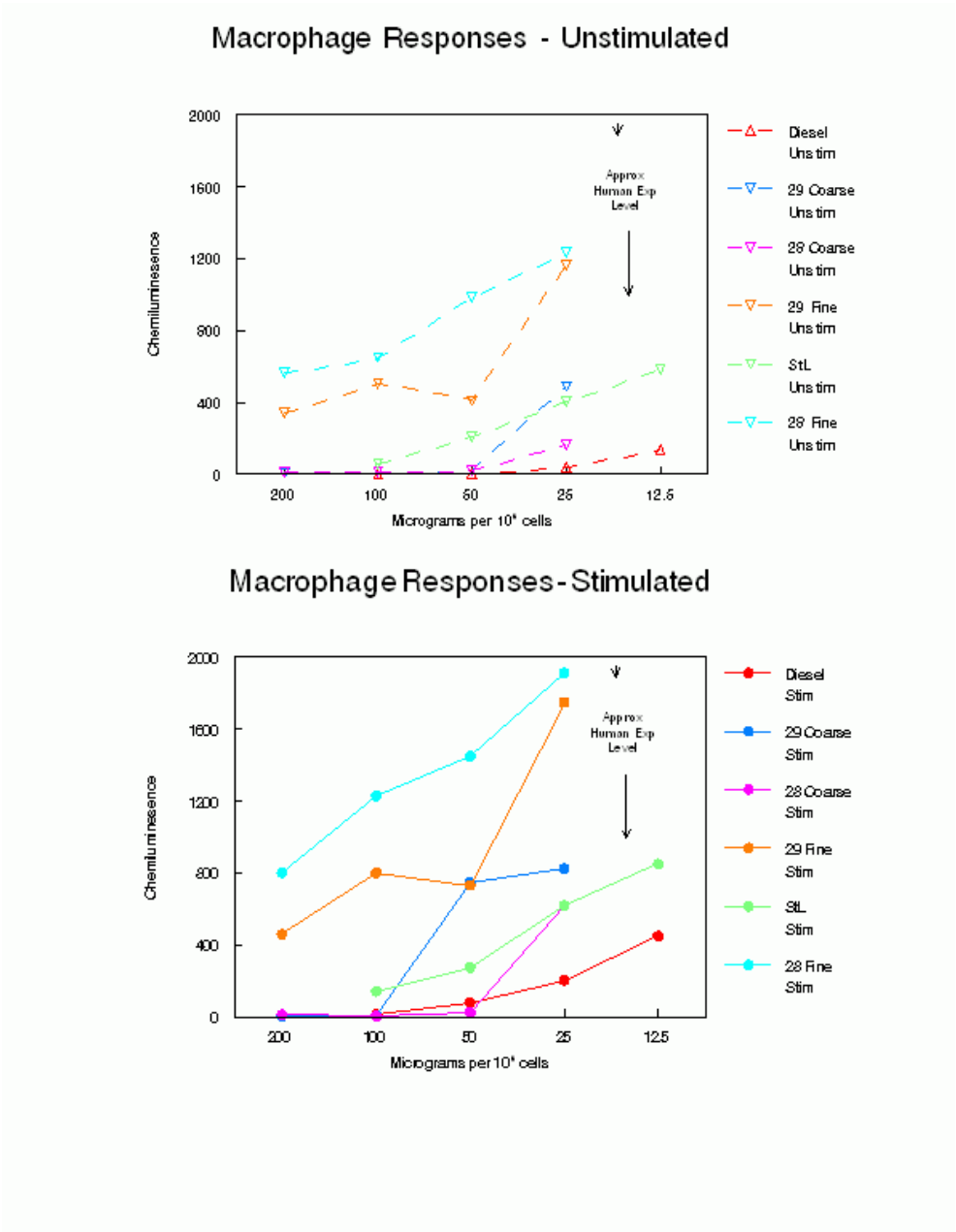


*Figure 7: Comparison on Respiratory Burst Activity in freshly isolated rat macrophages after 4 hr incubation with fine and coarse fraction particles collected in an industrial area in Utrecht, the Netherlands*

Coarse particles were more potent than fine particles in provoking macrophage responses, but both particle fractions showed dose-response relationships. There were no significant differences in the responses of the Wistar and young Fischer rats. Aged rats showed greater production of free radicals when stimulated with PMA. These data will be integrated with the results of the particle characterisation analyses and the data from other assays that are now in progress.

Although these findings have to be evaluated in relation to the composition, these results add to the data base on the coarse fraction of PM being also relevant to health effects. Results will be presented at the PM 2000 symposium in Charleston (USA) early 2000 (Cassee *et al.* 2000).

In October 1998 a project was started with the Leiden University Medical Centre (LUMC) to screen the toxicity of a large number of $PM_{10}$ and $PM_{2.5}$ samples in freshly isolated human airway cells and to link the observed toxic potency with PM composition. The specific investigations on collected PM samples were started during the summer of 1999 because of the delay in the OMEGAM sampling campaign. The preliminary results indicate (sampling) location specific effects and contain no consistent indications that $PM_{2.5}$ has a stronger toxicological potential compared to $PM_{10}$. Most samples induced a dose-dependent IL-8 induction (inflammatory mediator) and cytotoxicity (at higher doses). Cells were also primed with TNF-$\alpha$ or IL-4 to mimic asthmatic effects and only IL-4 pretreatment resulted in a shift of the dose-effect curve to the left. A full report on the results is expected in early 2000.

In September 1999, a project was started within the Research School of Environmental Chemistry and Toxicology in which the Wageningen University Research (WageningenUR) and RIVM collaborate. The aim of this projects is to critically evaluate indicators currently applied in toxicological studies on PM health effects and to identify new (more sensitive) biological markers for adverse health effects that can be applied in animal ánd human studies. A sideline of this project is the establishment of dose-time-effect relationships for selected health indicators.

### 5.2.3 Inhalation toxicity of primary and secondary PM components

To understand which PM constituents and size features are toxicologically important, inhalation studies were designed with model particulates representing primary (carbonaceous) and secondary (acid) aerosol components of ambient PM. Studies, performed in a collaboration between TNO and RIVM, were carried out by exposing healthy mice and rats as well as animal disease models (asthma, pulmonary hypertension, heart failure) to ultrafine (~30-50 nm) or fine (~300-500 nm) carbon black, ammonium (bi)sulfate, or ammonium nitrate, alone or in combination, in realistic mass and number concentrations. Collectively, the results revealed no evidence for marked or severe effects in the pulmonary or cardiac system. The results also suggest that, at environmentally relevant levels, primary and secondary PM model components like carbon black and ammonium nitrate exert only marginal inflammatory responses in the cardiorespiratory system in healthy or compromised mice and rats. Effects were only seen with the fine mode of the particles and not with the ultrafine mode. In contrast with other studies on ultrafines, exposure to ultrafines in our studies was maintained at conditions to avoid the formation of large aggregates. Results of these studies have recently been presented at the 3rd PM Colloquium at Durham and the 7th Particle Toxicology Symposium at Maastricht (Arts et al. 1999b) and manuscripts are in preparation for peer-reviewed publications.

## 5.3 Future activities

The future activities necessary for the discovery of the critical fraction of $PM_{10}$ will concentrate on those aspects that are essential for effective policy measures for air pollution abatement strategies. It will concentrate on questions as relative potency of different sources of air pollution (as traffic) and on the relative potency of different size classes of PM. Which is more potent from a toxicological point of view: is it $PM_{2.5}$ or $PM_{10}$? This means that research leading to more sensitive parameters, which are indicative for the epidemiological health effects, will be undertaken. The main effort though will lie with the experimental inhalation studies with concentrators for fine and coarse ambient PM. A number of replications is necessary to present results on which a sound policy may be built.

- Further use of the AFPC in $PM_{fine}$ inhalation studies at specific locations of interest in the Netherlands in close collaboration with US-researchers. Design and use of the AFPC in studies to investigate the co-pollutant effects of gases (ozone, $NO_2$ or CO).
- RIVM will also incorporate a coarse (2.5 - 10 µm) particle concentrator (ACPC) during 2000 to be able to compare the toxic potency between fine and coarse mode PM. The ultimate goal will be to perform human-clinical studies in collaboration with the LUMC, Department of Pulmonology. A feasibility study for this will take place early 2000.
- Toxicity analysis (*in vivo* and *in vitro*) of collected $PM_{10}$, $PM_{2.5}$, $PM_{coarse}$, $PM_{fine}$ and $PM_{ultrafine}$ samples to link toxicity with PM composition and sources.
- Continuation of the previously described collaboration between the Toxicology Department of the WageningenUR and RIVM facilitated by the Research School of Environmental Chemistry and Toxicology to study the dose-time-effect relationships of PM toxicity and to develop and apply novel or sensitive markers in PM effect research. A report on overall review of causality and plausibility of PM-associated health effects and possibly responsible fractions, components and sources is planned for the future.

# 6. Conclusions

## 6.1 Interim results

Concluding this interim report the five specific questions of the Ministry VROM concerning PM will be answered for as much as the current results permit.

1. How do the various indicators of PM compare as relevant for the causation of health effects?
2. What is the relationship between concentrations of ambient PM and health effects in order to make a substantiated choice for a PM standard?
3. What are the actual PM concentrations in the Netherlands and how big are the contributions of the different source categories to those concentrations?
4. Which indicator of PM is preferable, if next to health relevance also risk management considerations are taken into account?
5. What is the quantification of the total source risk chain now and in the foreseeable future?

Ad 1. The epidemiological and toxicological literature and the provisional results of the project do not yet allow a definitive answer to this question. All the five parameters ($PM_{10}$, $PM_{2.5}$, $PM_{0.1}$, $PM_{sec}$ and $PM_{carb}$) from the original “pentagon” still remain plausible candidates for the causation of health effects, which can all be substantiated from scientific literature. Apart from those five, also new candidates seem to emerge, as effects have recently been demonstrated in in-vitro laboratory test systems of collected PM. It is not only material from anthropogenic origin, for instance components from biological origin like LPS and pollen fragments also seem relevant from the toxicological point of view. Currently also a combination of PM with gases (CO, $NO_2$ etc) cannot be ruled out as causative. In the next few years these questions will be addressed in depth and the resulting relevant indicators for health effects will be reported.

Ad 2. As long as there are no new more definitive answers it is deemed to be too early to present information on which to make a substantiated choice for a different parameter for a PM standard than the currently used $PM_{10}$.

Ad 3. The research initiated in the past two years since the first assessment are focussed on better understanding of the occurrence and behaviour of PM and in particularly on the closure of the discrepancy between measurements and model calculations. The preliminary results of some of these research initiatives picture a rough, consistent set of arguments that reduce the uncertainties and might change the focus for abatement. As more results become available a more coherent assessment will emerge and enable estimating the impact of existing and proposed abatement measures compiled in different scenarios.

Ad 4. If the provisional results of the air quality measurements pointing to a more sizeable fraction of the $PM_{10}$ belonging to the fine PM ($PM_{2.5}/PM_{10}$ = 0.8-0.9 instead of 0.6) are substantiated by the rest of the data, important paradigm shifts will be necessary in the future. The relative importance of distant sources for the PM levels in the Netherlands is increased in such a situation and this implies that international agreements would become even more important for successful abatement policies to decrease health effects in the population. With the current level of uncertainty it is therefore not yet possible to indicate if a different indicator for PM is preferable.

Ad 5. The quantified risk of $PM_{10}$ for acute mortality is now approximately a factor of four lower than that in the previous interim document (Bloemen et al., 1998). The reason for this

difference is that it was now possible to use data from the Netherlands. Such a difference indicates that it is important to have figures which describe the local situation as closely as possible, instead of being forced to base risk estimates solely on foreign results, as was done in the previous risk estimation in 1998.

## 6.2 Future activities

In the paragraphs 2.4, 3.3, 4.3 and 5.3, concerning the various scientific fields of interest, the next steps to be taken on those topics have been presented. These steps of course will be fore filled vigorously and lead to more concrete results to be presented in the next report in 2001.

For the total project there are two essential elements that have not yet been mentioned previously. These are integration and internationalisation.

- Integration is essential in this complex field of permanently changing paradigms. All the research in this field has shown it to be complicated and most probably multi-causal. This means that on a permanent basis information and results of all the different research areas has to followed and integrated into an overall picture. This picture has to be studied meticulously and it has to coincide with the facts. Also it has to be born in mind that the project is not one for the sake of science but that it has to help policy makers in their job. For the total project the essential part is that the information concerning the different scientific specialities is integrated into one concept that allows policy makers to make substantiated choices for different policy options. Therefore it is essential to weigh the evidence from the various sides and present a well-balanced approach. The quality of an advice is not only dependent on the scientific content but also on the matter of acceptance of this advice.
- The second element that is essential in such a complex programme is internationalisation. The PM problem as such is trans-boundary in nature. It is too big to be solved by only one country and most probably also local influences might be important for the RM process. Therefore a close co-operation with neighbouring European countries will be envisaged in order to have our homework done for the evaluation of the European PM directive in 2003. Also co-operation with other researcher is actively sought after. For instance participation in a funded European project from the 5$^{th}$ EU Framework Programme, addressing the issue of the possible role of traffic emissions in PM health effects (a hybrid epidemiology-toxicology, multi-country design). *In vivo* toxicity studies with collected coarse, fine and ultra fine PM followed by an overall PM-toxicity-composition-traffic contrast analyses. This project will start early 2000, co-ordinated by Sweden. Another EU project, co-ordinated by Finland, will be submitted early 2000 aimed to improve the linking of urban air particle characteristics with short-term respiratory toxicity in Europe. In addition, a third project that focuses on the relationship between respiratory allergy and inflammation due to ambient PM (co-ordinated by Norway) will be resubmitted early 2000.

# Abbreviations

| | |
|---|---|
| ACGIH | American Conference of Governmental Industrial Hygienists |
| ACPC | Ambient Coarse Particle Concentrator |
| AFPC | Ambient Fine Particle Concentrator |
| APHEA | Air Pollution and Health a European Approach |
| ATS | American Thoracic Society |
| BaP | Benzo-a-Pyrene |
| CAP | Concentrated fine Ambient Particulate matter |
| CBS | Central Bureau of Statistics (in the Netherlands) |
| CEN | European Normalisation Committee |
| CI | Confidence Interval |
| CIIT | Chemical Industry Institute of Toxicology |
| CMD | Count mean diameter |
| COPD | Chronic Obstructive Pulmonary Disease |
| DCMR | Central Environmental Agency of Rijnmond |
| DGM | Directorate General of the Environment, ministry of VROM |
| DG-XI | Environment Directorate General, EU |
| DSS | Decision Support System |
| EC | Elemental Carbon |
| ECG | Electrocardiogram |
| ECN | Energy Centre of the Netherlands |
| EMEP | European Monitoring of Environmental Pollutants |
| EU | European Union |
| EUROS-PM | Short-term modelling tool for Particulate Matter |
| $FEV_1$ | Forced Expiratory Volume in 1 second |
| FVC | Forced Vital Capacity |
| HDO | Emission category of Trade, Services and Government |
| HVPS | High Volume Particle Sampler |
| ICRP | International Committee on Radiological Protection |
| IL-4 | Interleukin 4 |
| IL-8 | Interleukin 8 |
| IL-9 | Interleukin 9 |
| LAC | Laboratory for Anorganical analytical Chemistry |
| LML | National Air Quality Monitoring Network |
| LOC | Laboratory for Organical analytical Chemistry |
| LPS | Lipo Poly Saccharides |
| LUMC | Leiden University Medical Centre |
| MPPDep | Multiple Path Particulate matter Deposition model |
| NAAQS | National Ambient Air Quality Standards |
| NOKLUK | National research project on coal consumption |
| OC | Organic Carbon |
| OMEGAM | Environmental research institution of Amsterdam |
| OR | Odds ratio |
| PAH | Policyclic Aromatic Hydrocarbons |
| PEF | Peak Expiratory Flow |
| PM | Particulate Matter |
| $PM_{carb}$ | Carbonaceous Particulate Matter (EC + OC) |
| $PM_{coarse}$ | Coarse Particulate Matter (2.5 µm < $PM_{coarse}$ < 10 µm) |

| | |
|---|---|
| $PM_{fine}$ | Fine Particulate Matter (0.15 µm < < 2.5 µm) |
| $PM_{ultrafine}$ | Ultra fine Particulate Matter (0.15 µm < ) |
| $PM_{sec}$ | Secondary Particulate Matter (sulphate, nitrate and ammonium) |
| PSD | Particle Size Distribution |
| RIVM | National Institute for Public Health and the Environment |
| RM | Risk Management |
| ROFA | Residual Oil Fly Ash |
| RR | Relative Risk |
| QRA | Quantitative Risk assessment |
| SAVIAH | Small Area Variations in Air Pollution and Health |
| SOA | Secondary Organic Aerosol |
| TEOM | Tapered Element Oscillating Microbalance |
| TNF-α | Tumour Necrosis Factor alpha |
| TNO | Organisation for Applied Scientific Research |
| TSP | Total Suspended Particulate matter |
| UIA | University of Antwerp |
| USA | United States of America |
| US-EPA | Environmental Protection Agency in de USA |
| VOC | Volatile Organic Compounds |
| VROM | Ministry of Housing Physical Planning and the Environment |
| WageningenUR | Wageningen University and Research |
| WMO | World Meteorological Organisation |
| ..-y | number of years averaging time |
| ..-h | number of hours averaging time |

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# Appendix 3 (Poster) presentations during congresses and workshops

Van Bree, L., Muhle, H. (1999). “Methods, models, and Risk Assessment”. Platform session 5 at the 7th International Symposium on Particle Toxicology, 13-15 October, Maastricht, NL

Van Bree, L. (1999). “Who is susceptible to ambient PM and why ?”. Panel session at the 3rd Colloquium on Particulate Air pollution and Human Health, 6-8 June, Durham, NC, USA.

Van Bree, L., Vandenberg, J. (1999). “Risk Assessment and Risk Management of Ambient Air PM - scientific considerations for standard setting and targeted control policy”. A pre-colloquium workshop at the 3rd Colloquium on Particulate Air Pollution and Human Health, 6-8 June, Durham, NC, USA (summary published in proceedings).

Buringh, E., P.H. Fischer, G. Hoek (1999) Is SO2 a causative factor for the PM associated mortality risks in the Netherlands? Poster 3rd Particle Colloquium Durham, NC, p. 5-1 to p. 5-6 Proceedings of the third particle colloquium on particulate air pollution and human health.

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Cassee, F.R., J.I. Freijer, A.J.F. Boere, P.H.B. Fokkens, J. Bos, L. van Bree P.J.A. Rombout (1999). Health Effects of Particulate Matter - Toxicology and Dosimetry. Poster at the 7th International Symposium on Particle Toxicology, October 12-15, Maastricht, the Netherlands.

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Bloemen H.J.Th., Vissenberg H.A.,. Rombout P.J.A. Air Quality Assessment of Particulate Matter - Sigma Model Brussels January 1999.

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# Appendix 4 Lectures

Cassee, F. R. (1999). Int. Workshop on the Application of Particle Concentrators, HEI, May 8, 1999, San Diego, CA.

Cassee, F.R. (1999). Effects of Particle Composition in Animals.. Annual Conference XV Air Pollution: Understanding Air Toxics and Particles. May 9–12, 1999, San Diego, CA.

Cassee, F.R. (1999). Toxicological evidence for PM associated health effects. F.R. Cassee, Presentation at the Scientific Meeting Series of the RIVM, May 18, Bilthoven, the Netherlands.

Cassee, F.R. (1999). Mechanisms of action of PM10. Presentation at the VVM symposium on Health Effects of particulate matter, October 18, Bilthoven, the Netherlands.

Fischer, P.H. (1999) Lecture on health effects of PM for University of Nijmegen, Department of Toxicology and Epidemiology, 5 Nov. 1999

Fischer, P.H. (1999) Gezondheidsrisico's van fijn stof in Nederland. Wetenschappelijke vergadering 15 mei 1999 RIVM

Van Bree, L. (1999). What new PM research results are emerging ? What are the characteristics of PM that are important to human health - primary versus secondary particles? Presented at the EC-HEI Joint meeting on "The Health Effects of Fine Particles: Key Questions and the 2003 Review", Brussel, 15th January.

Buringh, E., (1999) Lecture on PM related epidemiology for University of Nijmegen, Department of Environmental Sciences, 13th April 1999

Buringh, E, (1999) What a PM risk manager wants to know about risk assessment? Invited lecture, pre-colloquium workshop 3rd Particle Colloquium, Raleigh, Durham, 5th june

Bloemen, H.J.Th., (1999) Fenomenologie van fijn stof , tijdens VVM cyclus Fijn Stof, het overzicht 30 september 1999 RIVM

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Rombout PJA, Bloemen HJTh, Buringh E, Fischer P. Following the particle from cradle to grave. The source effect chain of particulate matter. Invited lecture EU DG XII Symposium Brussels, October 20 1999

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