WP6 guidelines for intervention studies, health impacts of implemented strategies to reduce air pollution in Europe

Authors:
Susann Henschel, Patrick G. Goodman, Richard Atkinson, Ariana Zeka, Alain Le Tertre, Antonis Analitis and Olivier Chanel

Table of Contents

1.1 Summary of guidelines

The main focus of Work Package 6 of the Aphekom project was to review the impact of European fuel legislations reducing sulphur content in certain liquid fuels and assess the impact on air quality and human health.
Daily SO_2 air pollution and mortality data from 20 participating cities, spread all over Europe, were analysed employing time series plots and CUmulative SUM statistical technique in order to track and visualise general trends in SO_2 levels overtime and to assess, if a step change in SO_2 levels could be detected after the implementation of the fuel legislations .

In addition, a detailed analysis of hourly SO_2 concentrations dependent on data availability in the collaborating cities was conducted to identify city specific patterns including source appointment, to track changes over time and to analyse these changes in SO_2 concentrations with respect to the different sources, i.e. traffic, heating, shipping and industrial sources.

Furthermore the association between mortality and daily variations in air pollution overtime was assessed using generalized additive models (GAM) in the R statistical software environment. City specific effect estimates were combined using meta-analysis. The meta-analysis involved two steps: In the first step, individual-city data were analysed and city-specific effect estimates were obtained; in the second step, the SO_2 effects on mortality from each city were combined in order to provide overall estimates. Based on these overall relative risk estimates the attributable number of deaths for each individual city due to level changes in SO_2 was estimated.

In addition, an analysis of distributed lags was conducted to examine whether different lag structures apply to the relationships between cardiovascular and respiratory events and SO_2 concentrations, which will therefore result in differences in mortality impacts from regulation implementation.

1.2 Introduction

As part of the Aphekom study (Public Health Program EC Grant Agreement No.2007105: Improving Knowledge and Communication for Decision Making on Air Pollution and Health in Europe) we undertook a literature review of air pollution intervention studies (Henschel *et al.*, 2012).

Intervention\accountability studies play an important role in supporting and complementing scientific validation of the results of non-intervention studies, because they allow an examination of the hypothesized cause-effect relationship (Web-reference 1) providing direct evidence for specific interventions ideally having a clearer exogenous source of change in exposure compared to other epidemiological study designs and hence have less potential for confounding (Pope, 2010). Furthermore they also tell policy makers about the effectiveness or otherwise of specific interventions. Some of these “interventions” are not interventions in the pure sense of the word, but may be unplanned side effects attributable to political, economic or other societal

changes. Accountability studies are defined as a subset of intervention studies that attempt to assess policy-related, planned or controlled interventions usually reducing exposure (Pope, 2010).
The conducted review (Henschel *et al.*, 2012) aimed to give a summarized overview on a collection of most relevant, published intervention studies that assess the health impact of changes in air quality due to interventions, with the objective to identify different types of interventions and evaluation approaches looking at different health outcomes. Studies included were divided into 4 broad groups based on the change in the emission source(s), i.e. large (e.g. Closure and reopening of a steel mill in Utah (U.S.); the German reunification), traffic (congestion charging zone in London and Stockholm), domestic (e.g. the Irish coal ban) and Olympic Games (Atlanta 1996 and Beijing 2008).
We observed that the findings from the studies and the methods used in the analysis are quite varied, and hence limit the scope to directly compare results from the different studies. Furthermore the opportunities to assess the full extend/all aspects of an intervention are not always given as this is dependent on available funding, data availability, etc. Especially in retrospective studies such as the closure and reopening of a steel mill in Utah (Pope, 1989; Pope *et al.*, 1992) and the German reunification (Peters *et al.*, 2009; Suguri *et al.*, 2006) available data might not meet the ideal data requirements and hence limit the scope of a study.
In order to overcome some of those issues a standardized approach/protocol including guidelines on evaluating appropriate time windows surrounding interventions, required comprehensive monitoring networks to record pollutants, the data quality (health and air), the use of controls, size of the study population, statistical methods to detect subtle changes including adjustment for seasonal and other trends.
Overall the review showed that these various interventions irrespective of their nature have been successful at reducing air pollution levels. It has also shown that there is consistent published evidence that a number of these interventions have been associated with health benefits, mostly by way of reduced cardiovascular or respiratory mortality and or morbidity. In the majority of reviewed interventions the observed decrease in mortality exceeded the expected predicted figures which were based on observations from European multicity studies (Henschel *et al.*, 2012).

Another aspect of the Aphekom project (WP6) was to investigate the impact of the implementation of EU legislations on sulphur the effects of EU legislation to reduce the sulphur content of fuels (mainly diesel oil used by diesel vehicles, shipping and home heating). In detail the effect on air pollution levels of the implementation of the Council Directive 93/12/EEC and its amended version Council Directive 1999/32/EC including marine oils were analysed. The implementation of the two Council Directives encompassed three stages of implementation gradually reducing the sulphur content in certain fuels in the EU member states with stage (I) being implemented as laid down in the directive on 1st Oct. 1994, stage (II) on 1st Oct. 1996 and stage (III) on 1st July 2000.

In undertaking this analysis we have developed a methodology, some of which may be of use to other studies. Dependent on the scope of these studies, which may fall into different categories such as single- or multi-city studies, all or a subset of the following guidelines based on the work of Aphekom WP6 have the potential to be adapted and applied in their methodology, e.g. a single-site study wont be able to conduct the steps outlined for the conduction of a meta-analysis of pooled results.

The following guidelines outline, step by step, the procedure/ methodology applied in order to achieve the WP6 objectives.
Due to the fact that the analyses performed here requires statistical expertise, we strongly recommend involving an expert in statistics when planning a study to investigate the environmental and health impact of implementing a preventive measure.

1.3 Identification of Data Needs

In order to conduct a time-series analysis of the impact of an intervention, in our case the implementation of the Council Directives on air quality and health, we recommend considering the inclusion of the following variables/factors into the data request for an air pollution intervention study.

1) If an intervention is assessed, the time series data (Air pollution, health, weather, etc.) requested or used should ideally span a reasonably big time interval with the intervention event that is assessed roughly being in the middle of the study time period. This allows to compare the assessed variables pre- and post intervention and as well to get a picture of/some information about/account for long-term trends overtime.

2) The type of data ideally needed should be identified, e.g.
   - What is the detail of the measurements that is needed? Hourly, daily, weekly etc.
   - Validated data from state institutions or other sources?
   - Is the requested data complying with EU ISO standards?

3) Parameters measured/requested:
   - Air pollutants
   - Weather
   - Traffic flow
   - Information on local emission sources/emission inventories of the study area
   - Local events/changes which may have caused the emissions to change, e.g. major infrastructural changes pre/post intervention, changes in space heating
   - Details on vehicle fleet in study area, i.e. percentage of diesel vehicles, heavy and light vehicles
   - Local initiatives/ legislations, e.g. car free zones/coal bans/fuel changes
   - Main sources of space heating

4) For air quality measurements:
   - We recommend to request the following air pollutants [$\mu g/m^3$] for analysis: Ozone (O_3), Particulate Matter with a diameter of 10 micrometers or less (PM_{10}), $PM_{2.5}$, Black Smoke (BS), Sulphur Dioxide (SO_2), Nitrogen Oxides (NO_x)
   - What number of measuring stations should be used?

- What type of measuring station(s) (Traffic, city-centre, urban background, background, industrial) should be used and reflects assessed exposure the best?
- The correlation between the stations, if data from more than one station is used.
- What is the number of missing values?
- What is the measurement method and did it change overtime (exact time point)?
- What quality controls are performed (on site controls, established chain of calibration and traceability, internal and external audits, maintenance and supporting systems, data reviewing and managing)?
- What is the detection limit of the measurement equipment?

5) Weather data parameters:
    - Location of the monitor
    - A request as detailed as possible is desirable, we suggest to request the following parameters: Daily Temperature Minimum/Maximum, average Temperature, relative humidity, wind speed and direction, precipitation and atmospheric pressure
6) Health data:
    - We would recommend requesting daily mortality data from a validated source, if possible stratified by age, specifying the International Classification of Diseases (ICD-9 or ICD-10)that should be used for providing the data [ICD is the classification used to code and classify mortality data from death certificates (Web-reference 2)].
    - Dependent on the methodology mortality data stratified by age groups is desirable.
    - Data on influenza epidemics

Taking the Aphekom WP6 as an example, the following data needs, outlined in section 2.1.1 – 2.1.5, were identified and requested from all 26 European cities involved in the Aphekom project.

2.1 General Issues and Format of the Data Request of Aphekom WP6

In general as the Council directives were implemented in 1994, 1996 and in 2000 daily data from **1990 onwards** up to the most recently available date were requested from the centres. This allowed WP6 to assess trends in air quality and mortality before, during and after implementation of the legislations.
The WP6 data request took the form of a template contained within an Excel-worksheet and requested centre-specific pollution, weather and mortality data. This was circulated by email to all APHEKOM centres at the end of November/early December 2009. Furthermore a WP6 specific supplementary questionnaire was sent out to supplement information sought through the template. Table 2.1 shows the WP6 data request template and Table 2.2 the supplementary questionnaire. The primary deadline for the collaborating centres to send back the completed in WP6 data template and WP6 supplementary questionnaire was the 15th of January 2010.

If available, more detailed exposure data is desirable for any new study – what we specified in our data request was a minimum.

2.1.1 Requested Air quality Data for Aphekom WP6

- **Daily mean SO_2** in µg/m^3 from at least one or, if possible, averaged across a number of monitoring stations classified as:
  (i) Urban background,
  (ii) Traffic,
  (iii) Harbour - If a port was present in the centre, in order to allow the assessment of the impact of the 99/32/EC Directive, which includes marine oils.
- **Daily mean PM_{10}** in µg/m^3 from one or, if possible, averaged across a number of urban background stations
- **Daily mean BS** or **TSP** in µg/m^3 from one or, if possible, averaged across a number of urban background stations
- **Hourly SO_2** in µg/m^3 from at least one or, if possible, averaged across a number of monitoring stations classified as:
  (i) Urban background,
  (ii) Traffic,
  (iii) Harbour - If a port was present in the centre

2.1.2 Requested Weather Data

- **Daily average Temperature** in °C
- **Daily relative Humidity** in %

2.1.3 Requested Health Data

The information sources for mortality data were the national, regional or local mortality registries for the cities involved.

- **Daily status of influenza epidemics:** “0” indicating “no epidemic” and “1” indicating “yes, there is an influenza epidemic”
- **Daily mortality counts from all-causes** (excluding external causes) **ICD-9** (ICD9 < 800) for the age groups: 0-14, 15-64, 65-75 and ≥75
- **Daily mortality counts from respiratory causes ICD-9** (ICD9: 460–519) for the age groups: 0-14, 15-64, 65-75 and ≥75

- **Daily mortality counts from cardiovascular causes ICD-9** (ICD9: 390–459) for the age groups: 0-14, 15-64, 65-75 and ≥75

2.1.4 Supplementary information requested

- **Air quality data:** Number of measuring stations used, changes (time and nature of change) in measuring methods
- **Weather data:** Location of weather monitor
- **Influenza data:** Data source and definition of influenza epidemic used as basis for data collection
- **Emission source & changes in emission sources:** major local sources, relevant legislations/initiatives, changes of SO_2 content in fuels overtime, information on vehicle fleet composition, space heating, **exact implementation dates of the EU Council Directives 93/12/EEC and 99/32/EC** (as not all collaborating centres implemented the Directives according to the deadlines given in the legislation)

Date (dd/mm/yy)	SO2 *Urban Background*	SO2 *City Centre/Traffic*	BS *Urban Background*	PM10 *Urban Background*	Weather		Influenza epidemics 0 = NO 1 = YES	ALL CAUSE MORTALITY				RESPIRATORT MORTALITY				CARDIOVASCULAR MORTALITY			
	Daily mean SO2 [µgm-3]	Daily mean SO2 [µgm-3]	Daily mean BS [µgm-3]	Daily mean PM10 [µgm-3]	Daily average temp.	Daily relative humidity		Daily mortality of age group 0-14	Daily mortality of age group 15-64	Daily mortality of age group 65-74	Daily mortality of age group ≥75	Daily mortality of age group 0-14	Daily mortality of age group 15-64	Daily mortality of age group 65-74	Daily mortality of age group ≥75	Daily mortality of age group 0-14	Daily mortality of age group 15-64	Daily mortality of age group 65-74	Daily mortality of age group ≥75

Table 2.1: Data template for WP 6 data request

SO_2 data:	
• **Number of urban background stations?**	
• **Number of city centre/traffic stations?**	
• **Time of change in measuring methods and specify nature of change? (if any)**	
BS data:	
• **Number of urban background stations?**	
• **Time of change in measuring methods and specify nature of change? (if any)**	
PM_{10} data:	
• **Number of urban background stations?**	
• **Time of change in measuring methods and specify nature of change? (if any)**	
Weather:	
• **Location of the weather monitor:**	
Influenza data:	
• **Data source and definition of influenza epidemic used as basis for data collection:**	
Emission Sources:	
Please list any major local sources such as power plants or large industrial areas and their proximity to measuring stations.	
Local events/changes which may have caused the emissions to change. Please indicate the time point of change as accurate as possible!	
Local initiatives/ legislations, e.g. car free zones/coal bans/fuel changes *(Please indicate dd/mm/yy if possible)*	
SO2 levels in fuels (Please indicate changes over time from 1990 to the present.)	
Percentage of the diesel road vehicles (Please indicate changes in vehicle fleet composition over time.)	
Specify % for heavy and light vehicles, if possible	
Implementation date of EU Council directive 93/12/EEC on SO2 levels & eventual sought derogations	
Implementation date of EU Council directive 99/32/EC on SO2 levels & eventual sought derogations	
Major infrastructural changes post implementation	
Main sources of space heating	
Comments on major changes in space heating	

Table 2.2: WP6 supplementary questionnaire

2.2 Compilation of Data Sets and Feedback of Individual Centres

2.2.1 Implementation Dates of the SO_2 Directive 93/12/EEC and Directive 99/32/EC

One of the most challenging pieces of information to obtain was the exact implementation dates of the EU Directives. Where centres could not supply that information, the assumption was made, for data analysis purposes, that the Council Directives were implemented on the dates defined in the directives.

2.2.2 Format of the Compiled Datasets

Upon receipt of the completed in WP6 data request template and supplementary questionnaire from the individual centres, data for each centre were was transferred to a standardised spreadsheet template file in Microsoft® Office Excel®2007 for the air quality data analysis. In addition, the data were transferred to a standardised .csv file format in Excel for analysis in R statistical software environment to facilitate to read the data into R for each centre.

2.2.3 Quality Assurance on Aphekom WP6 Datasets

In order to assure data quality suitable for WP6 data analysis purposes compiled datasets were checked if data was sent in the requested format by the collaborating centres and upon coherence and completeness. In cases were required standards were not met supplementary questions and data requests were sent out to cities concerned.

2.3 Analysis of air quality data

Using the daily average pollutant values received from each of the collaborating Aphekom centres different types of graphs were plotted to assess air pollutant levels overtime. This allowed the detection of general trends in pollution levels overtime and the potential detection of a step change in pollutant levels arising from the points Council Directives.

2.3.1 Method

In order to plot the required graphs a standardised template was created in Microsoft® Office Excel®2007 in order to allow the automated calculation and plotting of monthly, yearly and seasonal averages as well as percentiles and interquartile ranges (IQR) for each pollutant and yearly averages of the mortality data. The number of graphs produced differed between the individual cities depended upon the data availability. The standardised template can be downloaded at www.apkekom.org. The provided template has several worksheets, in which the compiled daily pollutant concentration of a specific pollutant (worksheets provided in the template include, SO_2, BS, PM_{10}) can be pasted in the allocated columns in each worksheet. Calculation of averages etc. is automated in the worksheet. Graphs have to be relabelled with the name of the city used for analysis. If more or different pollutants of interest want to be investigated, the individual worksheets might be copied within the workbook and adapted accordingly.

2.3.2 List of Graphs plotted for each individual centre

Subject to data availability the following graphs were produced for each study centre:

(i) Plot of daily SO_2 average concentrations over the study period
(ii) Plot of daily average concentrations of all pollutants available for the study period on one graph
(iii) Plot of daily average concentrations of urban background (UB) SO_2 and daily temperature averages in one graph
(iv) Plots of monthly averages of all available pollutants across years
(v) Plot of yearly averages for whole study period
(vi) Seasonal plots: Seasonal averages were calculated for all four seasons with winter = December to February, spring = March to May, summer = June to August and autumn = September to November. A graph was plotted for selected cities for each individual season for seasonal averages over the whole study period and for all seasonal averages over time for all collaborating centres.
(vii) Plots for the whole study period for annual percentiles: Separate plots for 25th, 50th, 75th and 90th annual percentiles
(viii) For SO_2 only: Calculation of the IQR for the whole study period and for the time spans before, between and after implementation of the Council Directives.
(ix) CUSUM (Cumulative Sum) plots plot

Graphs plotted for mortality data available for each centre:

(i) Plots of yearly averages stratified by age groups and total number of yearly deaths over the study period for all-cause, respiratory and cardiovascular deaths

In Appendix III all plots for each individual centre can be found.

2.3.3 Summary plots

(i) Summary plots of all centres (only Paris was taken as a representative for the 9 French centres to avoid an "overcrowded plot") yearly UB SO_2, PM_{10}, BS averages
(ii) A summary plot of the 9 French centres of yearly UB SO_2 averages
(iii) Plots of seasonal and of monthly averages of UB SO_2 overtime in a selection of Aphekom centres including Dublin, Vienna, Stockholm, Athens, Bilbao, Budapest and Valencia
(iv) Plot of seasonal and of monthly averages of UB SO_2 overtime in the French of Aphekom centres

2.3.4 Annual minimum temperature

Due to the fact that we observed a rather abnormal SO_2 peak in a number of collaborating centres in the winter months of 95/96 and 96/97 we explored different options to explain the peaks.

One explored options was to look at meteorological conditions that might explain the SO_2 peaks, such as a cold wave, which would go hand in hand with increased fuel usage due to the increased space heating and electricity usage and as well as inversion The number of days of exceedance of annual minimum temperature was calculated for a selection of centres. A threshold value was arbitrarily defined depending on geographical region of the centre and associated general climatic conditions. A threshold value of 0°C for the London, Ljubljana, Vienna and Stockholm and of 3°C for Dublin and Brussels was defined.

2.3.5 Weekday mean values for UB SO_2 and all-cause mortality

In order to investigate if trends in concentration of UB SO_2 differ between the different days of the week, averages of SO_2 were generated for each weekday using daily data over the whole study period.

Furthermore, in order to see if trends in pollutant concentrations for the different weekdays for lag 0 and lag 1 coincide with changes in weekday specific all-cause mortality averages, averages for each day of the week for total all-cause mortality were generated.

A template allowing automated calculation of averages of SO_2 and mortality by weekday for the study period can be downloaded at www.apkekom.org Please note, if your study period diverges from the one WP6 examined, please adapt the provided templates accordingly (time period, weekday) and note the occurrence of leap years. A table with the automated output of the means of SO_2 and in this case all-cause mortality can be found scrolling to the bottom of the worksheet. Do not modify the content of the equations in this table unless your dataset requires you to do so.

2.3.6 Diurnal SO_2 profiles

Hourly SO_2 data was obtained from a number of centres involved in the Aphekom project. Analysis of available data involved the generation of individual diurnal SO_2 profiles (by season and by weekday for each year with data available) in order to:

- identify city specific patterns including source appointment and quantification
- track changes over time
- analyse the changes in SO_2 concentrations from different sources, i.e. traffic, heating, shipping and industrial sources, overtime
- assess the effect of the implementation of the afore mentioned EU air quality legislations.

Hourly plots by season and by weekday for each year with data available were generated. For this purpose a template facilitating an automatic calculation of seasonal and weekday SO_2 averages for each hour of the day (24hrs) for each year with data available was generated.
A template allowing automated calculation of hourly averages by year, by weekday and by season for the years 2002 to 2010 can be downloaded at www.apkekom.org Please note if your study period diverges from the one WP6 examined, please adapt the provided templates accordingly (time period, weekday) and note the occurrence of leap years!

For better understanding the following section provides an example of a selection of graphs to highlight different city specific patterns that were detected during that stage of the analysis and an example how to interpret observed patterns.

2.3.6.1 Examples for diurnal SO_2 profiles

Figure 2.1 and Figure 2.2 show plots of hourly SO_2 data from Dublin showing seasonal plots for winter (Fig. 2.1) and summer (Fig 2.2) for an urban background station for the years 2002 to 2008 (Please note that there is a change in the scale of the y-axis between the two Figures). There was no hourly data available prior to this time period.

Traffic related SO_2 peaks were observed throughout all seasons for the morning (peaking btw. 7-9am) and evening rush hour (peaking around 5-7pm). In addition to that the high winter readings around mid-night suggest heating systems.

In Fig. 2.1 the observed winter SO_2 levels in 2002 are markedly higher than later years and the peak patterns resemble the pattern found in the following years. The high values found in the evening until morning hours suggest that the observed high SO_2 levels during those hours were due to heating related emissions due to the cold weather. In comparison to following years no high SO_2 levels were observed for the summer 2002. Overall a decreasing trend in SO_2 levels overtime regarding the heating related emissions during night-time has been observed. On the other hand no obvious decrease has been observed looking at most likely traffic related SO_2 emissions, which can be clearly seen in the summer plots (Fig 2.2) where SO_2 levels stay quite constant during the whole day for the majority of the plotted years, ranging between ~4.0 and 0.5µg/m^3 without a clear trend throughout the years. It is not clear, if these SO_2 levels were decreasing and increasing due to high sulphur content in diesel fuel for vehicles or due to changes in the vehicle fleet, i.e. increasing/decreasing number of vehicles or of diesel vehicles, changes in commuting behaviour etc..

The shifts in SO_2 maxima between winter and summer are partially due to artificial changes in switching from summer to winter time and vice versa.

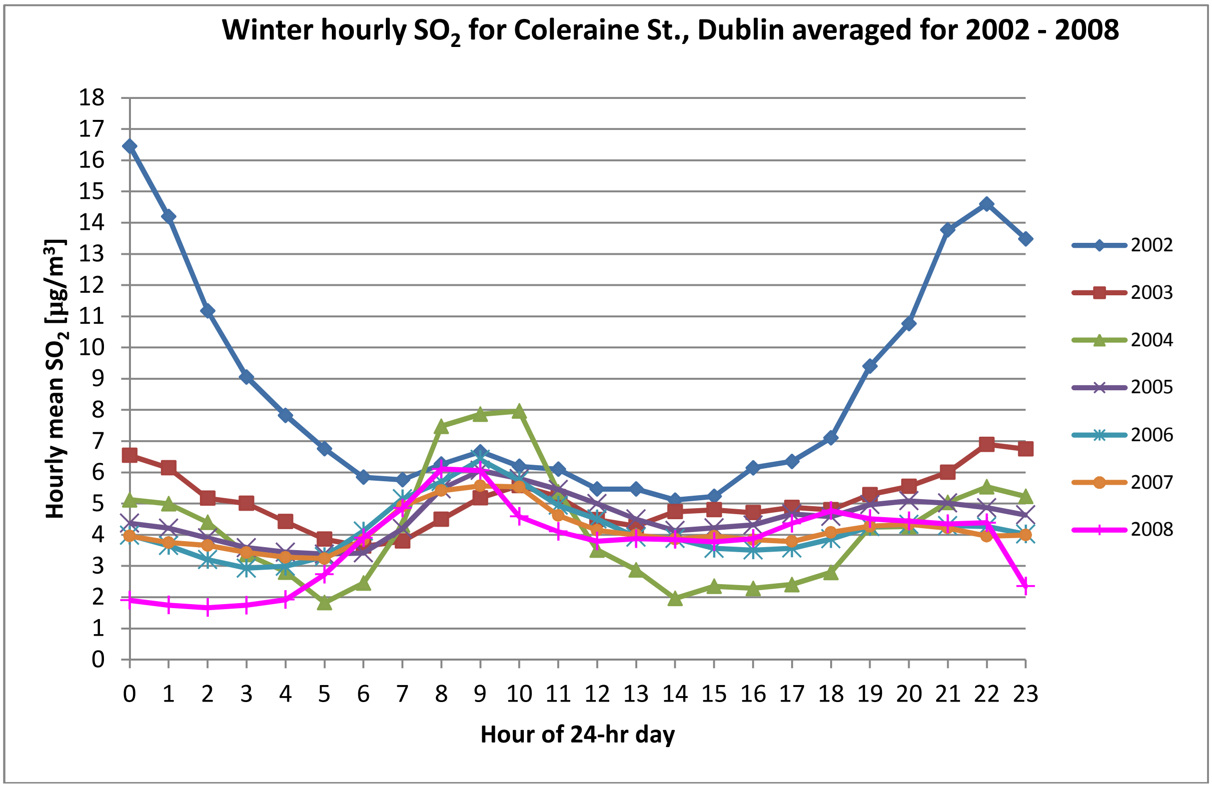


Figure 2.1: Diurnal plot of **winter** hourly SO_2 for an urban background station in Dublin from 2002-2008

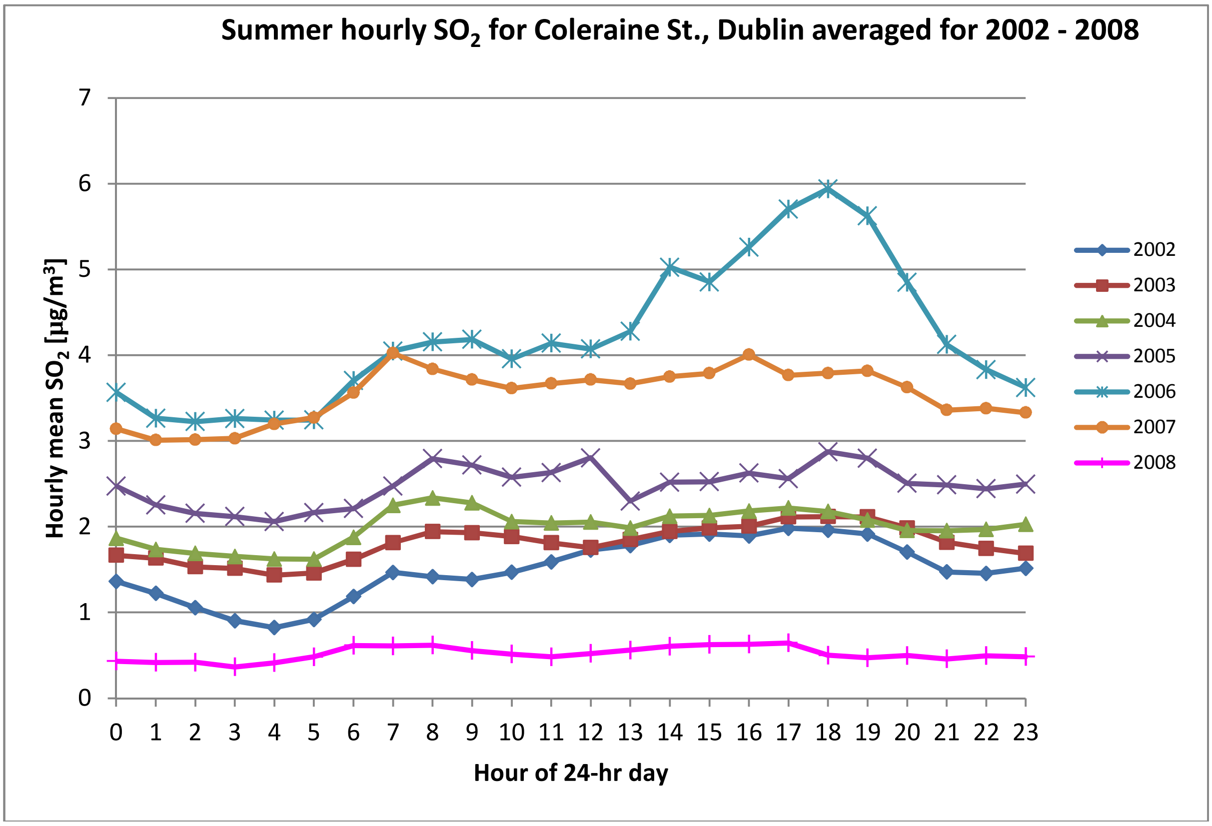


Figure 2.2: Diurnal plot of **summer** hourly SO_2 for an urban background station in Dublin from 2002-2008

Figure 2.3 to Figure 2.5 show plots of hourly SO_2 data from Dublin by weekday for an urban background station for the years 2002, 2004 and 2008 respectively.
Again a general downwards trend overtime has been observed throughout the years. Higher SO_2 levels peaking around midnight indicate emission levels due to space heating. Those heating related emissions show a marked decrease possibly indicating a shift in fuel usage with levels in 2002 as shown in Fig. 2.3 ranging around 4-8µg/m^3 and dropping to 2.5-0.58µg/m^3 in 2008. This corroborates findings from the seasonal plots. Furthermore a decrease for daytime SO_2 levels has been noted, which would most likely be related to traffic related emissions as a peak reflecting the morning and evening rush hour can be observed with varying intensity throughout the years.
In the weekday specific plots a stretched out peak on Thursdays was observed for the majority of the years as seen in Fig.2.3 and 2.4. A possible explanation for that would be a reflection of higher traffic related emissions due to late night shopping (Thursday shops are open until 9pm in Dublin).

Furthermore throughout all plots by weekday lower SO_2 levels were observed during daytime at the weekend (Saturday and Sunday) compared to the other weekdays, which most likely reflects a reduction or absence of industry related emissions, and the missing traffic volume due to commuters driving to and from work during the week.
In 2008 (Figure 2.5) levels in general are very low ranging between 2.9 and 0.4µg/m^3. It has to be noted that the detection limit of the measurement instruments is ~ 0.5ppb which is equivalent to 1.3µg/m3 and concentrations below that should be interpreted with caution. Background levels fell overtime from 2µg/m^3 in 2002/4 to 0.5 µg/m^3 which again could be due to the recession in 2008 and the associated "death of the Celtic Tiger" (a term describing the extraordinary economic growth that Ireland experienced 1995 to 2007).

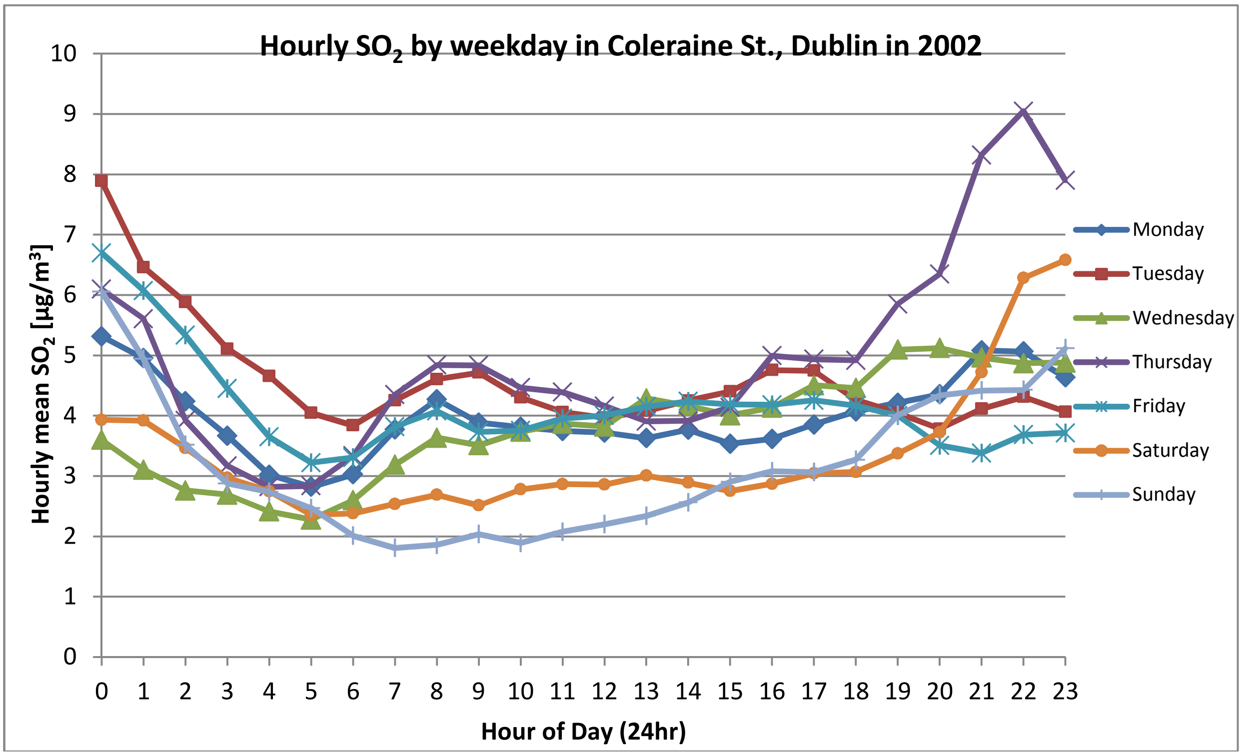


Figure 2.3: Diurnal plot of hourly SO_2 by weekday for an urban background station in Dublin in 2002

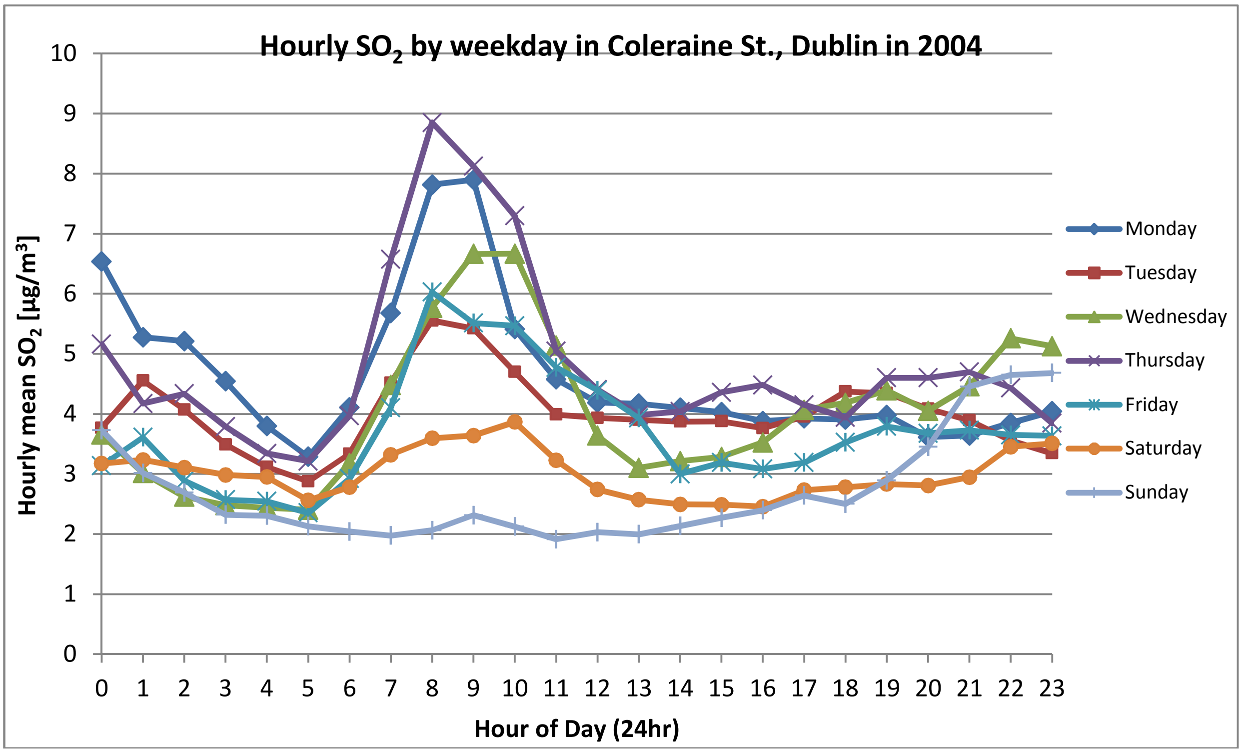


Figure 2.4: Diurnal plot of hourly SO_2 by weekday for an urban background station in Dublin in 2004

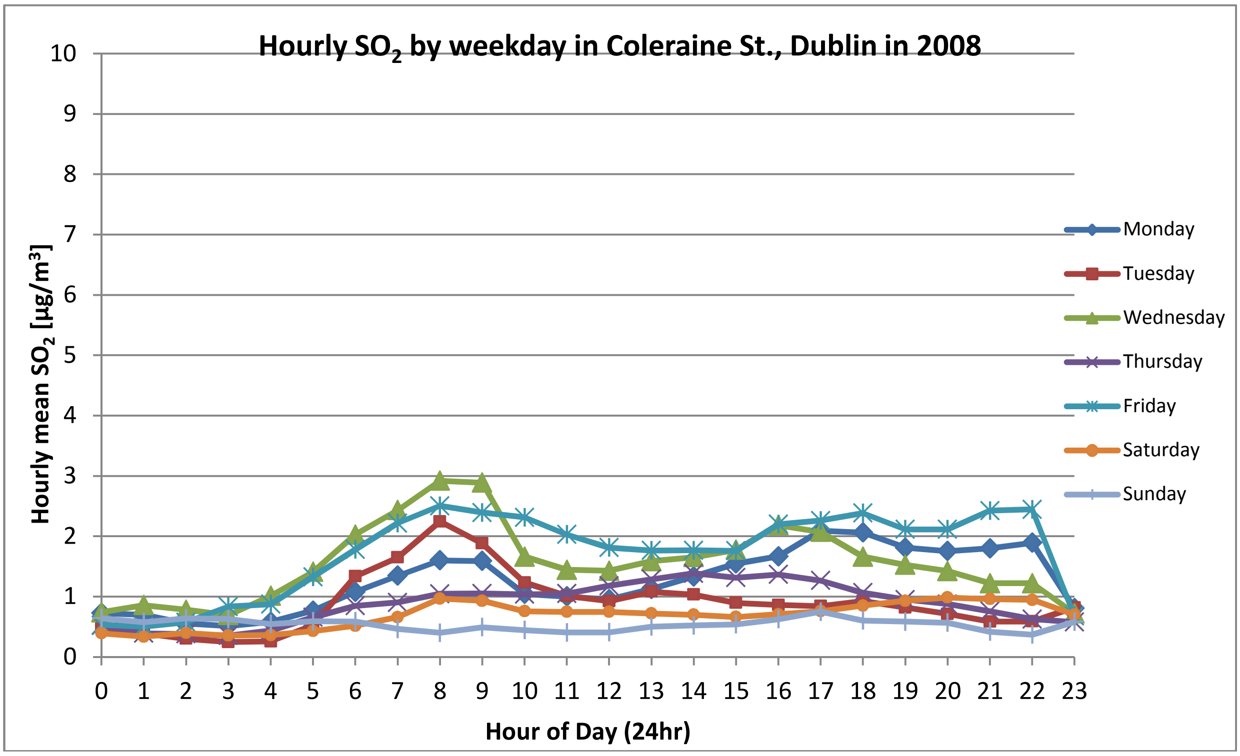


Figure 2.5: Diurnal plot of hourly SO_2 by weekday for an urban background station in Dublin in 2008

2.4 CUSUM

2.4.1 Introduction

The CUmulative SUM statistical technique, first proposed by Page (1954), was developed for use in industrial process control to detect deviations in production parameters from pre-determined values (Ryan 2000). The CUSUM approach has been used to study the performance of medical professionals, assess learning curves for trainees and the efficacy of treatments amongst others. In addition, Rossi *et al*. (1999) applied the CUSUM technique in an environmental epidemiological setting where they compared mortality rates in two distinct time periods in an area of Tuscany characterised by the presence of chemical plants. More recently, Barrart *et al.* (2007) investigated the use of the CUSUM in the identification of changes in mean pollution concentrations following traffic management interventions in London.

CUSUM methods apply to observations recorded over time (daily, weekly, monthly). The observations may be physical measurements, counts or rates and may be grouped or individual observations. The CUSUM methods of Lucas (1982) and Lucas and Crosier (1982) as applied to individual observations first compute the standardised deviations of observations from the desired or reference mean for the process or time series:

$$z_i = \frac{x_i - \bar{x}}{\hat{\sigma}_x} \qquad (1)$$

where x_i is the observed value at time *i*, $\bar{x}$ is the desired process mean (or 'reference mean') and $\hat{\sigma}_x$ is an estimate of the standard deviation of the observed values. These are accumulated over time to compute the CUSUM, S, at each time point *i* as follows:

$$S_i = S_i\text{-}1 + z_i \text{ where } S_0=0 \qquad (2)$$

Thus, if there is a shift in the process mean away from the target, then z_i will tend to be larger or smaller than the target average and the cumulative sum will steadily increase or decrease. Depending upon the magnitude of the shift in the mean, the CUSUM may not detect the change immediately and may require a number of observations at the new level before such a changed is picked up.

Lucas (1982) proposed to split S into two to help differentiate between mean increases (S_{Hi}) and mean decreases (S_{Li}) defined as:

$$S_{Hi}=\max[0,(z_i-k)+ S_{Hi-1}] \text{ and } S_{Li}=\min[0,(z_i+k)+ S_{Li-1}] \qquad (3)$$

The parameter, *k*, is the allowable 'slack' in the process and is usually set to be one half of the mean shift (in z units) one wishes to detect, i.e.

$$k = \frac{1}{2}\Delta \quad \text{where: } \Delta = \frac{x - \bar{x}}{\hat{\sigma}_x} \qquad (4)$$

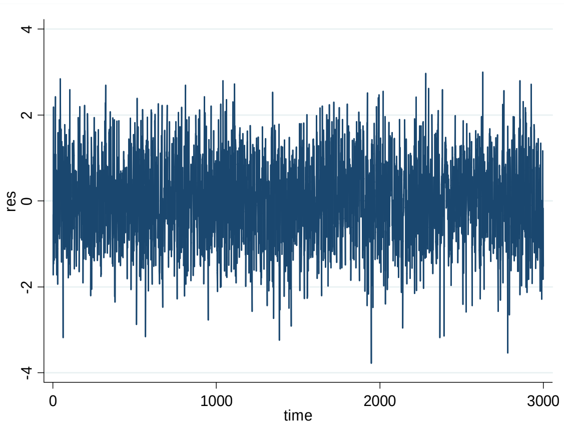
The usual choice of k = 0.5, is therefore the appropriate choice for detecting a 1-sigma shift in the reference mean. Deviations from the reference mean less than this factor will be ignored as process 'noise'. However, a balance has to be achieved between filtering out acceptable noise and reducing the sensitivity of the CUSUM output. Hence, alternative values for k may be required.

While time series data may be irregular or interrupted, the CUSUM technique was developed for applications where input data are normally distributed with no serial correlation between data points, neither of which are properties of air quality data, which are typically both skewed and correlated.

2.4.2 Example using simulated data

A random sample of 3000 observations was generated from a standard (mean 0, standard deviation 1) normal distribution (Figure 1a). The CUSUM plot (Figure 1b) shows, as expected, only random (i.e. not systematic or sustained) deviation from the mean of zero. Figure 2a) shows the same data but including (sustained) step changes of -0.1 and -0.2 at observations 1000 and 2000. The corresponding CUSUM chart (2b) identifies the step changes clearly. By comparison, Figures 3 & 4 illustrate the effects of adding a trend term to the data (decrements of 0.0001 and 0.001 per day respectively). A trend line (in red) has been added to these figures to help identify the trends. The corresponding CUSUM charts are shown in Figures 3b and 4b respectively. Both pick up the daily change in the series mean (-0.0001 and -0.001 per day respectively), chart 3b showing more noise and chart 4b showing a smooth, continuous curve downwards. Combining the two sets of changes (each daily decrement with the two step changes) gives Figures 5 and 6. The two step changes can be indentified when the daily trend is -0.0001 but not when the trend is -0.001. Step changes of -0.4 and -0.8 are required before the step changes become visible against a daily trend of -0.001(Figure 7). This simple analysis illustrates the feasibility of identifying step changes in time series providing they are not too small relative to any trend in the data. One approach to this problem is to first model trend in the time series to be analysed. However, this brings it own difficulties and these are illustrated in the analysis of the Paris data (Final WP6 Report Appendix A).

Figure 1a) 3000 obs from std. normal dist. **1b)** CUSUM



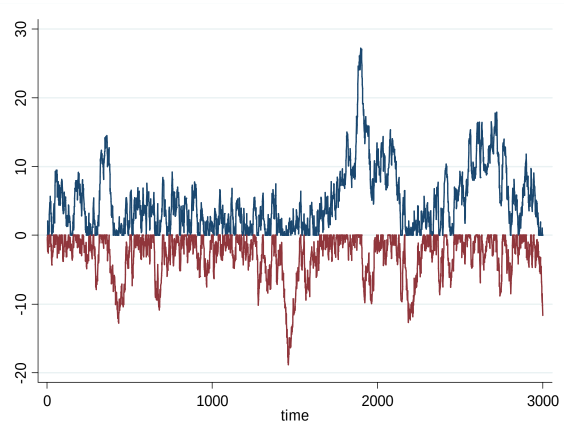
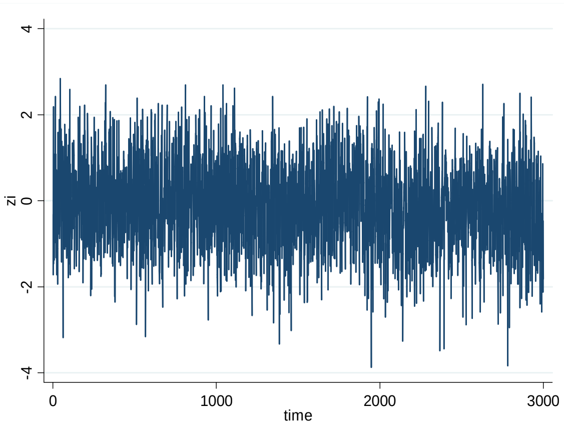


Figure 2a) As 1) plus – 0.1 and -0.2 at 1000 & 2000 **2b)** CUSUM



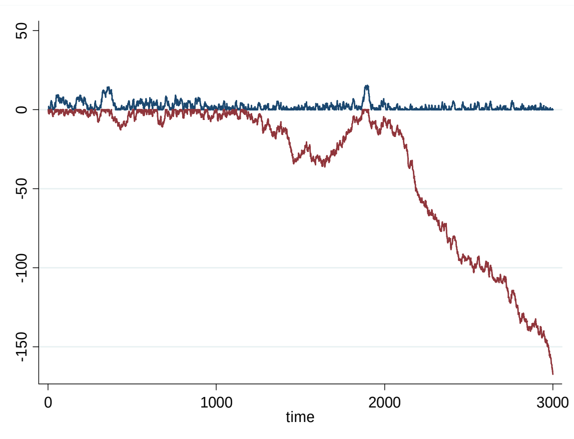
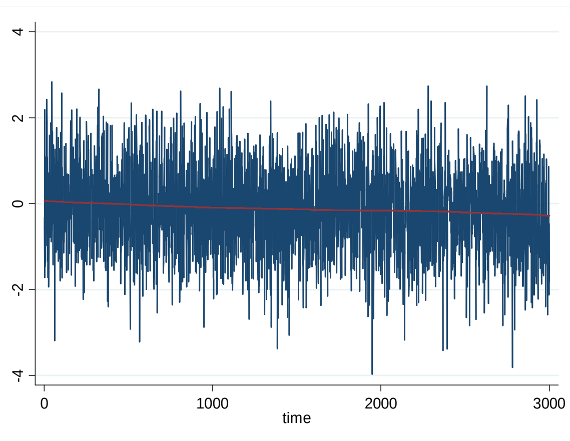


Figure3a) As1) incl. -0.0001 trend only **3b)** CUSUM



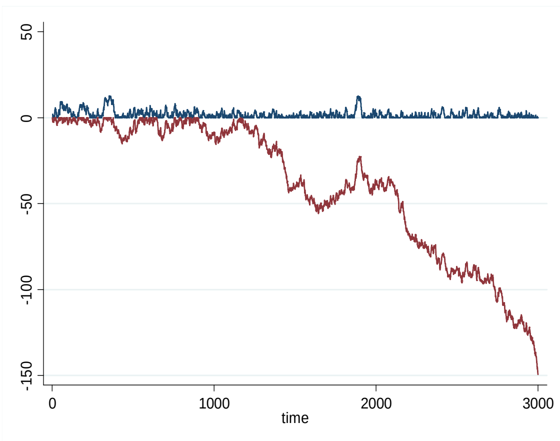
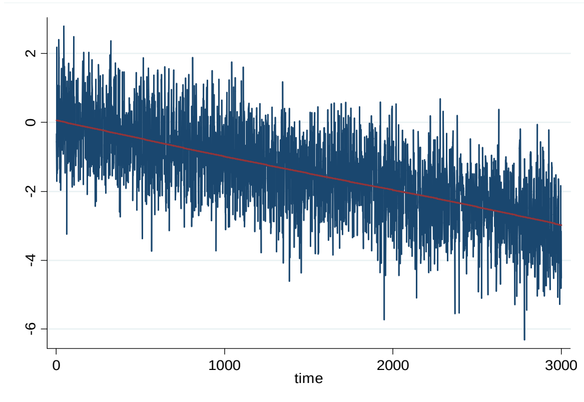


Figure 4a) As 1) incl. -0.001 trend only **4b)** CUSUM



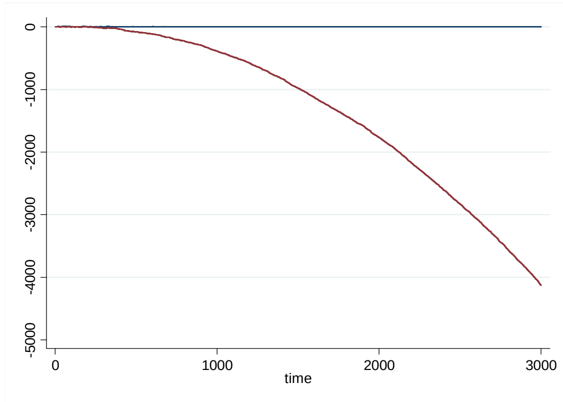
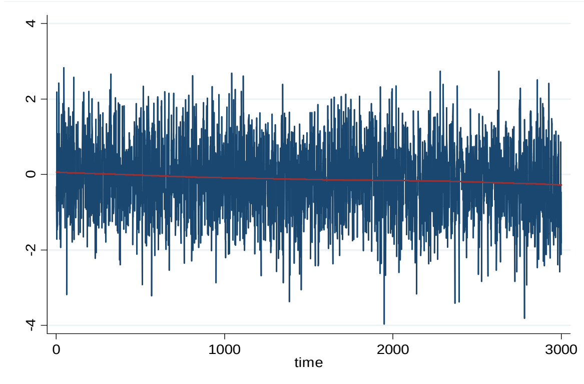


Figure 5a) -0.0001 & step changes -0.1 & -0.2 **5b)** CUSUM



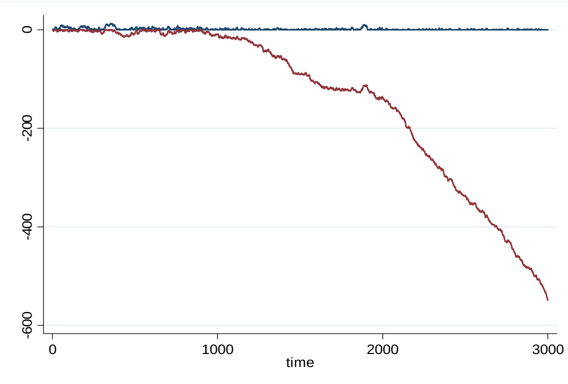
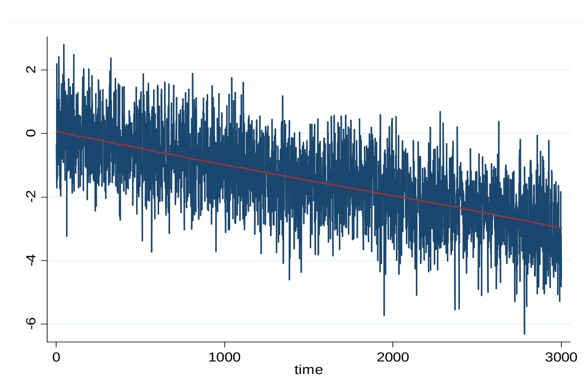


Figure 6a) -0.001 & step changes- 0.1 & -0.2 **6b)** CUSUM



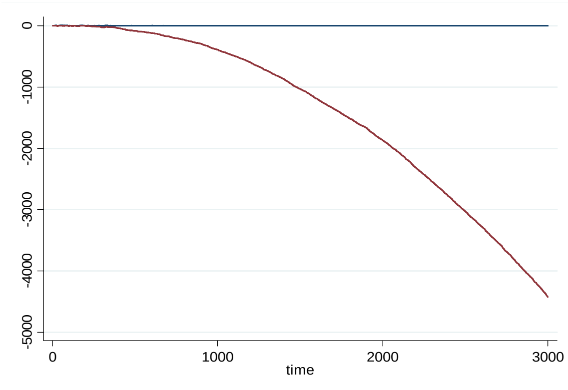
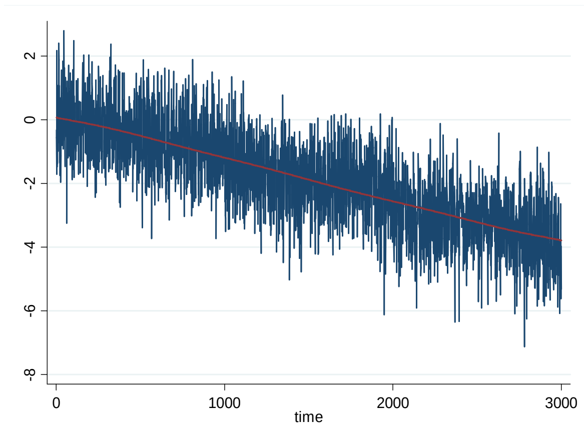
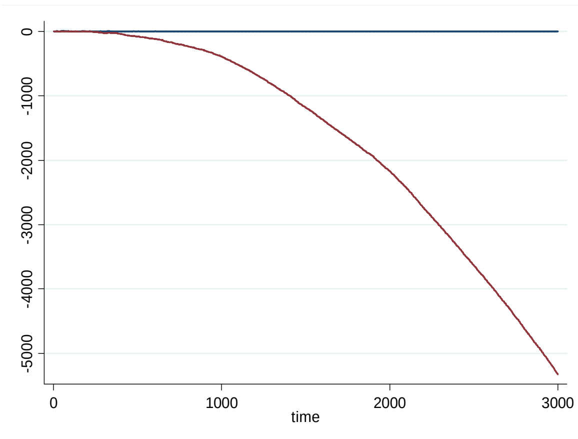


Figure 7a) -0.001 & step changes- 0.4 & -0.8 **7b)** CUSUM





2.5 Time-series analysis

2.5.1 Introduction to time-series study

The aim of the time-series component of the WP6 is to investigate associations between daily variations in air pollution levels with variations in daily incidence of deaths (all-cause, respiratory and cardiovascular) in each collaborating Aphekom centre. This analysis focuses on levels of SO_2 from urban background stations as these measurements reflect the exposure levels of the majority of a city's population much better than measurements from stations in close proximity to traffic sources.

2.5.2 R statistical software environment – Introduction

In order to conduct time-series analysis on the dataset of each individual city, R (R Development Core Team, 2011) statistical software environment 2.10.1 was used.
R is `GNU S'= a freely available language and environment for statistical computing and graphics which provides a wide variety of statistical and graphical techniques: Linear and nonlinear modelling, statistical tests, time series analysis, classification, clustering, etc. (Web-reference 3).
The latest version of R can be downloaded at the following webpage:
http://cran.r-project.org/bin/windows/base/ (Web-reference 4).

2.5.3 Generalised Additive Model

2.5.3.1 What is a Generalised Additive Model?

Generalised Additive Models (GAMs) extend of generalised linear models (GLMs) to incorporate non-parametric and semi-parametric functions.). In GLM, the transformed dependent variable values are predicted from (is linked to) a linear combination of predictor variables; the transformation is referred to as the link function. In addition to that, different distributions can be assumed for model residuals.
In GAMs the linear function of the predictor values is replaced by a smooth function (Wood, S.N., 2000).

2.5.3.2 The finalised Generalised Additive Model

2.5.3.3 Model development

A Generalised Additive Model (GAM) (Wood, S.N., 2006) was employed to assess the effect of daily changes in urban background SO_2 on daily mortality (all-cause, respiratory and cardiovascular) adjusting for temperature, weekday, seasonality and time trend.
Immediate and delayed effects of temperature were modelled using a natural spline with 3 DF each, and time using penalised cubic regression splines with number of DF chosen to minimize the absolute sum of the partial autocorrelation function of the model residuals. The exposure variable

used was the average of lags 1 and 2 of urban background (UB) SO_2 based on previous studies showing that the mean of lags 1 and 2 better reflects the effect of SO_2.

2.5.3.4 The Model

THE MODEL:

```
centregam2.lagmean2 <- gam( ALLM ~ SO2.UB.lagmean2 + ns(Temp, 3)

+ ns(Temp1to3, 3) + ns(Humidity, 3) + wday

+ s(time, k = nk, bs = "cr", fx = FALSE),

data=centre,na.action=na.exclude ,family=quasipoisson,  sp=centre.gam2$gam$full.sp)
```

The inclusion of other pollutants such as PM_{10} and BS into the model was not considered as data were insufficient in most centres. .

2.5.4 Inclusion of the Implementation Dates of the Directives into the Model

2.5.4.1 Creation of a dummy variable

Furthermore in a separate step of the analysis in order to include the different time points of the implementation of the Council Directives (in the model called: intervention), a dummy variable was included in the model with the number of levels according to how many stages of the fuel legislations were successfully implemented in each individual city. The exact time points of implementation as provided by the individual centres were used to construct the dummy variable, or in some cities where no information was available the time points as defined in the Directives were used.
In general the format of the dummy variable was:

```
centre$intervention <- factor ( ifelse (centre$newdate<"10/01/94",0,

ifelse(centre$newdate>="10/01/94" & centre$newdate<"10/01/96",1,

ifelse (centre$newdate>="10/01/1996" & centre$newdate<"07/01/2000",2,3))) )
```

The time period before any of the Council Directives were implemented:
*intervention = 0 (time prior to 1st October 1994)***;**
the time period between the two stages of implementation of Council Directive 93/12/EEC:
*intervention = 1 (time between to 1st October 1994 and 1st October 1996)***;**

the time period between the full implementation of Council Directive 93/12/EEC and implementation of Directive 99/32/EC:
intervention = 2 (time between to 1st October 1996 and 1st July 2000);
the time period after all stages of the two directives have been implemented:
intervention = 1 (time between to 1st October 1994 and 1st October 1996).

2.5.4.2 The model with the intervention term included

The intervention variable was incorporated into the GAM model using an interaction term between UB.SO_2 and the intervention variable.,

```
centregam2.lagmean2.intervention <- gam( ALLM ~ ns(Temp, 3) + ns(Temp1to3, 3)
+ ns(Humidity, 3) + wday + s(time, k = nk, bs = "cr", fx = FALSE)
+ intervention*SO2.UB.lagmean2, data=centre, na.action=na.exclude,
family=quasipoisson, sp=centre.gam2$gam$full.sp)
```

2.5.4.3 Calculation of the coefficients and SE for SO_2 for each intervention time period

By adding SO2.UB.lagmean2*intervention into the formula, the desired output is:
SO2.UB. lagmean2 + intervention + SO2.UB. lagmean2*intervention (3 terms), whereby the third term from the model output, the value of the 3rd term, alone is non-interpretable.

The coefficient (coef) of the mean of lag (1&2) of UB SO_2 for the time period before any implementation of the directives (intervention = 0) equals the beta-coefficient of "SO2.UB.lagmean2" directly from the GAM output. In the period of intervention = 1 (94 -96) the coefficient of UB SO_2 is calculated by addition of the coefficient of "SO2.UB.lagmean2" + coefficient of "intervention1: SO2.UB.lagmean2". And so on for the coefficients for SO_2 for the time periods of intervention = 2 and = 3.
The standard Error (SE) for the different time periods is obtained by taking the square root of the sum of (variance (coef SO2.UB.lagmean2) + variance (coef intervention* SO2.UB.lagmean2) + 2* covariance (coef SO2.UB.lagmean2 - coef intervention* SO2.UB.lagmean2)). This calculation was automated in the R script.

2.5.4.4 Calculation of effect estimates

The beta-coefficient obtained from the GAM output for each model run for each individual centre was multiplied with the factor of 1000 in order to obtain, approximately, the percentage rise in mortality associated with $10\mu gm^{-3}$ increase in UB SO_2.

In addition to that, the calculated effect estimates were multiplied with the IQR of the mean of lag 1&2 for UB SO_2 for the estimates derived from the model runs without the intervention term. For the estimates derived from the model runs with the intervention*SO_2.UB term included the specific effect estimates for each of the time periods (as described in section 4.5.3.3.1) were multiplied with the IQR for each respective time span.

2.5.4.5 Testing for the overall effect of the interaction

In order to test the overall statistical significance of the interaction an analysis of variance (ANOVA) was used. The ANOVA compares the model with and without interventions as an effect modifier on the relationship between mortality and SO_2.
The p-value obtained from the ANOVA applies to the complete interaction term for SO_2 and the implementation of the various stages of fuel legislations. This assessment is made across all centres in a meta-analysis of pooled effects across the collaborating centres.

2.5.5 Meta-Analysis

A two step hierarchical modelling approach has been applied to assess the overall impact of the implementation of the Council Directives in all Aphekom cities. In the first step, individual-city data were analysed and city-specific effect estimates were obtained as described previously. In the second step, the SO_2 effects on mortality in each city were combined in order to provide overall estimates. Variables representing potential effect modifiers were introduced in a second-stage regression models to investigate heterogeneity. Those were defined as yearly means of SO_2, PM_{10} and temperature. The combined estimate of the SO_2 effect on mortality was also used in HIA for the estimation of the attributable number of deaths.

One essential requirement in order to conduct the meta-analysis was that the centres from which the pooled results were used implemented the same number of intervention stages (i.e. the same number of implementation stages of the two assessed Council Directives).

Due to the fact that not all countries with collaborating cities have complied with the implementation dates laid down in the Council Directives due to various reasons, e.g. local derogations sought etc., the implementation dates and the number of stages implemented are not all the same for the assessed centres. Therefore the following 14 centres Athens, Bordeaux, Brussels, Dublin, Le Havre, Lille, London, Lyon, Marseille, Paris, Rome, Rouen, Stockholm and Strasbourg that implemented all three stages of the Council Directives were analysed as a group, while a separate pooled analysis of the remaining 6 centres Barcelona, Budapest, Bilbao, Ljubljana, Toulouse and Vienna that did not implement all 3 intervention steps was conducted focusing on the stage of implementation that was common to all 6 of them, namely the implementation of the 99/32/EC Council Directive.

Valencia was excluded from the meta-analysis, because the dataset was only up to 1999 and hence the implementation of the 1999 Council Directive could not be assessed.

2.5.6 Health Impact Assessment

To estimate the attributable number of deaths we need to define a baseline exposure. Let $\overline{Y}$ be the annual mean of daily mortality, which reflects the impact of mean daily SO_2 levels, $\overline{x}$. The baseline mortality incidence Y_F at the baseline PM_{10} level x0 can then be estimated as:

$$Y_F = \overline{Y} \times \left(1 - \frac{RR_{\Delta(x0-\overline{x})} - 1}{RR_{\Delta(x0-\overline{x})}} \right) \quad (1)$$

The attributable number of deaths when the SO_2 levels increase from x0 to x1 is:

$$AR = Y_F \times (RR_{\Delta(x1-x0)} - 1) \quad (2)$$

We defined as reference level, the SO_2 average before the first intervention, and calculated attributable deaths for each intervention period from this point.

A simplified excel file for HIA can be downloaded at: www.apkekom.org.

3.1 Conclusion

In these guidelines we detailed the statistical analyses conducted in Aphekom to achieve WP6 objective "to investigate the impact of the implementation of the EU legislations reducing the sulphur content of fuels in the collaborating Aphekom cities".

If the methods described here appear useful for other studies, they may need adaptation. And for instance, as mentioned in the introduction, if the study is conducted only for one city, the steps outlined for the conduction of a meta-analysis of pooled results will not be applicable.

In developing these guidelines, it is clear that there is no "one size fits all" approach to making a guideline for other researchers, but there are some clear lessons that others can take from this work.

The more data (cities and length of data sets) the more confidence one can have in the statistical analysis. Obviously more cities with a study will provide more statistical power, and allow for a meta-analysis.

Where possible some areas where no intervention has occurred (control areas) will be of assistance in any model.

It is desirable that a number of modelling approaches (techniques) be used; consistency between a number of different methods again gives added confidence in the results.
In any case, because the analyses performed here require statistical expertise, we strongly recommend involving an expert in statistics when planning a study to investigate the environmental and health impact of implementing a preventive measure.

The more information one has on the monitoring sites, and local conditions the better, as this will allow one understand the local issues. Therefore comparison/consistency between different monitoring sites within the area under consideration should be investigated, and any anomalies explained.

If hourly data is available for monitoring sites, this should be investigated for a number of pollutants as it can help understand the local sources and trends, similarly if one conducts a “weekday” analysis.

Meteorological data is extremely important and should be relevant and appropriate to the locations being studied.

In relation to heath data, quite often there can be significant long term trends which make it difficult to detect health effects from the intervention under investigation. With that said it is extremely important that in any analysis these long term trends are accounted for appropriately in any model.

4.1. References

Barrart B, Atkinson RW, Anderson HR, Beevers S, Kelly F, Mudway I, Wilkinson P. (2007) Investigation into the use of the CUSUM technique in identifying changes in mean air pollution levels following introduction of a traffic management scheme. Atmospheric Environment 41 (2007) 1784–1791

Henschel S, Atkinson R, Zeka A, Le Tertre A, Ananlitis A, Katsouyanni K, Chanel O, Pascal M, Forsberg B, Medina S, Goodman PG (2012 *IN PRESS*) A literature review: Air pollution interventions and their impact on public health. International Journal of Public Health, DOI: 10.1007/s00038-012-0369-6

Lucas JM (1982) Combined Shewhart–CUSUM quality control schemes. Journal of Quality Control 14, 51–59

Lucas JM, Crosier RB (1982) Fast initial response for CUSUM quality control schemes: Give your CUSUM ahead start. Technometrics 24, 199–205

Page ES (1954) Continuous inspection scheme. Biometrika 41, 100–115

Peters A, Breitner S, Cyrys J, Stölzel M, Pitz M, Wölke G, Heinrich J, Kreyling W, Küchenhoff H, Wichmann H-E (2009) The Influence of Improved Air Quality on Mortality Risks in Erfurt, Germany. *Health Effects Institute Research Report* **137**, Health Effects Institute, Boston, MA

Pope C.A. III (1989) Respiratory Disease Associated with Community Air Pollution and a Steel Mill, Utah Valley. *American Journal of Public Health* **79** (5), 623 – 628

Pope C.A. III, Schwartz J, Ransom MR (1992) Daily Mortality and PM_{10} Pollution in Utah Valley. *Archives of Environmental Health* **47** (3), 211-217

Pope C.A.III (Health Effects Institute, 2010) Appendix C. Accountability Studies of Air Pollution and Human Health: Where Are We Now and Where Does the Research Go Next?. Proceedings of an HEI Workshop on Further Research to Assess the Health Impacts of Actions Taken to Improve Air Quality. Communication 15. Health Effects Institute, Boston, MA. Accessed at the 21st Feb 2011 via: http://pubs.healtheffects.org/getfile.php?u=584

Rossi G, Lampugnani L, Marchi M (1999) An approximate CUSUM procedure for surveillance of health events. Statistics in Medicine 18, 2111–2122

Ryan TP (2000) Statistical Methods for Quality Improvement, second ed. Wiley, New York

Suguri D, Ranft U, Schikowski T, Krämer U (2006) The Influence of Large-Scale Airborne Particle Decline and Traffic-Related Exposure on Children's Lung Function. *Environmental Health Perspectives* **114**,282–288

Web-reference 1: www.nature.com/nrc/journal/v2/n9/glossary/nrc886_glossary.html (8th August 2009)

Web-reference 2: http://www.cdc.gov/nchs/icd.htm (30th March 2011)

Web-reference 3: http://cran.r-project.org/ (3rd November 2010)

Web-reference 4: http://cran.r-project.org/bin/windows/base/ (11th April 2011)

Wood SN (2000) Modelling and smoothing parameter estimation with multiple quadratic penalties. *JOURNAL OF THE ROYAL STATISTICAL SOCIETY SERIES B-STATISTICAL METHODOLOGY* **62**, 413-428