INTARESE Work Package 1.5: Cross-cutting issues in Risk Assessment

Susceptibility and Integrated Assessment of Health Risks

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Preface

The issue of susceptibility has been developed in the framework of INTARESE sub-project 1 (SP-1) that is focused on the methodology for integrated risk assessment. This manuscript has been planned as a distinct report of the work package (WP 1.5) dealing with the cross – cutting issues in the process of risk assessment, i.e. uncertainty, multiple exposure, susceptibility, and environmental justice. The cross-cutting nature of these issues may be attributed to all the sets of analytical techniques of the assessment chain. In more specific terms, the issues should be considered in the developments of methods to link sources to exposure (WP 1.2), methods to link exposure to health outcome (WP 1.3), and methods to characterize the resulting risks and impacts (WP 1.4). In any case, they belong to the more complex framework of INTARESE aimed at addressing the scientific problems affecting the risk assessment process.

Introduction

In the past years, some individual characteristics have been frequently reported in the scientific literature as factors that increase the probability of health effects attributable to different environmental exposures (i.e. susceptibility). There are several examples in the field of air pollution (Katsouyanni et al. 2001; Zeka et al. 2006), high temperature-related mortality (Stafoggia et al, 2006), and some factors have been suggested in the area of pesticides exposure (Giannandrea et al, 2008), radon in homes (Darby S et al, 2005), and arsenic in drinking water (Goering et al., 1999). Although some factors are clearly inherited (e.g. gender) and are related to the genetic individual make up (e.g. detoxification ability), more often we are dealing with acquired susceptibility such as age (children and the elderly), socio-economic status (people of lower socioeconomic status), pre-existing morbidity (e.g. respiratory and cardiovascular diseases, diabetes) and specific treatment (e.g. statins).

There are several possible reasons why susceptibility is becoming more and more recognized in the epidemiologic literature and certainly the availability of new epidemiological methods to analyse individual effect modifiers of the relationship between environmental exposures and health effects, e.g. the case-crossover design (Maclure, 1991) has played an important role. In addition, several large data sets are now accessible from multicentre studies or large cohorts (Pope et al, 2002; Beelen et al, 2008; Park et al, 2008; Krewski et al, 2009; O'Neil et al, 2009). Finally, new developments are available to model and to detect non linearity of the exposure-response relationship (Olin et al. 1995; Abrahamowicz et al, 2003; Samoli et al, 2005; Cheng et al, 2006). The new different approaches have been used to analyse the impact of both short-term (Goldberg, 2005) and the long – term effects (Brunekreef, 2003; Krewski et al, 2009) of air pollution in susceptible groups.

Overall, the issue of susceptibility is emerging in the health field and it has important implications for health impact assessment.

Why assess susceptibility?

The occurrence of a disease in a population depends on many individual and environmental factors. There is only a theoretical possibility of predicting in a deterministic way which individuals will develop the disease, if one was only able to know all the variables involved. However, adoption of the probabilistic model in public health reflects the need to "average out" some unknown individual characteristics that ultimately determine the occurrence of individual cases. In other words, a first level of susceptibility (who gets the disease within a homogeneous population) is incorporated and effectively removed by the probabilistic model, where each individual in the population has the same *probability* of developing the disease over a given time period. Such probabilities or rates also estimate the average health effect of an environmental exposure at a population level and provide an adequate picture of the situation when the population is homogeneous or when the groups of otherwise vulnerable individuals within the population are numerically limited. In a large population the average effect measure may be affected only to a small extent even when sub-groups have a markedly different susceptibility, as it may happens for children or ethnic minorities. On the other hand, a relevant change in the average effect may arise because of an important shift in the distribution that increases the proportion of seriously affected individuals within a population. (AIRNET, 2003)

Therefore, the first need of the risk assessors is to detect susceptible groups in a population, to estimate the size of these susceptible groups, and to assess the influence they have on the impact measures in a population.

A good example of the problem can be found in the results of multicity studies on air pollution where some factors measured at individual level were found to be effect modifiers of the particulate matter (PM) mortality association (Zeka et al, 2006; Forastiere et al, 2008). Different coefficients of PM_{10}-mortality relationship were found by gender and age. . In the American study (Zeka et al, 2006), pre-existing diabetes modified the effect of PM_{10} for respiratory and stroke mortality.

Increased effects has been reported also in specific subgroups of people as due not to their individual characteristics, but to higher levels of long term exposure. Those living in areas where the relevant pollution levels is high (e.g. near power plants, waste incinerators or in dense traffic areas) are considered as "population-at-risk". The case is even more extreme when the exposure distribution is markedly skewed with the majority of people is virtually unexposed but only a small group receive the exposure (e.g. asbestos, radiation, chemicals).

There is an additional condition conferring susceptibility, namely when the increased susceptibility is not due to personal characteristics, nor to increased exposure levels to the putative toxicant, but is due to concurrent exposure to some other toxicants that increase the probability of an health effects. This is a matter linked to the issue of multiple exposures, but it is also referred to susceptibility when an exposure factor is hypothesised to increase the probability of a health effect to other concurrent exposures. Good examples for this situation are those of exposure to radon in dwelling and smoking (Darby et al, 2005), air pollution and smoking (Wong et al. 2007) or air pollution and noise effects on ischemic heart disease (Schwela et al. 2005), or air pollution and chronic lead exposure (Park et al, 2008).

So, why to assess susceptibility? What are the reasons to target different groups of susceptible people? From a research point of view, this is clearly motivated by the need to improve the study of the causal relationship between an exposure and the health outcomes. However, from an impact assessment point of view the final aim is to gather correct information about the importance of susceptible groups and later to identify adequate risk management strategies. In fact, the nature and the size of susceptible groups in a population may potentially affect the impact that policy interventions have in preventing the health effects of the environmental exposures, overshadowing the positive impact of an intervention. On the other hand, ethic problems arise specially when the

susceptible groups are involuntary exposed, such as children. Though they do not limit the preventing impact of interventions in the general population, specific indications should be suggested for the threshold value of exposure.

What is susceptibility?

Several attempts have been made to define susceptibility. The AIRNET (2003) document on health impact assessment defines susceptibility as the presence of a population subgroup that may be affected to greater extent than general population following an environmental exposure and/or the presence of highly exposed individuals who are expected to have more serious health effect than general population due to the higher levels of exposure (AIRNET, 2003).

A WHO working group (WHO Europe CAFE 2004) defined susceptibility (innate or acquired) as the likelihood of producing a significantly larger-than-average response to a specified exposure to air pollutants; while vulnerability denotes the likelihood of being unusually severely affected by air pollutants either as a result of susceptibility or as a result of a greater-than-average exposure. The specific definition adopted from the WHO working group are reported in the box.

BOX
WHO working Group (2004): Definition of Susceptibility and Vulnerability

"The terms sensitivity, susceptibility and vulnerability are used, sometimes interchangeably and incorrectly, to describe a greater than expected response of an individual or group of individuals to air pollutants. We use the terms susceptibility and vulnerability as defined below. We have not used the term sensitivity.

Susceptibility: The likelihood of producing a significantly larger-than-average response to a specified exposure to air pollutants.

Vulnerability: The likelihood of being unusually severely affected by air pollutants either as a result of susceptibility to the effects of these substances or as a result of a greater than average exposure. "Susceptibility" is thus seen as a subset of "vulnerability".

Susceptibility

Susceptibility can be subdivided into innate and acquired susceptibility. Innate susceptibility may be due to genetic predisposition or to incomplete development of normal (adult) physiological functions. A young child may be susceptible to a given pollutant because detoxification processes are not yet fully developed. Such susceptibility is transient and disappears with age and growth. Acquired susceptibility may be due to disease, socioeconomic status or age. A number of mechanisms are known to play a part and are discussed below. It should be noted, however, that "socioeconomic status" is not a precise identification of a causal factor.

Vulnerability

In addition to the susceptible groups outlined above some individuals are vulnerable to the effects of air pollutants as a result of their greater than average exposure to these substances. Such exposure may be due to living near busy roads or spending long hours outdoors each day. It is important to distinguish clearly between vulnerability due to increased exposure and vulnerability due to innate or acquired susceptibility".

Following the definitions reported above and the given practical examples, we may distinguish different groups of the population at higher probability of harmful effects due to exposure to an environmental factor:

- those with higher exposure to an agent, who may be more affected as a result of their higher than average exposure;
- those with genetic predisposition;
- those who develop an increased susceptibility because of aging, illness (such as cardio-respiratory disease or diabetes);
- those living in settings with multiple social risk factors such as lifestyle, social context, living conditions, lack of access to protective resources,
- those with concomitant exposure to other toxic agents that increase the probability of their health effects.

Some confusion arises because of a different cultural background of these terms that may be interesting to recall. In everyday language, susceptibility has a positive value since it suggests the ability to answer the external influence and it is usually referred to the individual. In the medical language susceptibility is a term used to mean as well the ability of a person to answer the external influence developing a too strong reaction inducing often a disease. The two medical fields most often interested in dealing with susceptibility are infectious diseases and occupational medicine.

- In infectious diseases, susceptibility includes the ability to develop an inflammatory reaction against the infections (Anderson, 1992).
- In occupational medicine, susceptibility has been evaluated in the field of biologic markers to describe the biological relationship between exposure and disease development and to estimate the damage reversibility when decreasing or stopping the exposure (Schulte, 1991).

The term “vulnerability” comes from environmental sciences. It is a characteristic of the complex systems, such as the ecosystems, and it is defined as weakness to contrast degradation or damage from adverse factors or influences, due to an impairment of the system adaptation or to a reduced functional reserve [US – EPA, 2006]. This definition maintains the negative value it has in the current language.

Also, vulnerability has been used in psychiatry and gerontology to denote an impaired capacity of the body to respond to stressors, in older or mentally ill people. The term has being replaced by “frailty”, a more complex conceptualisation involving physical, cognitive/psychological, nutritional

and social factors (Paganelli et al, 2006; Levers et al, 2006).

On the basis of these conceptual definitions,, the term susceptibility should be reserved to those conditions that cause a higher probability of damage in subgroups of population exposed to defined levels of pollutants which causes less severe effects (or even no effect) in other groups. If we apply this definition to the above reported groups at higher probability of harmful effects, the term susceptibility should be used only for those with genetic predisposition (innate susceptibility), those who develop an increased susceptibility because of aging or illness (acquired susceptibility) and those with concomitant exposure to other toxic agents (susceptibility due to concomitant exposures). Those exposed to higher levels of pollutants or with multiple social risk factors should be defined vulnerable.

How to assess susceptibility?

The methods usually employed to evaluate the presence of susceptibility in epidemiologic studies include the classical approaches to test *the heterogeneity of response,* that is evaluation of effect modification**.** Testing the heterogeneity of the effect of an exposure in our contest means to analyse if specific population sub-groups, having an individual characteristic or being chronically exposed to higher values of the relevant exposure or being exposed to another specific factor, present effect measures heterogeneous with respect to other comparable groups in the population

The evaluation of effect modification is usually carried out with a test for interaction or by means of a stratified analysis. The test for interaction is generally performed adding an interaction term between the exposure and the hypothesised effect modifier and evaluating a potential departure from the postulated underlying model (additive or multiplicative). The stratification analysis estimates the effect measure in each of the groups under study and evaluates whether they differ between the strata. Some issues need to be considered :

1. The debate in the epidemiological literature about the biological and mathematical model of interaction underlines the problem of interpretation of the interaction term coefficients. The absence of statistical interaction in a multiplicative model implies risk additivity; as consequence (though a multiplicative model is not always explicitly hypothesised) the risk ratio (or rate ratio) homogeneity is often interpreted as indicating absence of biological interaction. However we would rarely expect the biological factors to act independently in all people, even if they act at different stages of the disease process (Greenland and Rothman 1998; Pearce, 1989; Knol, 2007). Thus risk ratio homogeneity has to be interpreted as some type of biological interaction; this means that the regression coefficient of the product term

should be interpreted as departure from additivity instead of from multiplicativity and the two biological factors as two causes both needed to produce the effect. Methodological solutions to turn in practice the additivity hypothesis have been suggested [Rothmans, 1986; Hosmer and Lemeshow, 1992]

2. Up to now, there are no rigid criteria for accepting or rejecting the homogeneity hypothesis in the stratification analysis, although statistical tests are available. For example some authors consider effect modification in a stratified analysis when the estimate is increased (or is reduced) by a factor of two or more regardless of statistical significance (Zeka et al, 2006). In the APHEA2 study (Atkinson et al, 2001), effect modifiers were defined as the factors that reduce the chisquared statistic by at least 40%. Specific criteria for a "suggested effect modification" have been recently proposed [Stafoggia et al, 2009; Stafoggia, et a, 2010] combining in the same definition an effect size larger than twofold in a specific subgroup in comparison to a reference group and a p-value of the relative effect modification in a 0.05 - 0.20 range. These criteria influence the definition of susceptible groups and affect the comparison between the studies.
3. Apparent absence of interaction may result from misclassification of the susceptibility characteristics, when susceptible groups are loosely defined (e.g., when distance from the pollution source is used), or when presence of a chronic illnesses is defined using sub optimal or not reliable diagnostic criteria. On the other hand, the statistical power to detect interaction is usually limited and lack of interaction may be simply due to insufficient power.
4. In some cases, it is the form of exposure-response curve that may differ in different subgroups. In many cases the assumption of linearity underlying the exposure-response curve should be adequately evaluated in specific subgroups. A linear relationship may be observed only after a threshold is reached: consider for example that the PM_{10} related mortality from deaths due to causes other than cardio-respiratory diseases have a threshold at 50 micrograms /m3 of PM10 (Daniels et al, 2000) or that the excess risk of leukaemia in children exposed to electromagnetic fields is evident only above the threshold of 0.4 microTeslas (Maslanyi, 2007).

Examples from the air pollution literature

Airborne particular matter (PM) is one of the most studied environmental factors in the last decade and its relationship with morbidity and mortality is well established. In order to provide a practical example of how to deal with susceptibility, we review some cases from the literature where the effect of PM was found to be modified in relation with different health outcomes. It is obvious that

for each specific exposure-outcome association to be used in the assessment a systematic search of the literature of the studied susceptibility factors should be performed.

Living along busy roads: Several studies have indicated that people living along busy roads receive a greater exposure to traffic-related pollutants and a range of health effects have been described in both children and adults (HEI, 2009). These are example of social vulnerability, but even the hypothesis of susceptibility has been supported by observing that short term effects on mortality of people living along high traffic roads were stronger than for other people. This observation was based on analyses of the air pollution effects stratified by spatial setting of sub-groups consistent with different long-term exposure. (Roemer and Wijnen, 2001)

Low socioeconomic status: several studies have shown that people of low socioeconomic status tend to live along more busy roads or close to industries and are more exposed to air pollution (O'Neill et al, 2003; Jerret, 2009). Poverty has been associated with increase morbidity and mortality and confers an high probability of harmful effects (Forastiere et al. 2006). Therefore, control for socio-economic status to remove confounding, as traditionally applied in epidemiological studies, may mask the occurrence of an effect modification. Statistical power permitting, interaction should be tested when such data are available.

Genetics: particulate matter has been associated with systemic inflammation indicated by blood markers. Susceptibility to ambient particulate matter may be partly genetically determined by polymorphisms that alter early physiological responses such as transcription of fibrinogen (Peters et al, 2009) or interleukin-6 expression (Ljungman et al, 2009).

Children: A strong effect on mortality in the first year of life has been detected (Schwartz, 2004) and high PM-related hospitalisations for asthma and bronchitis (Pope, 1989) has been detected in childhood.

Elderly: People older than 64 year show an increase in daily mortality higher than general population (Aga et al, 2003; Ostro et al, 2006, Forastiere et al, 2008) and Zeka (IJE, 2006) showed higher levels of inflammation biological markers in 75+ year-old people.

Cardio-vascular diseases: those with a previous heart failure showed a PM-related daily mortality up to 4.1 times higher than general population (Kwon et al, 2000); those with a previous acute myocardial infarction were hospitalised more frequently than general population during high air pollution days (von Klot et al, 2005).

Chronic respiratory diseases: COPD patients had a PM-related decrease in FVC and FEV1 stronger than healthy people (Lagorio et al, 2006), a higher access to hospital emergency departments for

heart failure and cerebro-vascular diseases (Peel et al, 2006) and a higher hospitalisation rate for heart failure (Zanobetti et al, 2000).

Diabetes: immediately after a sudden increase of PM, people with diabetes showed a higher frequency of hospitalisation episodes for cardiovascular diseases (Zanobetti & Schwartz, 2002) and an increased access to emergency departments for arrhythmia and cerebrovascular diseases (Peel et al, 2006) when compared with people without diabetes.

Exposure to other pollutants: the APHEA-2 study did indicate that the effects of PM10 on mortality were stronger in areas with higher NO2 levels (Katsouyanni et al, 2001) whereas the effects on hospital admissions for respiratory diseases were stronger with higher ozone level (Atkinson et al, 2001).

Impact of susceptibility and vulnerability in the risk assessment process

All the steps of the integrated assessment chain may be affected by the presence of susceptible/vulnerable groups in the study population.

In particular, one of the first steps in impact assessment is to *define the size of the population exposed, the population characteristics and the exposure levels*. In the first pass of the INTARESE Waste case study, an approach for the health impact assessment of landfills and incinerators has been applied in Italy, England and Slovakia (Forastiere et al, 2009). A total of 49 (Italy), 2 (Slovakia), and 11 (England) incinerators were operating in 2001 while the landfills were 118, 121 and 232, respectively. The study population consisted of residents living within 3 km of an incinerator and 2 km of a landfill. A direct relationship was found between social class and residence near waste facilities in Italy and England and an inverse relationship was found in Slovakia. The social class difference was particularly high for incinerators in England where 55.4% of population living within 3 km from the plant belong to the most deprived social class and only 3% to the most affluent class. These results reflect the fact that the property values decrease due to the presence of pollutant sources, and it is likely that lower economic prices attract inhabitants of lower SES. It should be noted that not only people of lower SES were more represented close to the plants, but also the PM_{10} and NO_2 exposure levels predicted with dispersion models within the area of 3 km were higher among poorer people in both England and Italy than in more affluent people indicating that the gradient of exposure is linked with individual characteristic of social vulnerability.

In a context where the sources of pollution are more than one, source apportionment techniques are increasingly used to identify the source of pollution mainly involved in causing the health effect.

These methods are based on assessing effects of the different components of particulate matter, which in turn, allow the identification of the source of pollution. For example, in American studies no effects were observed for crustal PM_{10} while important effects were detected for exposure to traffic-related PM_{10} and, to a lesser extent, to PM_{10} from coal combustion (Ostro et al, 2006; Seagreave, 2006; Laden et al, 2000). In this case, if the components of PM related to the specific sources have an heterogeneous spatial distribution and, at the same time, there is a different spatial distribution of high risk groups due to individual characteristics, the ability to assess the effect due to the components of PM may be hampered.

In order to *estimate the impact of the exposure levels on the health outcomes,* specific exposure-response relationships (or dose-response functions) should be defined. It is obvious here that one has to apply the specific dose-response function for the sensitive subgroup when there is evidence of effect modification. Even in cases when there is no evidence of effect modification, may be worth to calculate the effect for the different subgroups when they have different background rates (see for example radon, smoking and lung cancer). In the INTARESE Transport case study, the Rome and London policies involved zoning systems to prohibit the entry of old high-emission cars in the central districts of the city were evaluated. The policies in Rome and London resulted in PM_{10} and NO_2 emission decreases of about 30% (at street level) and 10% (city average level), respectively. At the city area level modelled changes in concentration of NO_2 and PM_{10} related to the policy interventions were modest (< 1 μg/m3). Predicted changes were larger for NO_2 than for PM_{10}. Consistent with the modest change in air pollution concentrations, the policies in Rome and London resulted in small gains in life expectancy and a small reduction in the number of hospital admissions, when expressed at the city area level. In Rome the decrease in NO_2 concentration was slightly larger in the lowest socio-economic class compared to the highest socio-economic class. Because baseline mortality rates were higher in the lowest socio-economic class, the difference in gain in life expectancy was more substantial between socio-economic classes. These findings allowed to conclude that the policy in Rome made a modest contribution towards reducing differences in health status between different socioeconomic groups.

The final possibility is the availability of information regarding the size of the susceptible groups, the specific disease background rates of these groups, and the specific exposure-response functions to be applied to these subgroups. In the Transport case study for Rome, different coefficients for long term PM10 exposure by educational level (as a proxy of socioeconomic status) are applied to evaluate the years of life gained for the effect of the traffic policy.

Concluding remarks

Once the results of the health impact assessment are ready, at least two questions arise with respect to the development of policy decisions: what kind of strategies should be implemented to address the problem of susceptible groups: an intervention for the entire population or an intervention only for the most sensitive individuals? are adequate technical solutions available to prevent the high exposure/high burden at the population level?

Thus when the harmful effects in subgroups are due to higher levels of exposure, reasons of environmental equity suggests to control the emissions of specific identifiable sources or to.move vulnerable groups from polluted areas. On the other hand, the presence of susceptibility suggests to use the precautionary principle to protect the weak groups in the population such as children or adopting measures to avoid exposure for susceptible groups, such as elderly or ill people. If the precautionary principle would be inspiring the policy intervention, a population strategy to face the problem of susceptible groups would lead to define pollution standards low enough to take into account the greater sensitivity of susceptible groups. In contrast, the adoption of the high-risk strategy would lead to preventive actions confined to high-risk groups, more sensitive to noxious exposure because of individual problems. These measures may be aimed at controlling the level of exposure for these specific individuals (for example air conditioning against high temperature and air pollution) and to protect against the damaging effect of such exposures (for example antioxidant supplementation to prevent the oxidative stress from air pollution). The weaknesses of the high-risk preventive strategy have been already underlined in the classical work of Geoffrey Rose, because of the poor ability to detect in advance the potentially susceptible individuals in the future and the small contribution to overall control of a disease (Rose, 1992). This point is of relevant interest when the susceptibility factor is also, at the same time, a possible direct effect of the noxious exposure, such as in the case of particulate matter (the exposure) leading to atherosclerosis (the susceptibility factor and the intermediate health effect) and myocardial infarction (the final health effect).

Whatever is the strategy to be adopted, the problem of the availability of adequate and acceptable technical solutions remains. In other words, even in presence of highly reliable methods to detect sensitive subgroups, the question remains, namely: do we have efficacious and affordable solutions to protect them? It is obvious that the risk assessor should ask the stakeholders to promote research and development of technical solutions in the policy risk management.

References

Abrahamowicz M, Schopflocher T, Leffondré K, du Berger R, Krewski D. Flexible modeling of exposure-response relationship between long-term average levels of particulate air pollution and mortality in the American Cancer Society study. J Toxicol Environ Health A. 2003 Aug 22-Oct 10;66(16-19):1625-54.

Aga E, Samoli E, Touloumi G et al. Short-term effects of ambient particles on mortalità in the elderly: results from 28 cities in the APHEA2 project. Eur Respir J 2003; Suppl 40: 28s-33s.

Anderson RM May RM. Infectious diseases of humans: dynamics and control. Oxford, New York, Tokio: Oxford University Press; 1992. (Oxford Science Publications)

Atkinson RW, Anderson HR, Sunyer J, Ayres J, Baccini M, Vonk JM, Boumghar A, Forastiere F, Forsberg B, Touloumi G, Schwartz J, Katsouyanni K. Acute effects of particulate air pollution on respiratory admissions: results from APHEA 2 project. Air Pollution and Health: a European Approach. Am J Respir Crit Care Med. 2001 Nov 15;164(10 Pt 1):1860-6.

AIRNET – health impact assessment report- 2003. (http://airnet.iras.uu.nl/).

Beelen R, Hoek G, van den Brandt PA, Goldbohm RA, Fischer P, Schouten LJ, Jerrett M, Hughes E, Armstrong B, Brunekreef B. Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study). Environ Health Perspect. 2008 Feb;116(2):196-202.

Brunekreef B. Design of cohort studies for air pollution health effect. J toxicol environ health, Part A, 2003; 66: 1723-1729.

Cheng H, Aylward L, Beall C, Starr TB, Brunet RC, Carrier G, Delzell E. TCDD exposure-response analysis and risk assessment. Risk Anal. 2006 Aug;26(4):1059-71.

Daniels MJ, Dominici F, Samet JM, Zeger SL. Estimating particular matter-mortality dose-response curves and threshold levels: an analysis of daily time-series for the 20 largest US cities. Am J Epidemiol 2000; 152: 397-406.

Darby S, Hill D, Auvinen A, Barros-Dios JM,et al. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. BMJ. 2005 Jan 29;330(7485):223. Epub 2004 Dec 21.

Environmental Protection Agency – Regional vulnerability assessment, glossary, march 2006

http://www.epa.gov/reva/glossary.htm

Forastiere F, Stafoggia M, Tasco C et al. Socioeconomic status, particulate air pollution, and daily mortality: differential exposure or differential susceptibility. Am J Ind. Med 2006; 50: 208-216.

Forastiere F, Stafoggia M, Berti G, Bisanti L, Cernigliaro A, Chiusolo M, Mallone S, Miglio R, Pandolfi P, Rognoni M, Serinelli M, Tessari R, Vigotti M, Perucci CA; SISTI Group. Particulate matter and daily mortality: a case-crossover analysis of individual effect modifiers. Epidemiology. 2008 Jul;19(4):571-80.

Forastiere F, Badaloni C, de Hoogh C, et al. Health impact assessment of waste management facilities in three European countries. ISEE; 2009; Dublin, 26 August 2009; 2009.

Giannandrea F, Settimi L, Figà-Talamanca I. The use of personal protective equipment in pregnant greenhouse workers. Occup Med. 2008; 58: 52-57. Epub 2007

Goering PL. Aposhian HV, Marc MJ, Cebriàn M, Beck BD, Waalkes MP. The enigma of carcinogenesis: role of metabolism. Toxicol Sciences 1999; 49: 5-14

Goldberg MS, Burnett RT. A new longitudinal design for identifying subgroups of the population who are susceptible to the short term effects of ambient air pollution. J toxicol environ health, Part A, 2005; 68: 1111-1125.

Greenland S, Rothman KJ. Concept of interaction. In Rothman KJ, Greenland S Modern epidemiology Philadelphia 1998 Lippincott-Raven Publishers, pp 329-342.

Health Effects Institute (HEI). Traffic-Related Air Pollution: A Critical Review of the Literature on Emissions, Exposure, and Health Effects (Preprint). 2009.
http://pubs.healtheffects.org/view.php?id=306

Katsouyanni K, Touloumi G, Samoli E et al. Confounding and Effect Modification in the Short-Term Effects of Ambient Particles on Total Mortality: Results from 29 European Cities within the APHEA2 Project. Epidemiol 2001; 12: 521–531.

Kim JJ, Smorodinsky S, Lipsett M, Singer BC, Hodgson AT, Ostro B. Traffic-related air pollution near busy roads. The east bay children's respiratory health study. Am J Respir Crit Care Med 2004; 170: S20-S26.

Knol M, van der Tweel I, Grobbee DE, Numans ME, Geerlings MI. Estimating interaction on an additive scale between continuous determinants in a logistic regression model. Int J Epidemiol 2007; 36: 1111-1118.

Krewski D, Jerrett M, Burnett RT, Ma R, Hughes E, Shi Y, Turner MC, Pope CA 3rd, Thurston G, Calle EE, Thun MJ, Beckerman B, DeLuca P, Finkelstein N, Ito K, Moore DK, Newbold KB, Ramsay T, Ross Z, Shin H, Tempalski B. Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality. Res Rep Health Eff Inst. 2009 May;(140):5-114; discussion 115-36.

Kwon H-J, Cho S-H, Nyberg F, Pershagen G. Effects of ambient air pollution on daily mortality in a cohort of patients with congestive heart failure Epidemiology, 2001; 12: 413-419.

Jerrett M. Global geographies of injustice in traffic-related air pollution exposure. Epidemiology. 2009 Mar;20(2):231-3.

Laden F, Neas LM, Dockery DW, Schartz J. Association of fine particulate matter from different sources with daily mortality in six US cities. Environ Health Perspect 2000; 108: 941-947.

Lagorio S, Forastiere F, Pistelli R et al. Air pollution and lung function among susceptible adult subjects: a panel study. Environ Health, 2006 5: 11 doi:10.1186/1476-069X-5-11.

Levers MJ, Estabrooks CA, Ross Kerr JC. Factors contributing to frailty: literature review. J Adv Nurs 2006; 56: 282-291.

Ljungman P, Bellander T, Schneider A, Breitner S, Forastiere F, Hampel R, Illig T, Jacquemin B, Katsouyanni K, von Klot S, Koenig W, Lanki T, Nyberg F, Pekkanen J, Pistelli R, Pitsavos C, Rosenqvist M, Sunyer J, Peters A. Modification of the interleukin-6 response to air pollution by interleukin-6 and fibrinogen polymorphisms. Environ Health Perspect. 2009 Sep;117(9):1373-9.

Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. Am J Epidemiol 1991; 133: 144 – 153.

Maslanyi MP, Mee TJ, Renew DC et al. Investigation of the sources of residential power frequency magnetic field exposure in the UK childhood cancer study. J Radiol Prot 2007; 27: 41-58.

Olin S, Farland W, Park C et al. Low dose extrapolation of cancer risks: issues and perspectives. Washington DC, 1995 (ILSI Press)

O'Neill MS, Jerrett M, Kawachi I, Levy JI, Cohen AJ, Gouveia N,et al. Health, wealth, and air pollution: advancing theory and methods.Environ Health Perspect 2003; 111:1861-70.

O'Neill MS, Ebi KL. Temperature extremes and health: impacts of climate variability and change in the United States. J Occup Environ Med. 2009 Jan;51(1):13-25.

Ostro B, Broadwin R, Green S, Feng W-Y, Lipsett M. Fine particulate air pollution and mortality in nine California counties: results from CALFINE. Environ Health Perspect. 2006 Jan;114(1):29-33.

Ostro B, Feng W-Y, Broadwin R, Green S, Lipsett M. The effects of components of fine particulate air pollution on mortality in California: results from CALFINE. Environ Health Perspect 2007; 115: 13 - 19

Paganelli R, Di Iorio A, Cherubini A et al. Frailty of older age: the role of the endocrine-immune interaction. Curr Pharm Des 2006; 12: 3147-3159.

Park SK, O'Neill MS, Vokonas PS, Sparrow D, Wright RO, Coull B, Nie H, Hu H, Schwartz J. Air pollution and heart rate variability: effect modification by chronic lead exposure. Epidemiology. 2008 Jan;19(1):111-20.

Pearce N. Analytical implication of epidemiological concepts of interaction. Int J Epidemiol 1989; 18: 976-980.

Peters A, Greven S, Heid IM, Baldari F, Breitner S, Bellander T, Chrysohoou C, Illig T, Jacquemin B, Koenig W, Lanki T, Nyberg F, Pekkanen J, Pistelli R, Rückerl R, Stefanadis C, Schneider A, Sunyer J, Wichmann HE; AIRGENE Study Group. Fibrinogen genes modify the fibrinogen response to ambient particulate matter. Am J Respir Crit Care Med. 2009 Mar 15;179(6):484-91.

Peel J, Metzger KB, Klein M, Flanders WD, Mulholland JA, Tolbert PE. Ambient air pollution and cardiovascular emergency department visits in potentially sensitive groups. Am J Epidemiol 2007; 165: 625-633.

Pope CA III. Respiratory disease associated with community air pollution and a steel mill, Utah Valley. Am J Public Health 1989; 79: 623-628.

Pope CA 3rd, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, Thurston GD. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA. 2002

Mar 6;287(9):1132-41.

Roemer WH, van Wijnen JH. Daily mortality and air pollution along busy streets in Amsterdam, 1987-1998. Epidemiology 2001; 12: 649-653.

Rose G. Sick individual and sick populations. Int J Epidemiol 1985; 14: 32-38.

Rose G. The strategy of preventive medicine. Oxford, New York, Tokio: Oxford University Press; 1992. (Oxford Science Publications)

Samoli E, Analitis A, Touloumi G et al. Estimating the exposure-response relationship between particulate matter and mortality within the APHEA multicity project. Environ Health Perspect 2005; 113: 88-95.

Samoli E, Touloumi G, Zanobetti A et al. Investigating the dose response relation between air pollution and total mortality in the APHEA-2 multicity project. Occup Environ Med 2003; 60: 977-982.

Schwela D, Kephalopoulos S, Prasher D. Confounding or aggravating factors in noise-induced health effects : Air pollutants and other stressors. Noise and Health 2005; 7: 41-50

Schwartz J, Laden F, Zanobetti A. The concentration-response relation between PM2.5 and Daily deaths. Environ Health Perspect 2002; 110: 1025-1029.

Schwartz J. Air pollution and children's health, Pediatrics 2004; 113: 1037-1043.

Schulte PA. Contribution of biological markers to occupational health. Am J Ind Med. 1991;20(4):435-46.

Seagreave JC, McDonald JD, Bedrick E et al. Lung toxicity of ambient particulate matter from Southern U.S. sites with different contributing sources: relationship between composition and effects. Environ Health Perspect 2006; 114: 1387-1393.

Stafoggia M, Forastiere F, Agostini D et al. Vulnerability to heat-related mortality: a multicity, population-based, case-crossover analysis. Epidemiol 2006; 17: 315 – 323.

Stafoggia M, Colais P, Serinelli M per il gruppo collaborativo EpiAir. I metodi di analisi statistica per la valutazione degli effetti a breve termine dell'inquinamento atmosferico nel progetto EpiAir. Epidem Prev 2009, Suppl 1

Stafoggia M, Forastiere F, Faustini A, Biggeri A, Bisanti L, Cadum E, Cernigliaro A, Mallone S, Pandolfi P, Serinelli M, Tessari R, Vigotti MA, Perucci CA, Epiair Group. Susceptibility Factors to Ozone-related Mortality – A Population-based Case-crossover Analysis. Am J Respir Crit Care Med. 2010 Mar 25 [Epub ahead of print].

Zanobetti A, Schwartz J. Cardiovascular damage by airborne particles: are diabetics more susceptible? Epidemiology 2002; 13: 588-592.

Zanobetti A, Schwartz J, Gold D. Are there sensitive subgroups for the effects of airborne particles? Environ Health Perspect 2000; 108: 841-845

Zeka A, Zanobetti A, Schwartz J. Individual level modifiers of the effects of particulate matter on daily mortality. Am J Epidemiol 2006; 163: 849-859.

Zeka A. Sullivan JR, Vokonas PS, Sparrow D, Schwartz J. Inflammatory markers and particulate air pollution: characterizing the pathway to disease. Int J Epidemiol 2006; 35: 1347-1354

Von Klot S, Peters A, Aalto P et al. Ambient air pollution is associated with increased risk of hospital cardiac readmissions of myocardial infarction survivors in five European cities. Circulation 2005; 112: 3073-3079.

WHO for Europe. Health aspect of air pollution – answer to follow-up questions from CAFE. Report on a WHO working group meeting Bonn, Germany, 15-16 January 2004.

Wong C-M, Ou C-Q, Lee N-W et al. Short-term effects of particulate air pollution on male smokers and never-smokers. Epidemiology 2007; 18: 593-598