Proceedings of the International Workshop on "*Combined Environmental Exposure: Noise, Air Pollutants and Chemicals*"

15-16 January 2007, Ispra

Editors: Stylianos Kephalopoulos, Kimmo Koistinen, Marco Paviotti, Dieter Schwela, Dimitrios Kotzias

JRC EUROPEAN COMMISSION — i*h*cp Institute for Health and Consumer Protection — European Environment Agency — World Health Organization Regional Office for Europe

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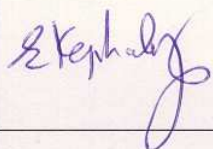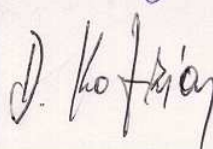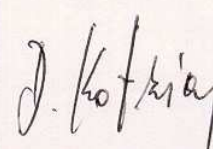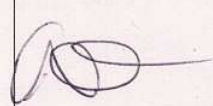Reproduction is authorised provided the source is acknowledged

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International Workshop

on

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Preface

The Joint Research Centre (JRC) of the European Commission (EC), Institute for Health & Consumer Protection (IHCP), Physical and Chemical Exposure Unit (PCE) in collaboration with the European Environment Agency (EEA), the World Health Organisation (WHO) and the CALM Network organised an exploratory workshop on **"Combined Environmental Exposure: Noise, Air Pollution and Chemicals"** in January 15-16, 2007, in Ispra (Italy).

The important issue of combined exposure to noise, air pollution and chemicals raised recently the interest of several bodies of the European Commission such as DG Environment, DG SANCO and DG Research in the context of the EC 7th Framework Programme. Therefore this issue needs to be thoroughly explored and investigated to help the EC to revise the existing standards and guidelines concerning combined exposure to noise, air pollutants and chemicals.

The health impacts of the combined exposure to noise, air pollutants, and chemicals are rarely considered in epidemiological studies. Combined exposures occur, for example, when people are exposed to road traffic where noise and air pollution co-exist. Recently, some studies have observed that the pathogenesis of allergies can be stimulated by adjuvant effects – i.e. air pollutants such as particulate matter from diesel exhaust and NO_2 as well as noise – especially during the night-time. There is also some evidence that exposure to noise and certain air pollutants could cause cardiovascular diseases. It is also observed that in the noise studies, possible effects of simultaneous exposure to solvents, asphyxiating agents or metals have not been considered, when studying the effects of noise on hearing impairment.

The effects of simultaneous exposure to noise and chemicals on the auditory system have been studied in the occupational environment since 1980's. Ototoxic (compound having a toxic effect on the structures of the ear) chemicals, however, also occur in residential indoor environments and for example in leisure time activities and during transportation in vehicles. A range of products typical in households including adhesives, biocides, glues, grease and spot removers, insulation, lacquers, liquid correction fluids, paint and paint thinners, resins, room deodorizers, rug cleaners, spray paint, varnishes and wood preservatives release ototoxic chemicals. Ototoxic organic solvents include benzene, benzyl alcohol, butyl alcohol, carbon disulphide, carbon tetrachloride, heptane, n-hexane, styrene, toluene, trichloroethylene and xylenes. Ototoxic heavy metals include arsenic, cobalt, lead, manganese, mercury and organic tin compounds. Carbon monoxide and hydrogen cyanide have also known effects on hearing impairment. The intrusion of vehicle emissions from garages and streets with heavy traffic contributes to ototoxic exposure.

There are open questions whether prevailing environmental concentrations of air pollutants and chemicals can lead to ototoxic health impacts. This workshop addressed these questions for environmental exposure to single and concomitant agents related to different health endpoints.

Objectives

The aim of the workshop was to review and discuss the existing scientific evidence whether prevailing environmental exposures to single and concomitant agents together with noise could lead to ototoxic or other health impacts. The final aim was to identify the research needs and to give recommendations for research and policy making in the EU level.

The following questions were used as a tool to meet the objectives:

1. *Which combined exposures occur, where they occur, which health endpoints occur, and what are the risks of the different pairs in occupational or non-occupational environments:*
    ➢ *noise and indoor air pollutants (environmental tobacco smoke)?*
    ➢ *noise and outdoor air pollutants (particulate matter, sulphur dioxide, nitrogen dioxide, carbon monoxide)?*
    ➢ *noise and asphyxiants (carbon monoxide, hydrogen cyanide)?*
    ➢ *noise and solvents (occupational, environmental)?*
    ➢ *noise and heavy metals (lead, mercury)?*
    ➢ *noise and pesticides?*
    ➢ *noise and variables related to housing (biological agents)?*
    ➢ *noise and vibration?*

2. *Which approaches are available to study combined exposures and which combinations should be recommended in either/both environmental and occupational environments?*

3. *Which confounding variables have to be considered in epidemiological studies of noise-induced health effects in the presence of air pollutants and other chemicals in the air?*

4. *What are the data gaps to be covered?*

5. *Which are the priority issues to be considered for future research and policy-making?*

This report describes the issue and the agenda of the Workshop and presents the results and recommendations given as an outcome of the Workshop.

Stylianos Kephalopoulos (JRC, IHCP/PCE, Italy) (*organiser*)
Dimitrios Kotzias (JRC, IHCP/PCE, Italy)
Dieter Schwela (University of York, UK) (*moderator*)
Anna Backman (European Environmental Agency, Denmark)
Rokho Kim (WHO European Centre for Environment and Health, Germany)

Workshop summary

Introduction

The Joint Research Centre (JRC) of the European Commission (EC), Institute for Health & Consumer Protection (IHCP), Physical and Chemical Exposure Unit (PCE) in collaboration with the European Environment Agency (EEA), the World Health Organisation (WHO) and the CALM Network organised the exploratory workshop on "***Combined Environmental Exposure: Noise, Air Pollution and Chemicals***". 28 experts from 12 countries in Europe and the USA participated in the workshop.

The issue of combined exposure to noise, air pollution and chemicals recently raised the interest of several bodies of the European Commission such as DG Environment, DG SANCO and DG Research in the context of the EC 7th Research Framework Programme. Therefore this issue needs to be thoroughly explored and investigated to assist the EC to revise in the future any existing standards and guidelines or institute new ones concerning combined exposure to noise, air pollutants and chemicals.

The health impacts of the combined exposure to noise, air pollutants, and chemicals are rarely considered in epidemiological studies. Combined exposures occur, for example, when people are exposed to road traffic where noise and air pollution co-exist. Recently, some studies have observed that the pathogenesis of allergies can be stimulated by adjuvant effects (i.e., air pollutants such as particulate matter from diesel exhaust and NO_2 as well as noise), especially, during the night-time. There is also some evidence that exposure to noise and certain air pollutants could cause cardiovascular diseases. It is also observed that in the environmental noise studies, possible effects of simultaneous exposure to solvents, asphyxiating agents or heavy metals need to be fully explored, when studying the effects of noise on hearing impairment and other health endpoints such as cardiovascular effects.

Objectives

The aim of the workshop was to review and discuss the existing scientific evidence whether prevailing environmental exposures to single and concomitant agents together with noise could lead to ototoxic or other health impacts. The stressors considered with noise were: ***indoor air pollutants*** (environmental tobacco smoke, VOCs), ***outdoor air pollutants*** (PM, SO2, NO2, CO), ***asphyxiants*** (CO, HCN), ***solvents*** (xylenes, styrene, toluene, benzene etc.), ***heavy metals*** (lead, mercury), ***pesticides*** (organophosphates), ***variables related to housing*** (biological agents), and ***vibration***.

The final aim was to identify the research needs and to give recommendations for research and policy making in this field in the EU level. This has been achieved through a set of questions the Workshop's participants (splitted into two working groups A and B during the seconf day of the Workshop) were asked to address and answer.

Results and conclusions

Combined environmental exposures

It was agreed that research in the future should be focused on well-established combinations (high correlations) and interactions (known effect) with the main perspective on the traffic related exposures. Further work should be focused on the area where the greatest contribution can be made and on residential, school, transit and office areas, indoors and outdoors.

Combined health endpoints

Those health endpoints which are common to noise, air pollutants, chemicals and vibration were summarised. Possible health effects were grouped into three categories: 1) **auditory effects** (speech understanding, hearing loss and tinnitus), 2) **non-auditory or physiological effects** (cardiovascular diseases, sleep disturbance and immune system dysfunctions) and 3) **cognitive or psychological effects** (cognitive function, annoyance, performance, accidents and injuries, stress and mental health or illness). Then, it was assessed whether the listed health outcomes are common for noise and other stressors.

It was discussed and agreed upon that the best knowledge exists on the health effects due to combined exposure to noise and solvents or heavy metals in occupational environments, especially on most of the auditory and non-auditory effects. Owing to the cross-sectional design of the studies available, however, it is unclear whether such effects have been caused by comparatively high (peak) solvent exposures in the past or can still be caused by exposures experienced in today's workplaces. In addition some data are available about the effects of noise and heavy metals interaction on cognitive effects. Concerning the same health endpoint, for the combination of noise and solvents these data are missing. Also, some data are available on health effects of vibration on auditory, non-auditory and to a less extent on cognitive effects. Some data are available about the health effects of indoor and outdoor air pollutants on non-auditory and cognitive effects, but a substantial amount of research is needed to determine possible and as yet unknown effects. Animal data is available on the auditory effect of combined exposure to noise and chemical asphyxiants (CO and HCN), but human data are scarce and rather unconvincing. Little is known about the health effects of biological agents and pesticides in combination with noise on auditory, non-auditory or cognitive effects. It was also concluded that there are few studies showing combined effects of noise and air pollutants. Some data exist only on respiratory disorders caused by combined effects of noise and outdoor air pollutants, balance disorders caused by occupational exposure to noise and solvents and effects on human growth caused by combined effects of noise and heavy metals.

Confounding factors

Possible factors that may have confounding or aggravating effects on the results of noise studies, and which should be taken into account when carrying out noise studies, were summarised. Such factors are: **age, gender, smoking, obesity, alcohol, socio-economic status, occupation, education, family status, military service, hereditary disease, medication, medical status, race and ethnicity, physical activity, noisy leisure activities, stress reducing activities, diet & nutrition, housing condition (crowding), and residential status**. Some additional factors should be considered such as hearing loss as vulnerability factor in children, work noise-home/school noise interactions (outdoor and indoor exposure mapping and special assessment methods e.g. irrelevant speech tests), spatio-temporal assessment of noise exposure (home vs. work/school, night vs. day noise exposure), time-activity-microenvironment-patterns, and exposure modification by behavioural measures ("active coping").

Research priorities for the future

The future needs for research in the field of combined effects of noise, air pollutants and chemicals were prioritised. The highest priority was given to issues related to research on noise and outdoor air pollutants. This is due to the fact that it may concern the largest population compared to the other stressors in this analysis and there is some evidence of serious health outcomes such as cardiovascular effects. The next priority was given to the research on the effects of noise and solvents in occupational settings and to research on noise and organophosphates.

Recommendations

For future research, priority should be given to:

1) Evaluation of existing data collections whether re-analyses are possible with respect to combined exposure from traffic sources (road, rail and air),

2) Analyses of existing data concerning noise and other stressors interactions in both occupational and environmental settings,

3) Detailed assessment of combined exposures to noise, vibrations and PM, CO, NOx, and VOCs with specific studies in urban areas and, especially, cardiovascular health endpoints should be studied as priority health endpoints,

4) Identification of causal mechanisms through careful review of toxicological experimental studies.

Among the combined effects discussed in this workshop, most knowledge has been obtained in the field of the combined effects of noise and solvents in occupational environments. Nevertheless, even in this field the available data are insufficient to address questions of dose-response relations, exposure-time relations, effect thresholds, etc. Further, preferentially longitudinal, studies in occupational settings are needed to address the relevance of the findings from existing cross-sectional studies before a revision of the existing standards and guidelines at the EU level can be proposed. Also, the combined effects of other stressors with noise need further research before new policies can be recommended.

A detailed description of the outcome of the discussions of the two Working Groups A and B are given in Appendix 4 and 5 respectively.

WORKSHOP PRESENTATION SUMMARIES

Preliminary Findings of WHO Study of Environmental Burden of Disease from Noise: Are We Seeing Combined Effects?

Rokho Kim, WHO European Centre for Environment and Health, Bonn, Germany

In the WHO European region, the environmental noise is becoming one of the major environmental health concerns for the policy-makers as well as the public. The European Union Directive related to the assessment and management of environmental noise (Directive 2002/49/EC 2002) addresses the action plans of EU Member States to reduce harmful effects of noise exposure. The Regional Priority Goal IV of Children's Environment and Health for Europe adopted by European Ministers of Environment and Health at the 4th Ministerial Conference in Budapest in 2004 states that children should be protected from exposure to harmful noise at home and at school.

WHO is carrying out the environmental burden of disease (EBD) from environmental noise project (Noise EBD project) to provide guidance in the estimation of burden of disease related to environmental noise, and to provide preliminary estimates of EBD from environmental noise in Europe. Operational definition of environmental noise for the Noise EBD project is the community noise emitted from such sources as road traffic, train and aircraft. Based on previous working group meetings on health effects of noise, noise-related health outcomes were selected: cardiovascular disorders, cognitive impairment, hearing loss, tinnitus, sleep disturbance, and annoyance. Topic-specific experts invited to the project included W Babisch, P Deshaies, T Gjestland, S Hygge, S Jovanovic, A Knol, Y Ku, C Mathers, H Miedema, R Mueller-Wenk, D Prasher, A Prüss-Ustün. Three sets of information is necessary to quantify EBD from environmental noise: Exposure distribution in the population, ER relationship, and disease burden estimates per disease in the population. The fraction of disease burden per disease is first calculated, and then applied to the global burden expressed as DALYs already published by WHO. The preliminary results of Noise EBD project were presented as below.

The burden of disease from noise can reflect the burden from air pollution, and vice versa. Cardiovascular disease, annoyance, and mild hearing impairment can occur in relation to the poor indoor or outdoor air quality. Those health outcomes with possible combined exposure and effects are highlighted in yellow.

Outcome	Exposure	Outcome	ER Relation	Impact fraction	DALYs in EUR-A
Cardiovascular disease	Traffic noise L_{day}	MI and IHD	Pooled estimate	3% of IHD	211 096
Sleep disturbance	L_{night}	Severely disturbed	Pooled estimate	2% of population	?
Annoyance	L_{den} and L_{dn}	Highly annoyed	Pooled estimate	15% of general population	278 174 (or 529 299)
Tinnitus	Traffic and leisure noise	Ringing sound causing sleep disturbance	Not available	3% of tinnitus (0.75% of population)	9 328
Cognitive impairment	L_{dn}	Reduction in cognitive function in children	Hypothetical curve	0.01%	45 036
Hearing loss	Leisure noise	Moderate hearing loss	Not available for env. noise	0.02% of 6-19 years old	6 800

It was strongly warned by Dr. Kim that these preliminary results of Noise EBD Projects are not final, and should not be cited or quoted until WHO publishes it by the end of 2007. As a conclusion, it was emphasized that there should be further investigations disentangling the combined exposure and effects between noise and air pollutants, considering that road traffic is the major source of noise and air pollution in Europe.

Assessment Possibilities and Data Availability

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Introduction

The EEA presentation addressed the issue of combined environmental exposures, with a specific focus on noise exposure. In recent years, the European Environment Agency has provided various levels of support to DG ENV within this area, such as preparations for a reporting mechanism for noise data, reported under the requirements of the Environmental Noise Directive (END); a project which described the details of both the content and format of the reporting. Another example of the support given is a project reviewing the noise related data reported in 2005 and 2006.

The presentation described the noise exposure data currently available and covered the main findings of the above activities described above. It included the expectations of the coming reports and the usage of Geographical Information System (GIS), and illustrations serving as examples of already reported information under END.

Data availability
The existing estimates of noise exposure in Europe cover either the whole European region with generic data or parts of the European region (e.g. regions or countries) with more detailed information.

> About 120 million people in the EU (more than 30 % of the total population) are exposed to road traffic noise levels above 55 Ldn dB. More than 50 million people are exposed to noise levels above 65 Ldn dB. (EEA 2001)

It is anticipated that when the new reports under END are available, access to information at a much more detailed level will be facilitated, e.g. per sources and 5 dB band of sound level along with its geographical location. This will open up the possibility for broader analyses and integrated assessments of a higher quality. By doing this, it should facilitate assessments of combined environmental exposure.

END Noise Data - harmonised to comparability?

One key aspect of the quality of reported data is the degree of comparability. END provides a framework for harmonised data, although some gaps will remain especially in the first phase of noise mapping and reporting.

Noise exposure information will geographically cover major agglomerations, defined by Member States and areas along major transportation lines and airports, above specified thresholds.

The indicators to be used in noise mapping under END are also harmonised: Lden and Lnight, where Lden consists of a day period of 12 hours, an evening period of 4 hours and a night time period of 8 hours. The noise indicator for the night time period, Lnight will cover 8 hours starting at 23.00 by default; however the start of the night time period may be altered by the Member States, and thus may vary from country to country. Since the traffic flow differs between the morning hours (06.00-07.00) and the late evening hours (22.00-23.00), this is likely to impact upon the exposure results.

The use of various interim and national assessment methods and the variation of in-put data in calculations assessment methods will also influence the noise exposure results in a disharmonised way. The use of harmonised assessments methods are foreseen in the Directive, but are as yet not in place.

Data should be reported by the end of 2007. However, previous experience from earlier reporting and opinions of national experts suggest that the delivery of reports may be delayed. Once information is reported, the data review and valuation ought to be carried out in order to enable integrated assessments of high quality. In conclusion, there is a time gap between the reporting deadlines and the point when data are available in integrated assessments.

Spatial information

Data reports under the Directive are expected to add a new feature which was previously not available at European level: the spatial information of the noise exposure. The ground for such expectation is found in the Directive, Article 7 and Annex VI which states that both a concise description of the agglomeration including location and a general description of the roads, railways or airports including location must be reported. In addition, there are explicit demands in some cases to send in actual noise maps.

The use of spatial information also follows the new INSPIRE Directive. INSPIRE aims to establish an infrastructure for spatial information in Europe with a key objective of making more spatially distributed data available. The use of GIS in reporting the strategic noise maps is currently being proposed in the proposal for an Electronic Noise Data Reporting Mechanism; a project run by the EEA. This proposal will be discussed with Member States in spring 2007.

The current proposal suggests that noise exposure data are reported per agglomeration and per airport. However, it proposes that road noise should be reported in an aggregated way for the whole road network, per country. For railway noise it proposes a similar aggregation for the railway network.

Review of reported data under the END in 2005/06

The deadlines for the first three reporting requirements have already been passed in accordance with Article 4(2), Article 5(4) and Article 7(1) in the Directive, and concern:

- competent authorities and bodies responsible for implementing the national provisions corresponding to END;
- relevant limit values;
- major roads, major railways, major airports and main agglomerations for which noise maps and action plans should be drawn up.

In 2006, the EEA conducted a review of this information with the assistance of the European Topic Centre for Terrestrial Environment, ETC-TE. The report summarises and standardises the data that were reported by Member States up until November 2006. By then most Member States had provided the Commission with their information. However, some of the reports were incomplete, missing either certain geographical areas or certain reporting requirements. The review has not been officially published and during 2007 the EEA will extend the review.

The review revealed that there is a variation of coverage between countries. This is of course due to differences concerning the number of inhabitants in countries as well as the distribution of population, and traffic intensity. But the variation is also due to national variations in definition and delimitation of agglomerations.

In total 129 agglomerations were found among the reports delivered by the end of 2006; some countries reported no agglomerations (e.g. Luxemburg and Cyprus) and a few countries together represented the majority of the reported agglomerations (e.g. 28 agglomerations alone in the United Kingdom).

The map below illustrates the major roads affected by END in France. The map is prepared by the EEA and shows the reported roads by their geographical location as attached to a transport network.
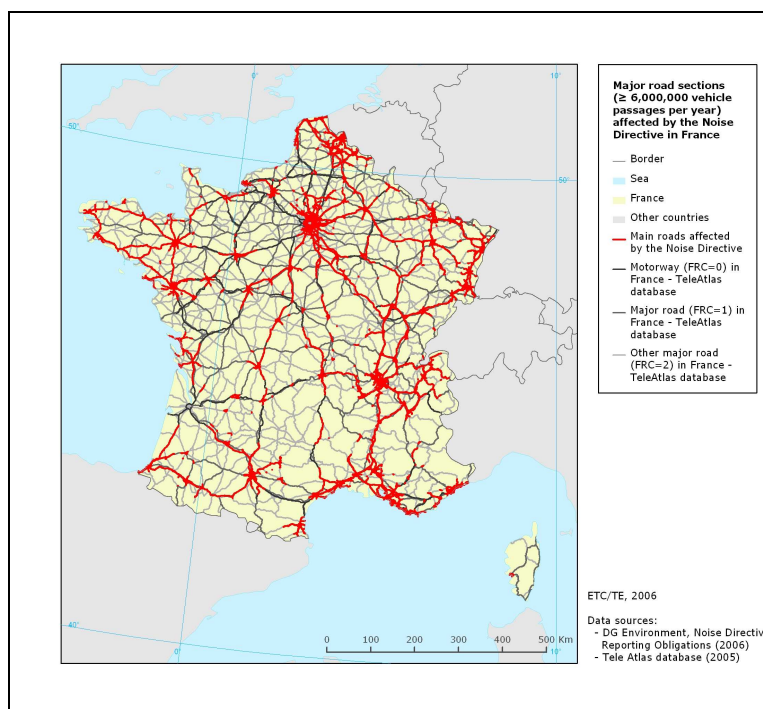
Figure 1. *Map of the major roads sections (> 6.000.000 vehicle passages per year) affected by END in France. (Data sources: DG Environment, Noise Directive Reporting Obligations (2006) and Tele Atlas database (2005).)*

The review explored the possibilities of comparing the reported information with existing European datasets, e.g. the population coverage. In conclusion, we got an understanding of the population that will be covered by the noise mapping activities in a comparable way. The below maps illustrate the procedures of overlaying raster information, derived from the reports and from the population density CLC2000.
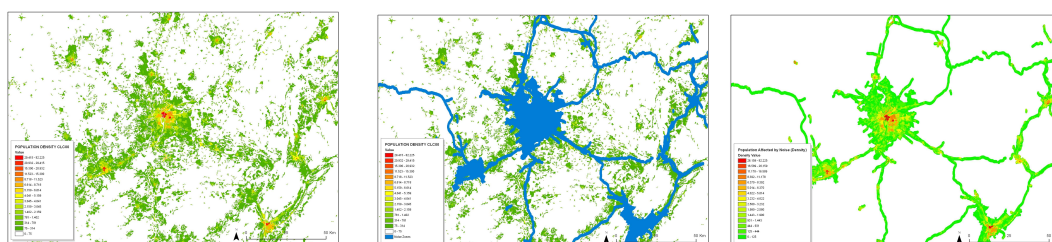
Figure 2. *Lyon, France: Population density CLC2000, areas to be noise mapped, and finally the population density for the areas to be noise mapped after processing the raster calculation between the two previous rasters.*

Similar methodology has been used in other studies. For example in 2006 the ENTEC study (ENTEC, 2006) proposed a methodology to assess population exposed to high levels of noise and air pollution at close proximity to major transport infrastructure, based on available information on transport infrastructures and activities as well as evaluations of population at risk.

Conclusions

Data, information and knowledge of noise exposure need to support noise policy design and noise policy evaluation. The possibilities to support noise policy makers through integrated assessments will increase with access to the new exposure data reported under the END. A new feature at EU level is the spatial dimension of noise exposure. The EEA is now in the phase of preparing the ground (technical, organisational and methodological aspects) for integrated assessments based on the noise exposure data. The possibility to facilitate integrated assessments of combined environmental exposures for policy support is a key objective in this context.

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ENTEC, 2006. *Development of a methodology to assess population exposed to high levels of noise and air pollution close to major transport infrastructure*, Final Report April 2006, Entec UK Limited.

Cardiovasular Noise & Outdoor Air Pollutants (particulate matter, sulphur dioxide, nitrogen dioxide, carbon monoxide)

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Introduction

Combined exposures to noise and air pollution occur commonly, in particular in relation to transport, road traffic being the most obvious source of exposure. In spite of this obvious co-exposure there is a lack of interaction between the scientific community dealing with health impacts due to exposure to noise and that dealing with air pollution. This lack means that the health impact of the combined exposures have so far been ignored in epidemiological studies in both fields. In this background paper we focus on cardiovascular disease and associated risk factors (hypertension, stress hormones), but respiratory disease (asthma) is also discussed briefly.

Environmental exposure to noise and air pollution has been associated with cardiovascular disease in several studies during the last decades, in particular in relation to road traffic. Air pollution studies have commonly used distance to road as a proxy for exposure, but not controlled for noise as a confounder (which it clearly is). The possibility of noise acting as a confounder has only recently been observed by air pollution researchers. Thus, Hoek et al (2002) note that "traffic noise associated with living near a major road could also affect cardiovascular health. However, in a large study on the relation between measured traffic noise exposure and cardiovascular disease, the association was not consistent". No attempt was made by the authors to control for noise, in spite of the fact that the strongest relation was found using "living near a major road" as a proxy for air pollution exposure.

In another study Peters et al (2004) note that "A rather crude measure of exposure to traffic was used in this study. Potentially, a combination of different factors, such as stress, noise, and traffic-related air pollution, may contribute to the observed associations. While persons are driving a car, symptoms of a possible arrhythmia may be common among those who are eligible for treatment with an implantable cardiac defibrillator. Chronic exposure to stress and noise is a well-documented risk factor for cardiovascular diseases, since such exposure can lead to elevated stress hormone concentrations" (Peters et al 2004). Nevertheless, no attempt was made to adjust for the potential confounding effects of noise.

A recent study also defined air pollution exposure by distance to major roads in addition to computed levels using monitor data (Gehring et al 2006). The authors note: "Furthermore, living in the vicinity of roads might represent a combination of factors such as noise and air pollution. It has been suggested that chronic exposure to noise might be a risk factor for cardiovascular diseases, and we cannot rule out the possibility that part of the observed effect

is attributable to noise." However, again, no attempt was made to adjust for road traffic noise.

Similarly, noise studies have not controlled for air pollution, and have only recently acknowledged the potential effects of co-exposure to air pollutants.

Cardiovascular disease

Air pollution

Suspended particulate matter, carbon monoxide and sulphur dioxide are important air pollutants with respect to the development or exacerbation of cardiovascular diseases. Studies on short-term exposure to elevated concentrations of fine particulate matter are associated with acute changes in cardiopulmonary health. Epidemiological studies on mortality rates and life expectancy have shown strong associations to long-term exposure to fine particulate matter and sulphates (Schwela et al, 2005).

Most studies have found positive associations between several different air pollutants and adverse health outcomes (Brunekreef and Holgate 2002, Brook et al 2004, WHO 2006). The results of observational studies are influenced by numerous factors, including characteristics of the air pollution, the population studied, and methodological issues, such as control of relevant confounders. The lack of complete uniformity is not surprising given that numerous variables (atmospheric conditions, geographic locations, cohort characteristics, sample sizes, exposure estimates, and statistical modelling) can affect the results. Our understanding of the relevant biological mechanisms involved also remains incomplete. Nevertheless, the existing body of evidence is adequately consistent, coherent, and plausible enough to draw several conclusions.

It is clear that short-term exposure to elevated PM significantly contributes to increased acute cardiovascular mortality, particularly in certain at-risk subsets of the population. Hospital admissions for several cardiovascular and pulmonary diseases acutely increase in response to higher ambient PM concentrations, in particular $PM_{2.5}$.

There are rather few long-term studies of air pollution and cardiovascular outcomes. Two of the largest studies of the health effects of long-term air pollution exposure that have served as the basis for the setting of annual average $PM_{2.5}$ standards (Dockery et al. 1993; Pope et al 1995) underwent complete reanalyses by independent investigators to ensure reproducibility (Krewski et al 2000). The reanalyses validated the quality of the data and replicated the original results without any substantial alteration in findings.

There has been a lack of understanding of the mechanisms potentially underlying the effects of air pollution on cardiovascular health. The putative biological mechanisms linking air pollution to heart disease involve direct effects of pollutants on the cardiovascular system, blood, and lung receptors, and/or indirect effects mediated through pulmonary oxidative stress and inflammatory responses. A general scheme illustrating potential mechanisms of the effects of PM on the cardiovascular system is shown in the figure below (Brook et al 2004).

Brook et al (2004) argue that "although there is a strong case that air pollution increases the risk of cardiovascular disease, there is a need to address a number of remaining scientific questions", such as:

- Improving our understanding of the underlying biological mechanisms;
- Identifying the differential toxicity of various constituents and sources of air pollution and

- Epidemiological investigations designed to address some of the limitations of prior reports, including studies that involve improvement of exposure estimates, examination of the relationships between traffic emissions and adverse cardiac effects, investigation of the roles of co-pollutants and confounders.

However, the authors do not recognize specifically the need to study simultaneous exposure to other (traffic related) emissions (e.g. noise).

Noise

In 1980, WHO noted that vasoconstriction and significantly increased levels of blood pressure or vasodilatation of blood vessels have been reported in persons exposed acutely to high levels of noise (WHO 1980). However, the associations were weak and their medical significance unclear. More recently, expert groups in WHO's normative work on guidelines for environmental noise reviewed the overall evidence for associations between noise exposure and cardiovascular morbidity (WHO, 2000a; Berglund and Lindvall, 1995). According to these publications noise may have a large temporary and permanent impact on physiological functions in man and may act as an environmental stressor.

Comprehensive reviews have been published, summarizing the results of studies that were carried out up to the end of the last century (Babisch 2000, van Kempen 2002). The strongest evidence of an association between community noise and cardiovascular endpoints was found for ischaemic heart diseases (IHD), including myocardial infarction (MI). Most of these studies included men exposed to road traffic noise.

By 2005, 61 epidemiological studies had assessed the relationship between transportation noise and cardiovascular endpoints (Babisch 2006). Most studies referred to road traffic noise or aircraft noise and were commonly cross-sectional, but some studies used case-control or cohort design. Confounding factors were not always adequately considered. Few studies provided information on dose-response relationships.

Relative risks of ischaemic heart disease found in 17 studies (12 road traffic noise, 5 aircraft noise) illustrate the heterogeneity of the results from different studies, but there is commonly an increase in risk with increasing noise level. The common set of covariates considered were age, sex (only males) social class, education, body mass index, smoking, employment status (including shift work), physical activity, family history of IHD and prevalence of pre-existing diseases. A recent German study showed an excess risk of myocardial infarction related to traffic noise, but only in men (Babisch et al. 2005).

Whereas the mechanisms behind the cardiovascular effets of air pollution have been recognised only recently, mechanisms for noise associated cardiovascular effects have been well established in laboratory studies.

Laboratory experiments and field quasi-experiments show that if noise exposure is temporary, the physiological system usually returns, after the exposure terminates, to a normal or pre-exposure state within a time in the range of the exposure duration. If the exposure is sufficiently intense and unpredictable, cardiovascular and hormonal responses may appear, including increases in heart rate and peripheral vascular resistance, changes in blood pressure, blood viscosity, blood lipids, and shifts in electrolytes (Mg/Ca) and hormonal levels (epinephrine, norepinephrine, cortisol). The great interest in the first four comes from an interest in noise-related coronary heart disease (Ising and Günter, 1997).

Hypertension

Air pollution

The literature relating blood pressure to air pollution is sparse, and two recently published studies show contradictory results (Zanobetti et al 2004, Ibald Mulli et al. 2004). A recent study concluded that that increases in air pollution may be associated with increases in systemic inflammation in older adults, and that associations between pollution and short-term increases in inflammatory markers with larger associations suggested for individuals with diabetes, obesity, hypertension, and elevated mean inflammatory markers. (Dubowsky et al 2006).

Noise

The evidence of an association between hypertension and community noise has increased throughout the recent years. In general, relative risks were found to be higher when mediating exposure factors like residence time, room orientation and window opening habits were considered in the analyses. However, results are equivocal both with respect to blood pressure increases (Pulles et al. 1990; Babisch et al. 1990; Lercher 2000) and the prevalence of hypertension (Knipschild and Sallé 1979; Herbold et al. 1989; Bluhm et al. 2001; Maschke 2003). A recent cross-sectional study indicated an exposure response relation between residence distance from a Swedish airport and hypertension (Rosenlund et al. 2001). Similar results were found in a community sample around a military airbase on Okinawa and in a cross-sectional survey around Schiphol airport (Matsui et al. 2004; Franssen et al. 2004). A study on airport related noise and risk of hypertension (HYENA, funded by the European Commission) will be reported in 2007 (Jarup et al. 2005).

WHO stated that the overall evidence available at the time suggested a weak association between long-term noise exposure and BP elevation or hypertension, and that cardiovascular effects are associated with long-term exposure to $L_{Aeq,24h}$ levels in the range of 65-70 dB(A) (Berglund et al. 1999). However, a recent German study suggested that traffic noise at lower levels might increase the risk of myocardial infarction and high blood pressure, finding an increased odds ratio for medical treatment of hypertension in subjects with an exposure during the day/night of more than 60/50 dB(A) compared with subjects with an exposure below 60/50 dB(A) (Maschke, 2003). Recent studies suggest that nighttime exposure might be particularly relevant for health (Lercher and Kofler 1993; Babisch et al.1999; Maschke 2003; Health Council of the Netherlands 2004).

Stress hormones

Stress hormones are useful indicators to study mechanisms and interactions between noise and health outcomes such as blood pressure (Babisch et al. 2001). The cortisol level is a good indicator of stress (Wust et al. 2000). Salivary cortisol correlates well with free levels of cortisol in serum, and correctly collected saliva samples have the advantage of being stable for long periods at room temperature (Hofman 2001), which facilitates their use in multicentre studies. Saliva sampling has the advantage above collection of blood specimens that it is easy and cheap to administer. The study subjects can easily be instructed to collect samples themselves. Hence many samples can be collected and this makes it possible to study circadian disturbances in cortisol regulation.

There are three aspects of saliva cortisol assessments that are crucial in relation to reactions to long-lasting stressors such as aircraft noise. Firstly, as long as subjects have retained ability to up-regulate cortisol, levels may become elevated. This may be particularly relevant during

the early morning hours. Secondly, when the life situation has been disturbed for a long time the ability to down-regulate cortisol may be inhibited. This is particularly relevant during the late hours when cortisol excretion in normal subjects is much lower than during the early hours immediately following awakening. Finally, it is believed that subjects who have suffered from severe stressors for a long time may have exhausted the ability of the cortisol system to regulate in the normal way. In such cases levels become abnormally low and show very little variation. Saliva cortisol measurements may show high and low levels, and high as well as low variability during exposure to long-lasting stressors. The group with exhausted ability is however small in most studies of normal populations. Therefore, long-lasting stressor exposure may result in elevated cortisol levels, and perhaps lowered ability to decrease levels at night before bedtime.

Allergy and asthma

In the past few decades, increases in the incidence and prevalence of asthma worldwide have resulted in increased morbidity and mortality and have sparked renewed interest in both basic and clinical research related to this disease. There is sufficient epidemiologic and animal data to suggest that some synergism exists between exposure to air pollutants (primarily outdoor) and biological agents (primarily indoor) in the induction of asthma in children and possibly adults (Selgrade et al 2006, Gilmour et al 2006).

Although extensive evidence shows that ambient air pollution exacerbates existing asthma, a link with the development of asthma is less well established. This is primarily because few prospective studies with extensive exposure data have been conducted. However, in the past few years, some limited data sets have emerged to support associations between air pollution and incidence of asthma. The ambient air pollutants studied have included particulate matter (PM), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3) (Gilmour et al. 2006)

Ising et al. (2003) observed that the pathogenesis of allergies can be stimulated by adjuvant effects – i.e. air pollutants such as particulate matter from diesel exhaust and NO_2 as well as noise –especially during night-time. They investigated the combined effects of chronic exposure to traffic related air pollution and noise, on the risk of skin and respiratory diseases in children. The paediatricians' diagnoses of 400 children were analysed together with their parents answers regarding the density of road traffic on their street and several confounding factors. Multiple regression analyses resulted in relative risks of asthma, chronic bronchitis and neurodermitis, which increased significantly with increasing traffic load. A comparison with the literature on such effects caused by air pollution as the only stressor, showed that traffic noise during the night might have an adjuvant effect on the pathogenesis of the mentioned diseases.

A recent German study found that residential exposure to truck traffic (noise) may adversely affect the health of children (Behrens et al. 2004).

Conclusions

Several air pollutants are well-established risk factors for cardiovascular disease and there is increasing (but still inconclusive) evidence that noise may be a risk factor for cardiovascular morbidity. As air pollution and noise exposure commonly occur together, investigations on impacts of noise on cardiovascular health should consider air pollution exposure as a potential confounding variable. Similarly, air pollution studies need to consider not only the

impact of specific air pollutants but also consider the confounding or modifying effects of noise on cardiovascular disease risk.

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Cardiovascular Effects of Road Traffic Noise with Adjustment for Air Pollution

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Summary

Living near a major road has been associated with effects on cardiovascular morbidity and mortality (Hoek et al. 2002; Maheswaran and Elliot, 2003). Studies into potential mechanisms and epidemiological studies indicate that cardiovascular health effects may be related to both environmental noise and air pollution. There is increasing evidence that exposure to environmental noise can induce stress related health effects including hypertension and cardiovascular diseases. Epidemiological studies indicate that environmental noise exposure increases the risk for cardiovascular disease in adults (Babisch et al., 1999; Babisch et al., 2003 and reviews by Babisch, 2000; Babisch, 2004; Babisch 2005; Passchier-Vermeer and Passchier, 2000 and a meta-analysis by Van Kempen et al., 2002). Also, associations have been found between air pollution and an increased relative risk for cardiovascular morbidity (Koken et al., 2003; Peters et al., 2001), cardiovascular mortality (Samet et al., 2000), and cardiopulmonary mortality (Dockery et al., 1993; Hoek et al., 2002; Pope et al., 2002). Road traffic is, in addition to noise, an important source of air pollution. Therefore, when studying the effects of road traffic noise on hypertension, air pollution should be taken into account. This paper presents a method for exposure assessment, and includes the preliminary results of a large study on cardiovascular effects of road traffic noise, accounting for air pollution.

Exposure Assessment

We applied an approach for detailed long term exposure assessment of subjects to noise and air pollution, taking local spatial variations into account. Exposure calculations for road traffic noise (L_{den}) and particulate matter (PM_{10}) were carried out for a prospective cohort study in Groningen, the Netherlands. Exposures were assessed for the City of Groningen sample (N = 40 856), and a selection of subjects that next visited the outpatient clinic (PREVEND cohort; N = 8 592) was made.

General approach

When assessing the relationship between road traffic noise exposure at home and cardiovascular effects, refined exposure assessment is needed. Exposure assessment is carried out with noise and air pollution models combined with advanced GIS techniques. The models correspond to the different steps in the causality chain (Activity → Emission → Exposure → Effect), where the activity of a source (road traffic) causes emissions (noise and air pollution), leading to exposure of and effects in the study population.
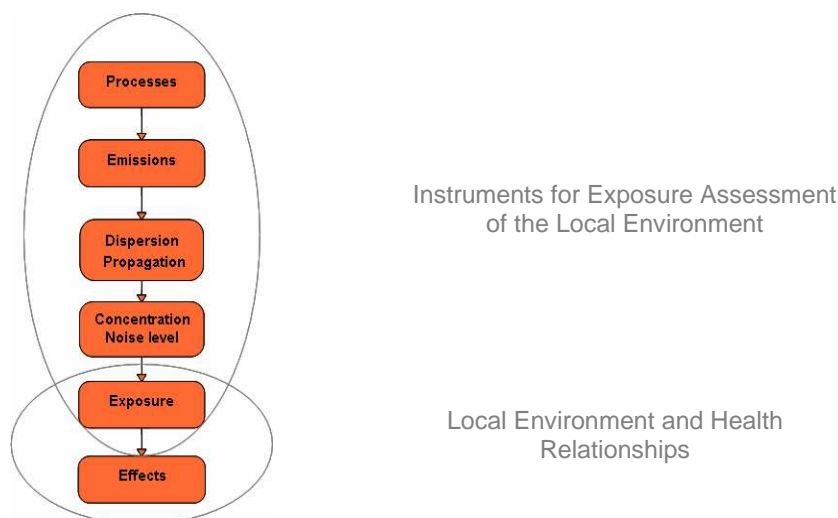
Figure 1. *Schematic overview of noise causality chain.*

Following the causality chain, first data on road traffic are collected. Relevant road traffic data are the day-, evening- and night-time traffic intensities for each road segment, traffic composition (percentages motorbikes, light duty, medium duty, and heavy duty vehicles), road surface type, and speed. For the detection of small scale variations, detailed data concerning road traffic activity and spatial locations of sources (roads) are needed. By assigning the road traffic characteristics to the road network, a (digital) road map is obtained where traffic characteristics are attributes of road segments (Figure 2).
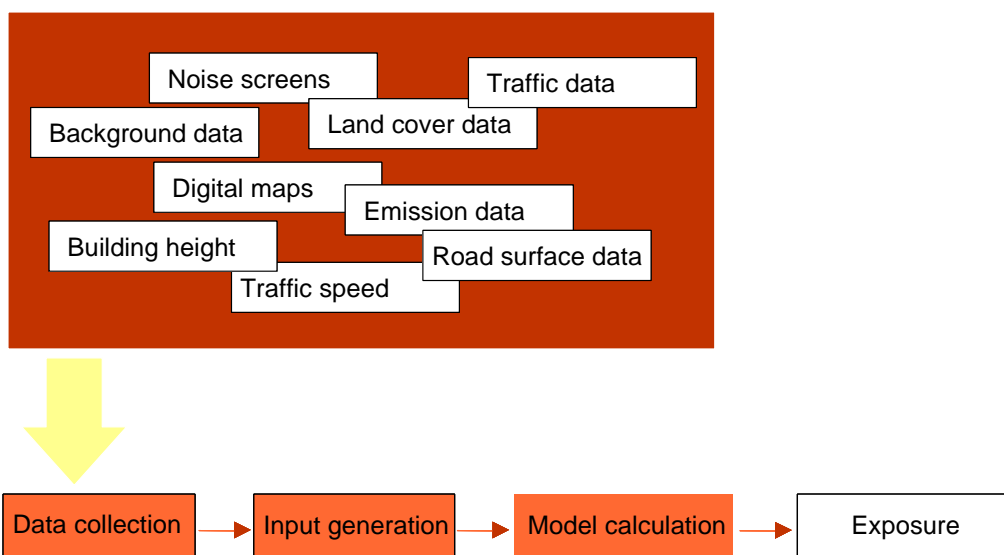
Figure 2. *Schematic overview of exposure assessment steps.*

The (noise or air pollutant) emission is calculated for each road segment on the basis of its attributes by applying emission models. These emissions, in turn, are input for the exposure calculation, together with data describing the local physical environment, including spatial data on the geographical location of objects, such as (digital) maps of noise screens and buildings with their height, presence of trees, and (digital) maps of land cover. The exposure

(sound level or concentration of an air pollutant) is calculated with transmission models (noise) and a combination of monitoring and dispersion models (air pollution), for receptor points at the façade of dwellings of subjects in the study sample. Receptor points can be placed at the most exposed facade of a dwelling, but also at the least exposed side, so that estimates of the (variation in the) exposure for each participants dwelling are obtained (Figure 3).
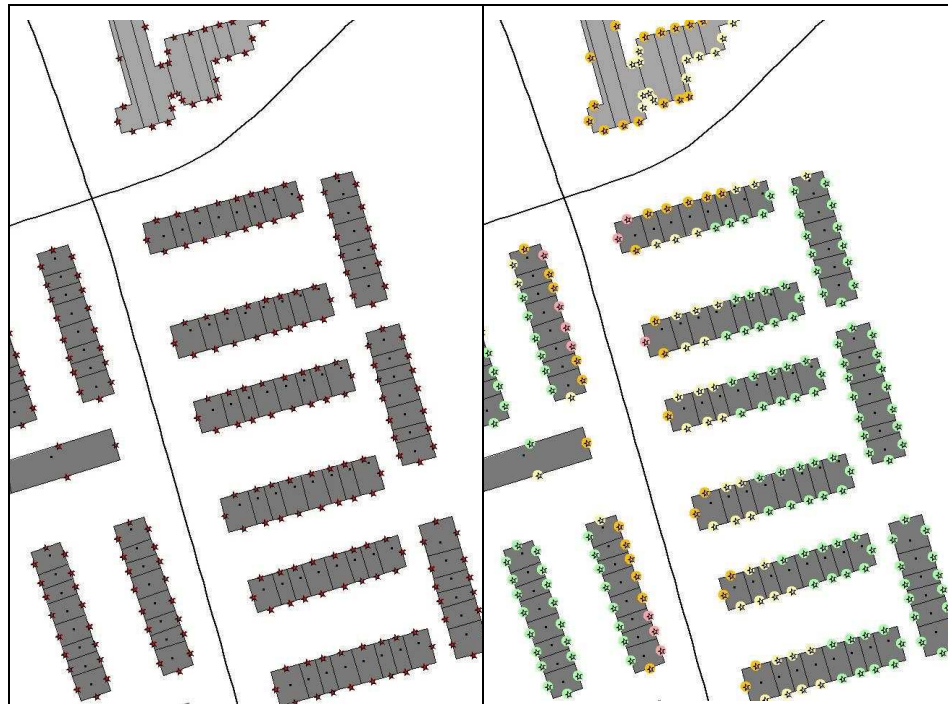
Figure 3. *Placing receptor points at the façade of dwelling. Left: receptor points; Right: noise levels at receptor points.*

Figure 4 shows an example of model calculations for noise mapping (left), and exposure calculation at the façade of dwellings (right).
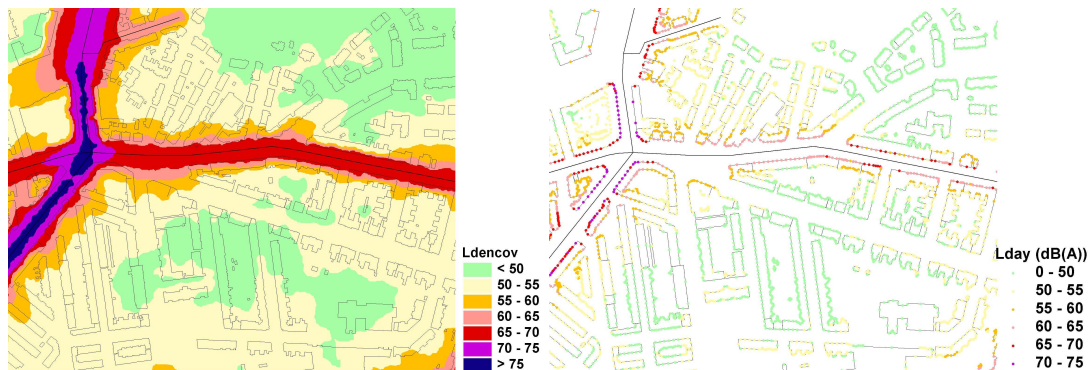
Figure 4. *Example: Noise modelled following the steps of the causality chain. Left: "Noise mapping"; Right: calculation at the dwelling facades. Model: SKM2; sophisticated version of the Netherlands' standard method for noise modelling and producing noise maps, implemented in URBIS.*

Noise exposure

The road traffic noise exposure of the subjects was calculated at the most exposed façade of the dwelling with standard method SKM2 in accordance with requirements of the EU Environmental Noise Directive (END). For the analyses we used the EU standard noise metric L_{den}. L_{den} (day, evening night level) is an "average" sound level over 24 hours in which sound levels during the evening and the night are increased by 5 dB(A) and 10 dB(A), respectively. SKM2 is the sophisticated version of the Netherlands' standard method for noise modelling and producing noise maps (VROM, 2004) in compliance with the END. SKM2 is implemented in Urbis (Borst and Miedema, 2005) that was used here for the exposure calculations. Noise calculations are carried out in two steps calculating first the emission and then the transmission. The emission calculations take into account traffic characteristics, including traffic intensities, traffic composition (percentages motorbikes, light duty, medium duty, and heavy duty vehicles), speed, road height and surface type. The transmisson calculations take into account the distance between source (road) and dwelling façade, air attenuation, effects of (yearly) meteo conditions, ground attenuation, object screening, reflection of objects opposite the dwelling, and statistical diffraction for transmission. Noise exposure is calculated at the height of the centre of the dwelling façade of the exposed subject. Very low noise exposure levels (below 45 dB(A)) were recoded as 45 dB(A) since this can be considered to be a lower limit of the ambient noise in urban surrounding.

Input for the noise emission calculations were detailed digital maps describing traffic characteristics for each road segment (Figure 5).
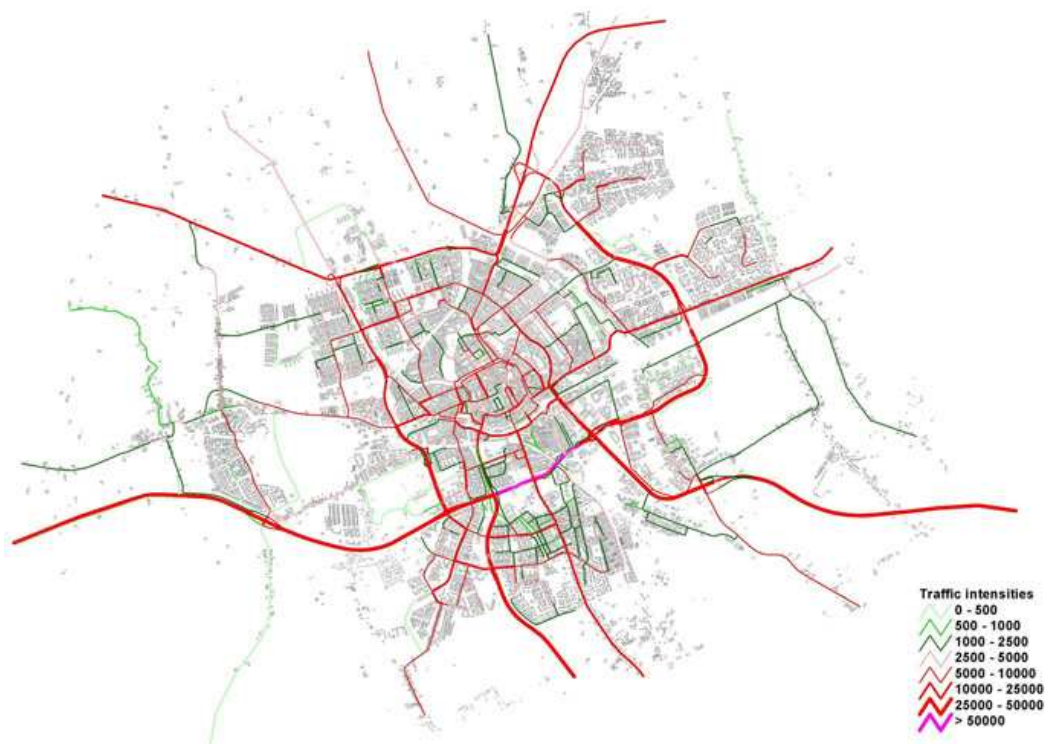

Figure 5. *Road network with traffic information; example: traffic 24h intensities.*

The geographic location of roads in these maps was extracted from the National Road Network (NWB; containing all streets, country roads and highways) obtained from the Netherlands Ministry of Housing, Spatial Planning and the Environment (VROM/DGR). The traffic flow data attached as attributes to the road segments were obtained from the local authorities of Groningen for a dense network of roads, including highways, arterial roads, main streets and principal residential streets. Basis for the noise transmission calculations were digital maps with precise information on the geographic situation of buildings and ground characteristics (Topographic Service data (TOP10) obtained from VROM/DGR). Building height was derived from the Actual Height Information Netherlands (AHN), a 5m x 5m grid with height information based on laser altimetry. In addition, a dataset on the geographical location of noise screens with their height was obtained from the local authorities. The geographic location of dwelling facades was derived from the building façade dimensions, divided into dwellings on the basis of the address coordinates available from the local authorities of Groningen.

Air pollution exposure

Air pollution exposure was assessed to adjust for possible confounding. Particulate matter (PM_{10}) concentrations were obtained using a combination of measurement data and modelling techniques. Regional background concentrations based on measurement data were used, supplemented with the calculated contribution of the local road traffic, to account for the spatial variation within the city. Regional background concentrations were available from the National Institute for Public Health and the Environment (RIVM), which annually estimates the background concentrations based on measurement data of the national air quality monitoring network. Combining these monitoring data and nation wide air pollution modelling, they each year generate a national map (1 km x 1 km) of annual average concentrations for the most important air pollution components. Exposure concentrations, taking into account spatial gradients within the city, were obtained by summing the regional background concentration and the local traffic contribution, calculated using Netherlands' standard Dutch models for local air pollution calculations: the street model CAR II (for the contribution of a street to locations in that street), and a Gaussian (plume) dispersion model based on 'Pluim'(the Netherlands' National Model which is the default to calculate annual average concentration contributions) for all other contributions to a location from within the urban area. PM_{10} emissions for the different vehicle categories (light duty vehicles, medium duty vehicles, heavy duty vehicles and busses), were calculated by multiplication of the amount of vehicles per category by the speed dependent national emission factor for that category, available from the RIVM. The air pollution exposure is described by the annual average concentration, expressed in $\mu g\ m^{-3}$.

Study Population

City of Groningen sample

All inhabitants of the city of Groningen (the Netherlands), between the age of 28 and 75 years, in total 85 421 subjects, were sent a one-page postal questionnaire (regarding demographics, use of medication, smoking behaviour, family history of cardiovascular disease, and pregnancy) and a vial to collect an early morning urine sample. Altogether 40 856 people (47.8%) responded (referred to as the City of Groningen sample). Subjects were defined as hypertensive when they reported to use medication for an elevated blood pressure, and were classified as smokers if they reported smoking or having smoked cigarettes during the previous 5 years. A family history of cardiovascular disease was considered present if at least one first degree relative had documented angina pectoris, myocardial infarction or stroke before the age of 65 years.

PREVEND cohort

Further analyses were carried out on a selection of subjects that next visited the outpatient clinic. This study cohort consists of all responding subjects with a morning urinary albumin concentration of 10 mg/L or above, together with a randomly selected control group of the total study population with morning urinary albumin excretion of <10 mg/L, and who gave informed consent to participate in a long-term follow-up program. Insulin using diabetic subjects and pregnant women were excluded. Altogether 8592 subjects underwent a screening program of two visits in an outpatient clinic. These visits included anthropometric measurements and fasting blood samples. Both visits included blood pressure measurements (with an automatic Dinamap device). Blood samples were taken for various measurements, including fasting plasma levels of cholesterol. All 8592 subjects completed an extensive questionnaire on demographics, cardiovascular and renal and family medical history, use of antihypertensive medication and smoking status. Systolic and diastolic blood pressure measurements were calculated as the mean of the last two out of 10 successive measurements of the two visits. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure of ≥ 90 mmHg or the use of antihypertensive medication based upon pharmacy reports. Smoking was defined as currently smoking or stopped smoking less than 1 year ago. Education was coded in two categories: university or higher professional education versus other. A family history of cardiovascular heart disease (CHD) was considered present if at least one parent had CHD before the age of 65. The PREVEND study was approved by the medical ethics committee and conducted in accordance with the guidelines of the declaration of Helsinki.

Analysis

We carried out cross sectional analyses in a large random sample (N = 40 856) of inhabitants of Groningen city, and in a subsample (the PREVEND cohort; N = 8 592).

Results and Conclusions

Figure 6 presents the noise exposure distribution over the city of Groningen sample and the PREVEND cohort population.
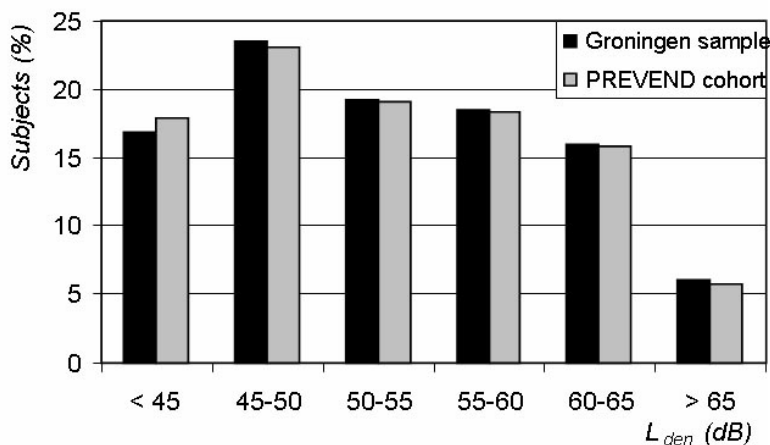
Figure 6. *Distribution of exposure of subjects at their home for the City of Groningen sample (%) and the PREVEND cohort over road traffic noise classes (L_{den}) [dB].*

Road traffic noise was shown to be associated with self-reported antihypertensive medication use in the City of Groningen sample. Adjusted odds ratios were significant for the 45-55 yr age group, as well as at higher exposure ($L_{den} > 55$ dB) in the full model adjusted for PM_{10}. In the PREVEND cohort, road traffic noise was associated with clinically confirmed hypertension. The adjusted odds ratio was again significant for the 45-55 yr age group. Results are presented in more detail in de Kluizenaar et al., 2007.

This study shows how epidemiological studies can make us of advanced modeling techniques, combining noise and air pollution.

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Mechanisms Controlling the Interaction between Noise and Particles

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Abstract

Stress (eustress) is, a priori, a functional system of dynamic equilibrium, which, by means of any number of exogenous and endogenous (including cognitive and emotional) stimuli, can trigger non-specific, activating, and regulative psychophysiological processes with the goal of optimising and perfecting human behaviour and securing a high quality of life.

Noise is a stressor in this sense.

Stress becomes pathogenic (becomes dysstress) when an individual's regulative system is overstrained. This generally becomes evident in neuropsychological, psychoneuroendocrinological, psychoneuroimmunological, or chronobiological dysregulations.

Environmental noise becomes dysstress when it provokes a negative experience over a longer period of time (e.g. annoyance, anger, fear, helplessness) or diminishes (nocturnal) rest.

The effects of noise (dys)stress can be seen in all functional systems, but are especially evident in the cardiovascular system.

Human beings can be simultaneously exposed to noise and other environmental factors, e.g. dust and nanoparticles in the air. Inhaled (ultra)fine particles are deposited in the lungs and can, in principle, remain in the epithelium and provoke inflammation processes there, or become transported deeper into the connective tissue or the blood stream.

The translocation into the blood stream could constitute a mechanism for inhaled particles to have a direct impact on the cardiovascular system (leading to increased plaque formation).

Inflammation in the lungs can be interpreted as a form of stress that is caused by free radicals. Free oxygen and nitrogen radicals in cells and tissues lead to an up-regulation or suppression of cytokines and mediators. Since cytokines activate the hypothalamus-hypophysis-adrenal cortex axis, stress—oxidative stress—is triggered by the inhaled particles.

Therefore, chronic impairments of the cardiovascular system can be triggered both by inhaled particles as well as by noise. We can therefore assume that there will be clear interactive effects, since both pathogenetic mechanisms are integrated in the same network. In view of

the interlinked pathogenetic mechanisms, we propose the following four theses pertaining to this interaction:

1. An overstraining of the regulation (dysstress) is usually over-cumulative (additive), due to a simultaneous strain from both noise and particles, as compared with the single effects arising from exposure to noise and particles

2. With simultaneously occurring stress due to noise and particles, an increased translocation becomes evident and could lead to a reinforcement of unwanted particle effects.

3. With an increased translocation of particles from the lungs, the risk of a disturbance of the electrolyte metabolism could be amplified.

4. With a simultaneous strain from noise and particles there could be a higher risk of neurological illnesses (e.g. migraine), as compared with the effects of particles alone.

In view of the publications we have consulted, in the matter of (ultra)fine particles it is our assumption that cardiovascular diseases are triggered in the first place by oxidative stress and are intensified by the direct effects of particles. In the case of additional noise-induced stress it is to be expected that the resulting total stress will increase over-cumulatively and that the direct effect of particles will also be intensified.

In the case of combined effects, such as with road traffic, the interaction between particle effects and noise effects should always be taken into consideration.

Introduction

When the national mortality and morbidity data in ninety metropolitan areas in the United States was analysed (NMMAPS), the particle concentration was found to be more strongly associated with mortality than were gaseous substances. Results in Europe were similar. When particles are inhaled or instilled, there are morphological signs of inflammation and damage to the lungs. This led to the hypothesis that (ultra)fine particles are responsible for the epidemiological association between particle concentration and health effects.

This paper investigates what pathophysiological processes are to be expected when there is a simultaneous strain from noise and particles. Dysstress plays a key role in this context.

The stress system

In the seventy years since H. Selye put forward his concept of stress in 1936 (Selye 1936) and his formulation of the general adaptation syndrome (Selye 1946), there has been a meteoric development in the field. The function of stress was no longer restricted to the hypophysis (ACTH)-adrenal cortex axis and came to be characterized as a psychoneuroendocrine stress system regulated by the central nervous system (Krieger 1983; Voigt and Fehm 1983; Guillemin 1978; Snyder 1980, 1977; Wuttke et al. 1980; Cooper and Martin 1982; Hellhammer et al. 1988; Voigt and Fehm 1990, etc.). Today we speak of a stress system or an emotional stress system, in which are also included fear, pain, helplessness, and so forth (Rüegg 2006).

The neuro-hormonal functional complex of emotional stress is today also referred to as the hormone-transmitter spectrum (Voigt and Fehm 1990).

Psychoneuroimmunology developed in close association with psychoneuroendocrinology (Ader 1976, 1981; Fredrikson et al. 1986, Guillemin et al. 1985; Hellhammer et al. 1988; Jankovic et al. 1987; Locke et al. 1985, Locke and Hornig-Rohan 1983; Staines et al 1987; Roit et al. 1987; Schedlowski and Tewes 1996; Schubert and Schüssler 2003).

The stress system is the main point of intersection of these two fields, and both aim at developing knowledge of it further and of coming up with a systematic assessment of its functions (Chrousos and Gold 1992; Schubert and Schüssler 2003).

On the psychoneuroendocrine system
The psychoneuroendocrine stress system is much more comprehensive than the classical "endocrine" stress concept (Selye 1936, 1953). Selye's concept of stress is now only of historical significance. It should not be considered on its own, except perhaps for didactic reasons, as it only describes a partial range of functions.

The hormone-transmitter system and its forms of communication
Due to their functional connection and the associated communicative function they fulfil within organisms, hormones and neuropeptides are also referred to as peptide hormones and described as an integrated regulative system. Hormones and neuropeptides are produced in endocrine organs (hypophysis, adrenal cortex, thyroid, gastrointestinal tract) as well as in cells of the central and peripheral nervous system. The known neuroendocrine regulatory circuits functionally include, at minimum, the stress system, the hypothalamus, the hypophysis, and peripheral effector organs or target cells (Voigt and Fehm 1993). Corresponding to their various communicative functions, four cellular forms viz. their respective functions are distinguished:

- Endocrine function (adenohypophysis, gastrointestinal tract),

- Paracrine function (gastrointestinal tract),

- Neurosecretion (cells in the hypothalamus, adrenal medulla, neurohypophysis),

- Neuromodulator function (signal transmission via the CNS and vegetative nervous system synapses).

Hormones with a transmitter function are not only able to have an effect after their secretion into the blood stream, but also by means of various other functions, such as the synaptic transmitter function.

The peptides in the neurons normally have the same effects as transmitters and are referred to as neuropeptides or as neuromodulators. In the peripheral nervous system, neuropeptides are emitted from the nerve endings in symbiosis with the classical transmitters acetylcholine and noradrenaline. The efferent destinations (the gland epithelium, the smooth muscle of the blood vessels, and the digestive tract) of the neocortex have specific receptors at their disposal. These get those vegetative regulatory processes going that so far have only been associated with the sympathetic and parasympathetic nervous systems (Brown and Fischer 1984). The various forms of communication in the neuroendocrine system are shown in Figure 1.

a) Endocrine adenohypophysis gastrointestinal tract	b) Paracrine gastrointestinal tract
c) Neurosecretion hypothalamus adrenal medulla neurohypophysis	d)Neuromodulator (synaptic) CNS, autonomic nervous system
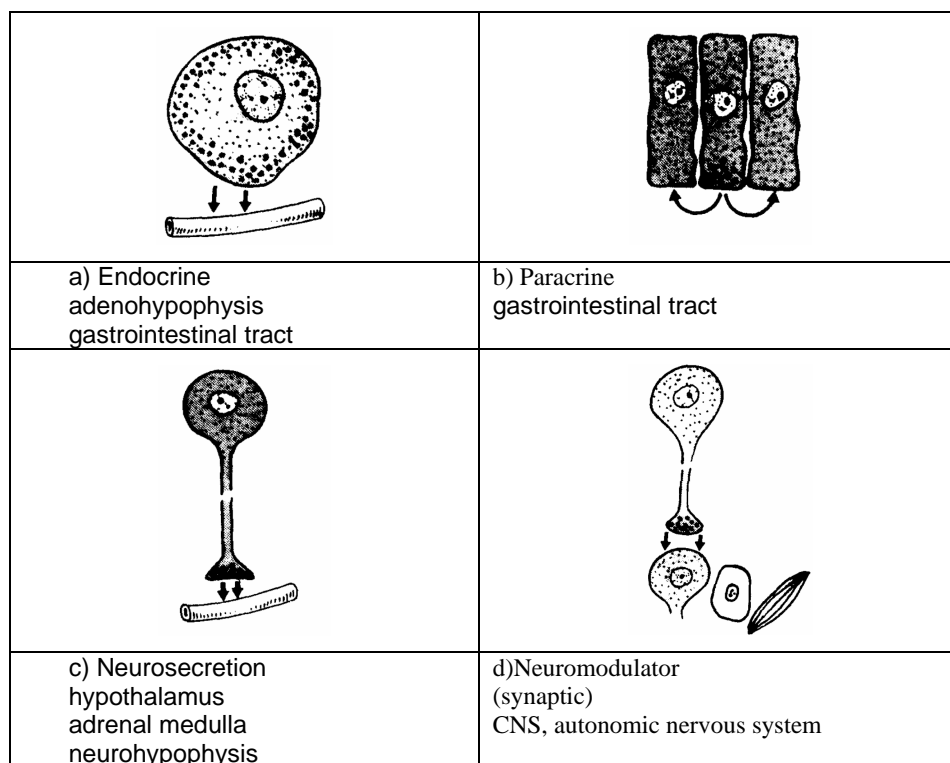
Figure 1. *The different structures of the neuroendocrine system's forms of communication according to Voigt and Fehm (1983).*

Voigt and Fehm (1983) developed the following simple diagram of the regulatory circuits of the psychoneuroendocrine functional system (Figure 2). Particular attention should be paid to the term "internal clock" (synchronizer). It is meant to show that all of these processes occur rhythmically, e.g. in a circadian rhythm.
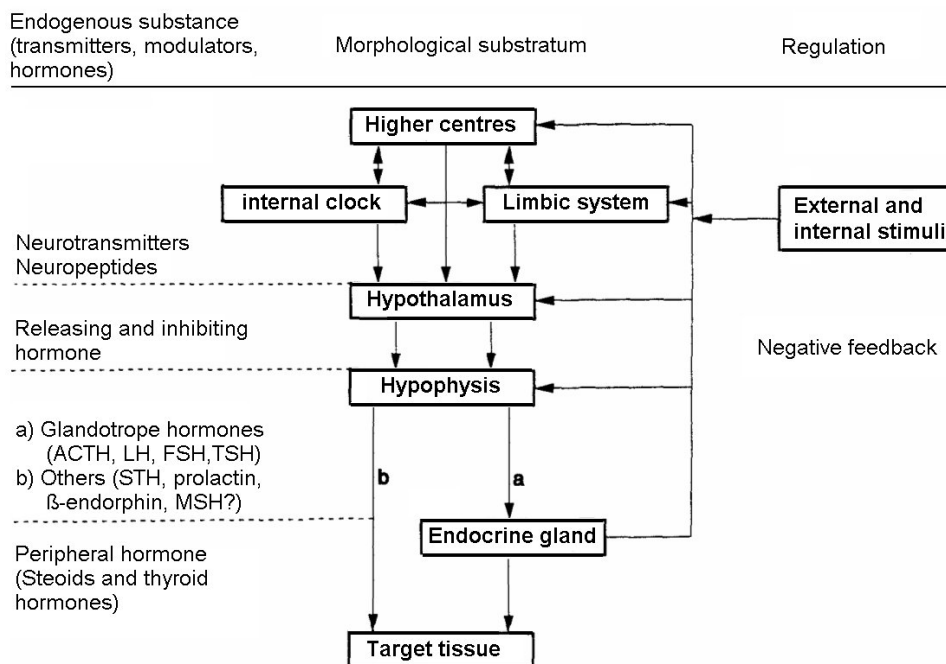
Figure 2. *Simplified diagram of neuroendocrine regulation according to Voigt and Fehm [1983]*

The immunological network in the psychoneuroendocrine system

In the course of the development of psychoneuroendocrinology and psychoneuroimmunology, it was discovered that the hypophysis is not an autonomous endocrine system with influence primarily on the functions of the adrenal gland, but is rather controlled by and dependent upon the hypothalamus. This is equally important to both fields (Hellhammer et al. 2003; Deetjen and Speckmann 1994; Kiecolt-Glaser et al. 2002; Ferrucci et al. 1999; Dantzer and Kelley 1993).

For this reason, the term hypothalamus-hypophysis-adrenal cortex axis (HHAC) has come to be of great significance to the disciplines of psychoneuroendocrinology and psychoneuroimmunology. The diagram in Figure 3 makes it clear that the HHAC axis is a neuroendocrine immunological network with negative feedback.
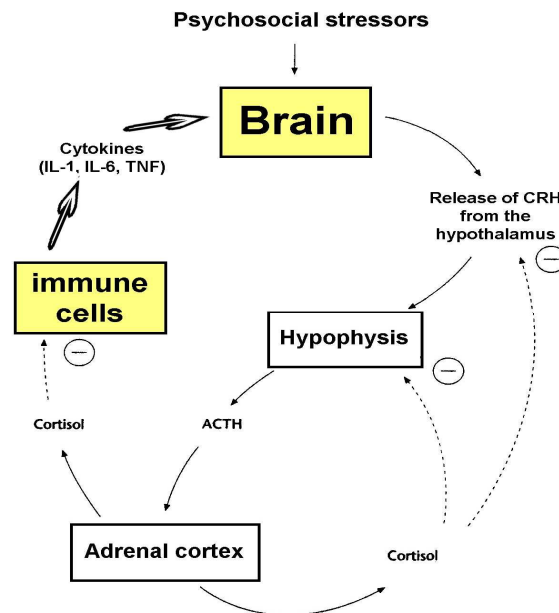
Figure 3. *The HHAC axis and the neuroendocrine-immunological network in the functional stress system (according to Hellhammer et al 2003)*

Both psychological stressors as well as cytokines associated with inflammation (e.g. IL-1, IL-6, TNF) can activate this functional system via the higher centres of the brain.

An inhibiting negative feedback, both to the hypophysis as well as to the hypothalamus, prevents, e.g., an excessive rise of cortisol in the blood and tissues. This protects against immunological derailment (Besedovsky and del Rey 1986; Besedovsky et al. 1986). The particular clinical relevance of the results achieved in numerous studies has been described in detail, e.g. by Hellhammer and Birke (1996).

Attempt at a current definition of stress

To define stress is a difficult undertaking. Not even Selye was able to come up with a universally satisfactory definition. He writes (1981) that stress is "the nonspecific reaction of the body to a demand of any kind."

This definition is an expression of the relationship between demand and reaction. The assumption is that the nonspecific reaction allows for the necessary readjustment to an individual's particular homeostasis. Selye (1981) also differentiated between eustress, which is pleasant or beneficial, and distress (we use the spelling dysstress; dys = disturbed, irregular, faulty), which is unpleasant and morbid.

Selye further postulates that stress is not something that must be avoided. Stress by definition cannot be avoided; complete freedom from stress is death (Selye 1981).

The functional processes that today are understood as stress have been described in many different ways. Before Selye (1936), Cannon (1911a and b, 1914) already described it as an emergency reaction. Hoff (1952) described the vegetative switch; Pischinger (1990) the puncture phenomenon after venipuncture. Finally Duffy (1972) postulated nonspecific activation and Lindsley (1951, 1970) nonspecific emotional activation.

We believe that all the functions listed here can be understood as symptoms. Emergency reactions, stress, the vegetative switch, the puncture phenomenon, nonspecific activation, and emotional nonspecific activation are described as functions whose purpose is to adapt to changes in the environment and to adequately respond to demands, thereby correcting life processes through learning processes. All these processes take place through the absorption and processing of information in the CNS and through memory activities (storage and recall); they are also part of emotional reactions, in which all the mentioned regulative systems become involved when necessary.

The concept of emotional stress allows us to cover all the listed reactions with one term. In principle, all these reactions refer to the same process of physiological adaptive regulation. We could therefore refer to it as activating regulating adaptive stress, which gives a more comprehensive definition of eustress and points to its physiological character. We suggest the following formulation:

Activating regulative adaptive stress (eustress)

Activating regulative adaptive stress (eustress) is a functional system of dynamic equilibrium that prompts and realizes nonspecific, activating, and regulative psychophysiological processes by means of any number of exogenous and endogenous (including cognitive and emotional) stimuli that are included in the central nervous system's information processing, with the goal of optimising and perfecting human behaviour and securing a high quality of life.

The structural-regulative substratum of the regulative stress system in the narrower sense, which is under the controlling influence of the neocortex and the limbic system, are:

1. the locus coeruleus noradrenaline system (LCAS), which is located in the brainstem and functionally regulates all peripheral functional systems, including the cellular matrix, through the vegetative nervous system

2. the corticotropin releasing factor system, which is represented by the paraventricular nucleus (PVN) of the hypothalamus and which, as a functional and structural system, regulates the individual functional (organ) systems by communicating via hormones and neuropeptides with the adenohypophysis and the epicrine, neurocrine, and neuromodulating cells

3. the synchronizer system. This includes the nucleus suprachiasmaticus, which regulates melatonin, the peptide hormone of the epiphysis (pineal gland), by means of which the sleep-wake rhythm, crucial for human beings, as well as the circadian rhythm (possibly also the individual rhythm of many cell groups of nerves or muscles) [Wever 1966], are maintained. (Analysing the stress system without considering the synchronizer system must be considered an omission).

4. the ground substance of the extracellular matrix (Heine 1991, 1992). It mediates between nerves and the hormone and immune systems on one hand, and parenchyma cells on the other.

5. the nonspecific reaction of the organism to outside influences (not just to stressors). In this context particular attention must be paid to oxidative stress (free radicals).

Just as with emotional stress, there is a physiological and pathophysiological component at work in oxidative stress.

In the physiological case, free radicals serve as a defence against attacking pathogens. Negative feedback prevents them from overshooting. We refer to this as activating regulative adaptive oxidative stress.

Destructive deregulative maladaptive stress (dysstress)

This kind of stress occurs when the human regulative system demonstrates an insufficiency, which is generally expressed in neuropsychological, psychoneuroendocrinological, psychoneuroimmunological, and chronobiological dysregulation of a kind that, in accordance with the WHO's definition of health (1987), restricts the ability of human beings to function physically, mentally, socially, and economically and threatens their ability to take care of themselves into old age. Chronic dysstress results in dysregulation. The nonspecific reaction of emotional stress means that the dysregulations can affect various of the regulative systems (see Table 1). The way a particular system is affected most likely depends upon the condition of the regulatory apparatus in Virchow's sense.

As a result, dysstress plays a leading role in the pathogenesis of all chronic diseases.

Table 1: *Effects of dysstress (chronic) (compiled according to (Voigt and Fehm 1983a,b; Bierbaumer and Schmidt 1996))*

Functional Change	Pathophysiological Effect
suppression of immunoreactivity	lowered resistance against many diseases
mobilisation of energy accompanied by the inability to store it	diabetes mellitus myopathies asthma
increased output in the cardiovascular system	essential hypertension
suppression of the digestive function	ulcers or infections of the stomach and intestines
chaotic tension in various muscle groups (or parts)	neck, shoulder, and back pain, headaches
peripheral vasoconstriction or dilation	migraines disturbed blood flow in the legs (Reynaud Erk)
inhibition of growth disturbance of the mineral metabolism	psychogenic dwarfism osteoporosis
neural dysreactions change in the perception threshold	accelerated aging of the cognitive functions (e.g. the memory)
suppression of the reproductive function	infertility, anovulation, impotence, loss of libido

Just as with emotional stress, there is a pathophysiological component at work in oxidative stress. Lack of exercise, excessive alcohol or caffeine consumption, but also an imbalanced or excessive diet can cause disturbances in the neuroendocrine-immunological regulatory circuit (cf. Figure 3). In addition, pollutants that are ingested by breathing, eating, or drinking can trigger or promote the formation of free radicals. Of note in this context are flue gases, e.g. fume and soot particles, sulphur dioxide (SO_2), carbon monoxide (CO), nitrogen oxide (NO, NO_2), dioxins, and furans (Ivcovice 2004; Klannig et al. 1999; Gotz et al. 1994, Thomas 1999, Ischiropoulos et al. 2003; Witte et al. 2000; Eaton 1991). As a result of a disturbance of the regulatory circuit, the tissue can become flooded with free radicals and the metabolism can become disturbed. We refer to this as destructive dysregulative maladaptive oxidative stress.

An excess of free radicals is considered to be one of the causes of chronic diseases and to be harmful to the immune system (autoimmune diseases) (Lunec et al. 1987, Lunec 1992; Chinery et al. 1997, Knight 1997; Spector 1995; Cerutti 1991; Beckman 1997). Associated diseases include arteriosclerosis, rheumatoid arthritis, allergies, cancers, Parkinson's disease, Alzheimer's, neuropathies, and diabetes, as well as premature aging of the skin and a general acceleration of the aging process.

Is noise a stressor?

In response to the question as to whether noise is an emotional stressor, we maintain that an emotional stressor has to fulfil the following requirements, given the above definition:

- The noise stimulus has to be involved in the processing of information and provoke a nonspecific reaction.

- In the case of acute stimulation the reaction should be reversible, but can also continue to exist once the stimulation has ceased.

- Furthermore, there is to be no noise stimulus specificity, but rather an individual specificity in the response to noise stimulation.

Noise perception and information processing

The sense of hearing serves a warning function. This is why the ears do not close and constantly take in information from all directions. The acoustic perception of a sound event essentially proceeds via tone quality, volume, and temporal structure. The sound event is a consciously perceived experience, making it possible to get one's bearings in space and time (distance, movement, speed) and so also to be warned of danger and receive associated information. This includes localization, determination of the direction from which the sound is coming, and how distant it is.

Acoustic perception further serves the purpose of linguistic communication and the experience of music and nature. The perception of unwanted sounds (noise) can have a lasting detrimental effect on communication and experience.

Intermediate summary:

The perception of sound is thoroughly integrated in the information-processing device of the human being.

Nonspecific, reversible reactions to sound stimuli
Nonspecific, reversible reactions to sound stimuli can be experimentally substantiated e.g. for the cardiovascular system. International data banks list more than 300 publications on this topic (cf. (Maschke et al. 2003)). Heart rate can be taken as an example:

In many laboratory experiments, heart rate accelerated under noise exposure (e.g. Dudek 1991). The observed rise in heart rate however also exhibited large individual variations (e. g. Griefahn 1994) and was moderated by psychological states (e.g. Mannchen 1971; Figure 1 shows typical heart rates before, during, and after an exposure to traffic noise or to pink noise, in women and in men separately (Parrot et al. 1992). On the contrary, Scheidt (1986) and Gruss et al. (1977) report heart rates that remained constant or partially decreased under the influence of noise.
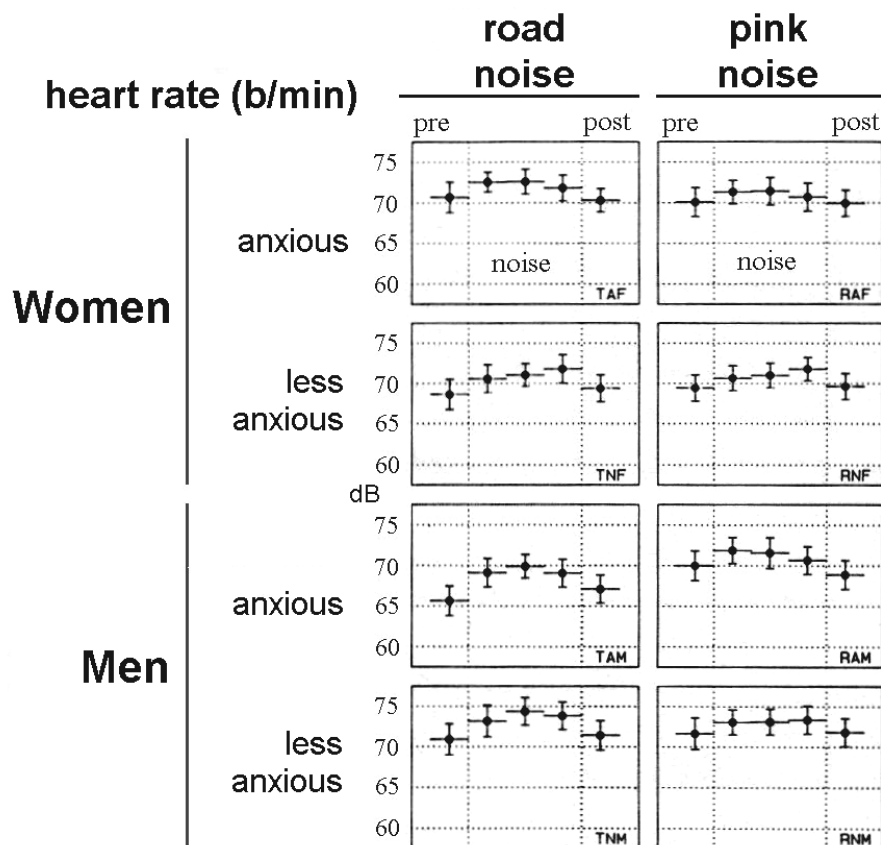
Figure 4. *Change in heart rate before, during, and after an exposure to traffic noise or to pink noise at 75 dB(A). The heart rate is averaged over a period of five minutes and is shown separately for anxious as well as less anxious women and men (source: according to Parrot et al. 1992).*

We can confirm that there is no noise stimulus specificity, but rather an individual specificity in the response to noise stimulation (e.g. Klosterkötter et al. 1974).

Intermediate summary:
Noise is a classic stressor, triggering a nonspecific activation called stress.

Can noise-induced stress take on the character of dysstress and function pathogenically?

This question is far more difficult to answer. Stress is a priori a physiological process that under certain conditions can function pathogenically.

As we were able to show, dysstressivity and thus also pathogenicity depend on the particular situation of strain. Important quantities in this context are the intensity and duration of the noise effect, sufficiency of recovery periods, as well as the subjective experience of the noise (e.g. anger, fear, helplessness).

Constantly returning strain exhausts the reserves of the body and disturbs and reduces the effectivity of organic function regulation, especially counterregulation (McEwen 1998, Sapolsky 1997).

In relation to the pathogenicity of environmental noise, the following has to be considered:

- It is difficult to substantiate pathogenicity using mean values because, as with all stressors, individuality plays an essential role in the effects of noise stressors.

- In order to assess pathogenicity, not only must the noise exposure be known, but also the overall situation created for the individual by the noise exposure as well as his dominant emotional state in this regard. If, for example, he finds himself in a state of helplessness as a result of the noise, then we must assume that a pathological condition will develop, since the helplessness syndrome is already an expression of dysstress. Uncertainty is a second important point, as well as conditioning and dishabituation (see e. g. Maschke & Hecht, 2005).

- The pathogenicity of environmental noise cannot be established by experimental noise effect research alone. (Even proof of a changed cortisol distribution is not a definite indicator: First, in the case of chronic strain, an exhaustion of the hormonal system in the sense of Selye can already have taken place. Second, the dynamic function of stress, in which cortisol can function as a "stress brake", has to be considered.)

- Today the question of the pathogenicity of environmental noise must pay particular attention to chronobiological stress ("dysrhythmia"), or disturbed sleep-wake rhythms.

Nocturnal noise, sleep, and chronobiological stress

No other medical discipline is as closely tied to chronobiology as is sleep medicine. The psychophysiology of sleep can be understood today only on the basis of the rhythmic sequence of the wake-sleep cycle, the REM and non-REM cycle, and the Basic-Rest-Activity-Cycle (BRAC) (Kleitman 1963, Webb et al.1981, Hume 1983, Zulley 1985, 1993, 1994a,b, 1995a, 1995b, Mistelberger 1989, Dinges 1989a, 1989b, 1989c, Monk 1989, Graeber 1989, Roehrs et al.1989, Perry et al.1990, Waterhouse et al.1992, Ehlenz et al. 1993, Hildebrandt et al. 1993).

Sleep is embedded in a circadian rhythm and itself proceeds cyclically. Because of the circadian rhythm, time spent in the deep stages of sleep (slow wave sleep) decreases with the duration of sleep, while time spent in REM sleep increases with the duration of sleep. The cyclical sequence of the stages of sleep is part of an ultradian periodicity. These rhythms also characterise endocrine regulation and are particularly evident in hormones (Born et al. 2000). The periodicity of a normal sleep is demonstrated on the following figure.
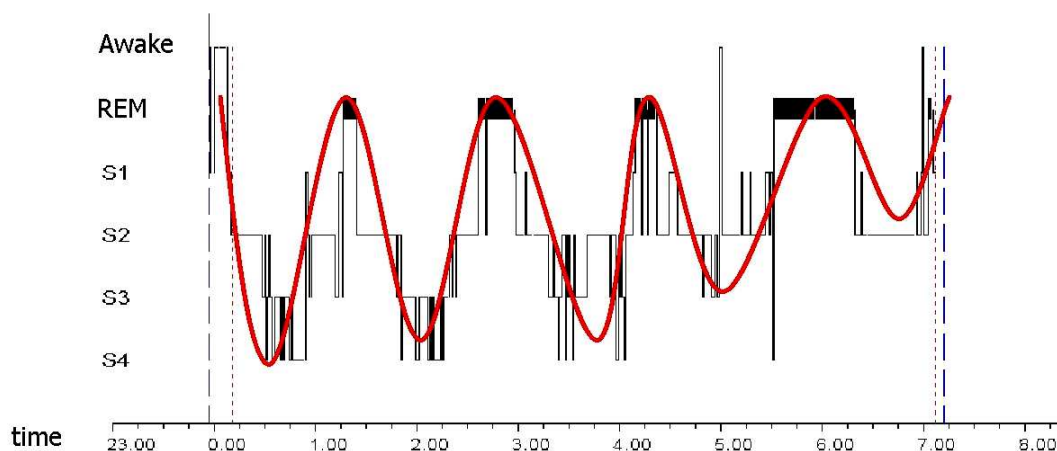

Figure 5. *Sleep profile of a healthy man, registered with an ambulatory sleep analyser (Quisi). The ultradian periodicity of the sleep is underlined by the red curve.*

Nocturnal noise results in fragmented sleep patterns in the case of intermittent sounds (e.g., noise from airplanes) and in superficial sleep in the case of quasi-continuous noises (e.g., street traffic noise). Both kinds of noise frequently lead to a decrease in deep sleep (stages 3 & 4) and REM phases. Noise-induced activation can go as far as waking the sleeper.
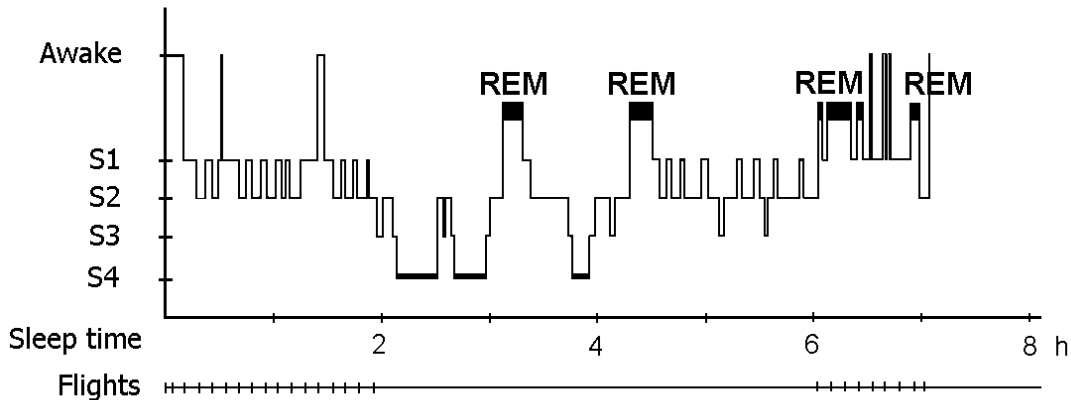

Figure 6. *Sleep profile under night flight noise (according Schuschke et al. 2002)*

Arousal—biological rhythms and sleep disturbances

Along with the concept of activation, the concept of "arousal" has become established in sleep medicine. Sleep medicine understands arousal as a temporally restricted change in condition, which raises the organism from a lower to a higher level of excitement. Arousal is a protective reflex under physiological conditions. We have to distinguish between vegetative, motor, and EEG arousals:

1. Vegetative arousal can be expressed in a temporary rise of blood pressure and heart rate, a change in breathing, in the cerebral supply of blood, or in endocrine secretion. Normally there is a rise in the sympathetic nervous system.

2. Motor arousal takes place when there is a shifting in position, coughing, or muscle twitching and is normally accompanied by an EEG and/or a vegetative arousal.

3. EEG arousal includes a temporary reduction of theta and delta waves as well as an induction of alpha and beta waves. Today, the most commonly used definition of EEG arousal was given in 1992 by the American Sleep Disorders Association (ASDA). According to the ASDA, the duration of an EEG arousal is three to thirty seconds. An arousal frequency of less than 21 an hour is considered normal (healthy).

A frequent occurrence of arousal provokes a fragmentation of sleep, which leads to a reduction in performance, and sleepiness and tiredness during daytime. The fragmentation of sleep causes a considerable rise in the sympathetic nervous system at night. As a result, the quality of sleep and the waking threshold sink. For people with cardiovascular problems or diseases (e.g. cardiac insufficiency), long-term sleep fragmentation can lead to a worsening of the myocardial function (heart attack). Overall, a fragmentation of sleep has a deteriorating effect on the clinical symptom complex (Zuberi-Khokhar 1996; Bonnett and Arand 1995; Biberdorf et al. 1993; Mercia and Gaillard 1991; Hanly et al. 1989).

Nocturnal noise—threat to recovery

Frequent brief interruptions of sleep caused by (traffic) noise, as arousal functions, provoke an activation of the central nervous system as well as of the hormonal and vegetative system (Rühle et al. 2001; Hall et al. 1996). They can disrupt the balance of the autonomic nervous system, which in effect corresponds to a stress reaction (chronobiological stress). Borbely's two-process model of sleep regulation (1982) can serve as an explanatory model for this kind of chronobiological stress. When, because of external disruptions such as noise, the homeostatic "S" process (the sleep readiness mode dependent on sleep-wake-behaviour) does not correspond to the "C" process (the circadian rhythm of sleep readiness), dysregulation and dysstress occur. This is inextricably tied to hormonal regulation, e.g. when the activation (cortisol) - deactivation (melatonin) oscillation loses its rhythm. It is well known that cortisol (in conjunction with, among others, T3 thyroid hormones and dopamine) and melatonin (in conjunction with, among others, growth hormones and prolactin) are determined by a contrarily day-night process (Arendt 1988; Armstrug 1985).

Furthermore, the reaction to nocturnal noise can be conditioned by the information-processing capacities of the waking human being (cf. Spreng 1999).

Intermediate summary:

Chronobiological stress that can be provoked by nocturnal noise occurs during the human being's most important recovery phase, and thereby jeopardises the urgently necessary nocturnal recovery from the demands of the day. Given that disturbed recovery processes are increasingly named as explanations for pathological developments, it is imperative to avoid chronic disturbances of nocturnal sleep.

Pathogenetic mechanisms of (ultra)fine particles

Inhaled (ultra)fine particles ((U)FPs) become deposited in the lungs. The probability with which particles are deposited in the various parts of the lungs depends on one hand on their physical characteristics, on the other on the breathing pattern and anatomy of the lungs, which changes with growth or age as well as due to pulmonary or respiratory diseases. A healthy adult breathing calmly eliminates most particles measuring 5 µm or greater into the mouth-pharynx area and into the large bronchi (cf. Heyder et al. 1986; ICRP 1994). But smaller particles also end up in the lung periphery, so that they are deposit both into the small bronchi as well as into the respiratory bronchioli and alveoli.
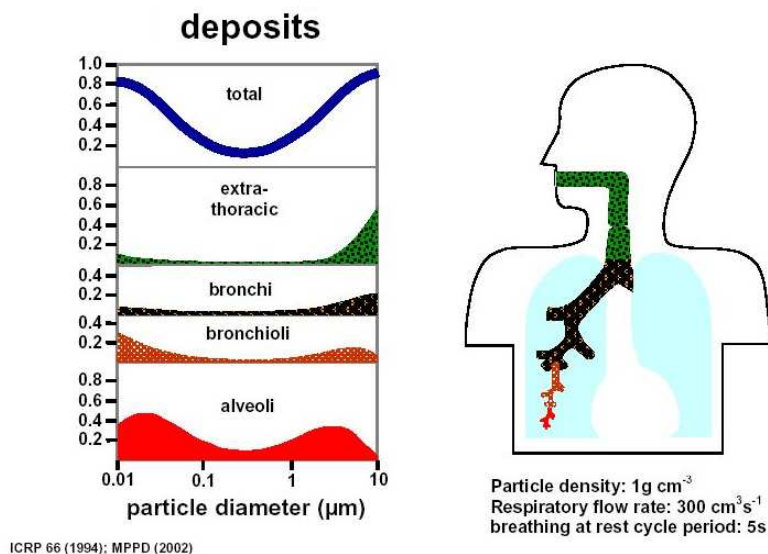
Figure 7. *Deposits of inhaled particles are dependent on size*

Different regions of the lungs have at their disposal different mechanisms for the removal of foreign matter. In the upper (extra-thoracic) respiratory tracts, the trachea and the bronchi, particles are bound by mucus. In the normal cleansing processes, the mucus transport conveys them to the larynx within one to three days and they are swallowed.

The period during which particles stay in the alveolar area can however be significantly longer, and, depending on solubility, amount to years. Free-floating alveolar macrophages can recognize particles as foreign matter and phagocyte them. If such an alveolar macrophage moves to the bronchi, the particles along with the entire macrophage are transported through the mucus to the larynx and into the gastrointestinal tract. In this way the gastrointestinal tract is polluted by particles from the lungs in addition to particles from food and drink.

We must assume that ultrafine particles are for the most part absorbed by epithelium cells and that phagocytosis by alveolar macrophages plays less of a role than with larger particles. Particles absorbed by epithelium cells can stay in the epithelium and cause inflammation or become transported on into the connective tissue or the blood stream (e.g., Ferin et al. 1992).

The extent of extrapulmonary translocation is highly dependent on particle surface characteristics / chemistry, in addition to particle size (Oberdörster 2006). Translocation to the blood stream could provide a mechanism for a direct effect of the particles on the cardiovascular system. This would explain epidemiological findings of cardiovascular effects associated with inhaled ambient UFPs. In addition to direct alveolar translocation of UFPs, cardiovascular effects may also be the corollary of a sequence of events starting with particle-induced alveolar inflammation, which initiates a systemic acute phase response with changes in blood coagulability, which in turn affects the cardiovascular system.

Once UFPs have translocated to the blood stream, they can be distributed throughout the body. The liver is the major distribution site followed by the spleen as another organ of the reticuloendothelial system. The discussed mechanisms are represented by Oberdörster in the following figure.
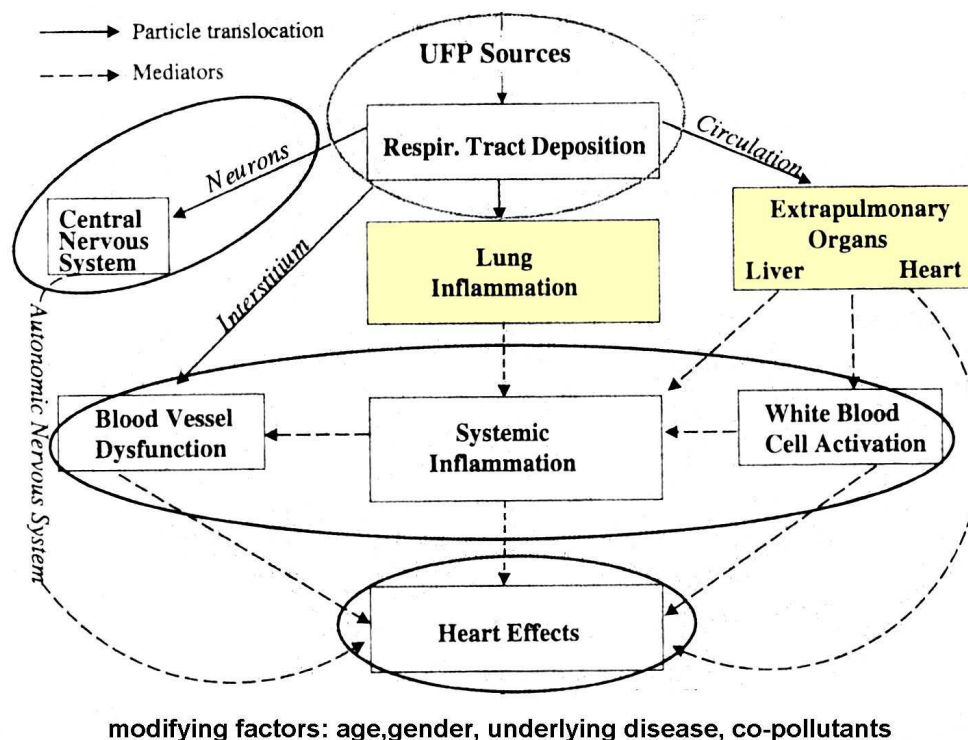
Figure 8. *Discussed mechanisms of ultrafine particle effects (Oberdörster et al. 2006)*

Intermediate summary:
Inhaled (ultra)fine particles are deposited in the lungs and can in principle remain in the epithelium and cause inflammation or be transported on into the blood stream (translocation). This translocation could be a mechanism for inhaled particles to have a direct effect on the cardiovascular system.

(Ultra)fine particles and stress associated with inflammation
The reactions of the immune system are not independent of the nervous system. The paraganglia of the vagus nerve act as sensor for the immune system. They react to the neurotransmitters produced by the immune system, thereby registering the strength of an inflammation or the immune response. This message from the immune system is carried to the brain by the vagus nerve. The main neurons in the hypothalamus and the hippocampus respond to the information from the immune system on the one hand via the sympathetic nervous system (Elenkov et al. 2000) and the vagus (cf. Tracey 2002), on the other via the hypothalamus-hypophysis-adrenal cortex axis (cf. section 4.3.). With a certain degree of delay, neurotransmitters can also reach the brain through the blood, thereby intensifying the message conveyed to the immune system by the nerves. In this sense, inflammation processes in the lungs can be described as stressors.

Free radicals are made responsible for triggering the inflammation processes brought about in the lungs by (ultra)fine particles (Kreyling et al. 2005). Oxygen and nitrogen radicals in the cells and tissues are said to change signal-transduction processes in the cell nucleus, resulting in the up-regulation or suppression of cytokines and mediators, which together can trigger proinflammatory processes. Since cytokines for their part activate the hypothalamus-hypophysis-adrenal cortex axis, we speak of oxidative stress in this context.

The following parameters of ultrafine particles as causal triggers of free radicals are currently being discussed (Kreyling et al. 2005):

- the large specific surface area (per mass) of ultrafine particles with particular physical structures and chemical components,

- the unusual form of ultrathin but extremely long nanotubes, whose biological persistency is similar to that of asbestos fibres,

- the contribution of transition metals like iron, nickel, zinc, chrome, manganese, and vanadium and

- reactive organic connections that can trigger oxidation-reduction reactions (redox reactions) in the biological system.

Intermediate summary:

In biological systems, ultrafine particles lead to the formation of free radicals that trigger oxidative stress and constitute a defensive reaction against inflammation processes.
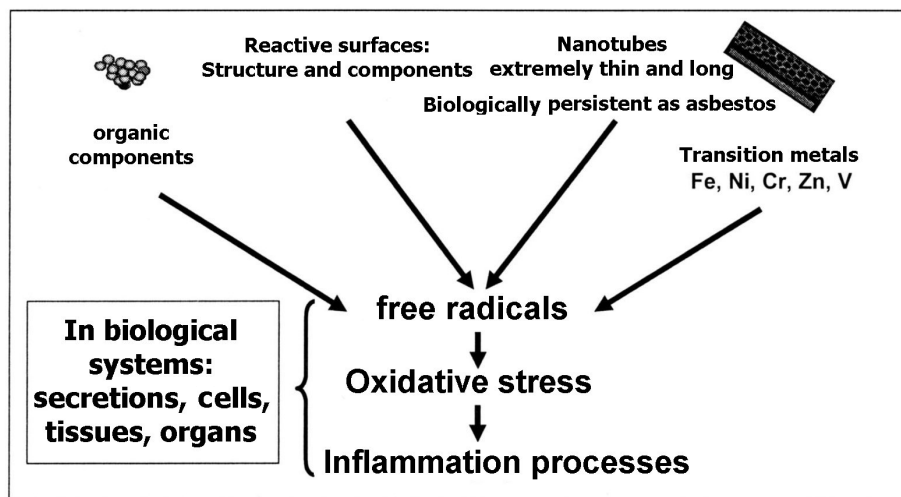
Figure 9: *Parameters of ultrafine particles that can be considered causal triggers of oxidative stress and processes (according to Kreyling et al. 2005)*

Theses on the interaction of noise and particulate matter

Environmental noise triggers emotional as well as chronobiological stress while particles trigger oxidative stress. Each of these stress lines can overstrain the regulation (dysstress) and in that way contribute to the pathogenesis of respiration and heart circulation diseases.

The fact that respiratory diseases can also be triggered or exacerbated by chronic noise-induced stress is suggested by such studies as the WHO LARES study. The LARES study demonstrates a connection in children between severe strain from neighbour noise and respiratory diseases (Niemann et al. 2004). This is revealing, since neighbour noise in contrast to road traffic noise is less associated with (ultra)fine particles. Respiratory diseases in children do not seem to be caused only by (ultra)fine particles, but — as can be seen in the case of neighbour noise — also by stress. Thus a Spanish study also shows that the equivalent sound level (L_{eq}) and the PM_{10} concentration (averaged 24h values) are the two essential risk factors for the admission of children under the age of fourteen to hospital for respiratory diseases (Linares et al. 2006).

If noise and particles works together, the individual regulation capacity is most likely over-cumulatively exhausted.

Thesis 1

An overstraining of the regulation (dysstress) is usually over-cumulative (additive), due to a simultaneous strain from both noise and particles, as compared with the single effects arising from exposure to noise and particles.

An over-cumulative (over-additive) effect is reported in recent studies (Ising et al. 2003, 2004), in which the combined effects of chronic exposure to traffic-related air pollution and noise on the risk of skin and respiratory diseases in children were studied. These studies provide the first empirical proof that the risk of respiratory diseases in children due to motor vehicle exhaust is over-additively high when combined with the exposure to nocturnal heavy-goods vehicle noise. It was observed that the combined effects were associated with a significantly higher relative risk of respiratory disease in children than was the case with isolated exposure to noise or air pollutants.

Furthermore, there are indications that the translocation of ultra-fine particles into the blood stream is increased during stress (e.g. Meiring et al. 2005). The biological cause could be the more rapid removal of ultrafine particles from the lungs.

Thesis 2

With simultaneous stress due to noise and particles, an increased translocation becomes apparent and leads to a reinforcement of unwanted effects from particles.

In addition, heavy metals are able to block the receptors for essential minerals (e.g. calcium or magnesium) in the tissue (connective tissue and cells). This may cause a disturbance of the electrolyte metabolism (overview in Hecht et al. 2005) and increase the occurrence of free radicals (oxidative stress). This interaction can therefore be seen as a cyclical process in the sense of a vicious circle.

Noise-induced stress and oxidative stress can make the blood-brain barrier permeable (e.g. Landgraf et al. 1979). This allows ultrafine particles to penetrate into the brain (e.g. those particles that reach the blood from the lungs).

Thesis 3

At an increased particle concentration, the risk of a disturbance of the electrolyte metabolism is heightened (e.g. an increased translocation of particles from the lungs due to noise-induced stress).

In the blood-brain barrier, the endothelial cells of the blood vessels are connected by so-called "tight functions," which combine the endothelial cells in such a way as to allow only those substances important to the brain to reach the neurons.

The selective regulation of the permeability of certain metabolic products can also be disrupted by stress. As a result, the "tight functions" break open and the selective permeability is disabled, which means that the blood-brain barrier allows additional substances to come in. These substances then enter the extra-cellular space of the brain and

are able, for instance, to change the osmotic pressure, to cause oxidative stress, and in extreme cases trigger brain cell degeneration or cerebral oedema.

Thesis 4

With a simultaneous exposure to noise and particles there is a higher risk of neurological illnesses (e.g. migraines), compared with the effect of particles alone.

There is the potential for particles to have neurodegenerative consequences (neurological disorders). Histological evidence of neurodegeneration has been reported in both canine and human brains exposed to high ambient particulate matter levels (Peters et al. 2006).

Conclusion

Chronic diseases of the cardiovascular system can be triggered both by particles and by noise.

There is some evidence that a boosted interaction exists, because, as we have shown, both pathogenetic mechanisms are integrated into a common network.

An increased cardiovascular risk from (ultra)fine particles can in principle be demonstrated in particle-related animal testing and in "in vitro" experiments (cf. Kreyling et al. 2005). However, the exposure levels in which translocation effects were measured in the lab were up to two times higher than was to be expected from the epidemiological studies (cf. Kreyling et al. 2005). It was hypothesised that translocated ultrafine particles enhance the activation of the coagulation mechanisms in vascular cells (Oberdörster et al. 2005). The elevated coagulation hypothesis is still being researched.

The fact that cardiovascular diseases can be triggered or exacerbated by noise-induced stress has been well documented in the literature e.g. by Ising (2005) on the basis of animal experiments. According to the publications available to us, stress is to be assigned the higher biological plausibility with regard to increased cardiovascular risks.

We can furthermore assume a positive interaction when:

- lung permeability and therefore the translocation of ultrafine particles is increased by stress, or
- the coagulation mechanisms in vascular cells are influenced by stress.

There is some evidence that cardiovascular diseases are primarily triggered by oxidative stress and intensified by particle effects. In the case of additional noise-induced stress, there is evidence of a boosted interaction because the pathogenetic mechanisms are predominantly identical.

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Noise and Indoor Air Pollution: Combined Exposure and Interaction

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Introduction

A national assessment of the burden of disease (measured as the loss of disability adjusted life years, DALY) due to different environmental contaminants and stressors, was performed by RIVM in the Netherlands. The total contribution of all environmental contaminants considered to the burden of disease was less than 5%. Of this particulate air pollution contributed 60%, environmental noise 24% and indoor air pollution (ETS, radon, dampness) 6%. As also some 80% of the total exposure to particulate air pollution of ambient origin occurs indoors, exposure to indoor pollutants and noise can be claimed to overwhelm the environment caused burden of disease. (de Hollander *et al.* 1999)

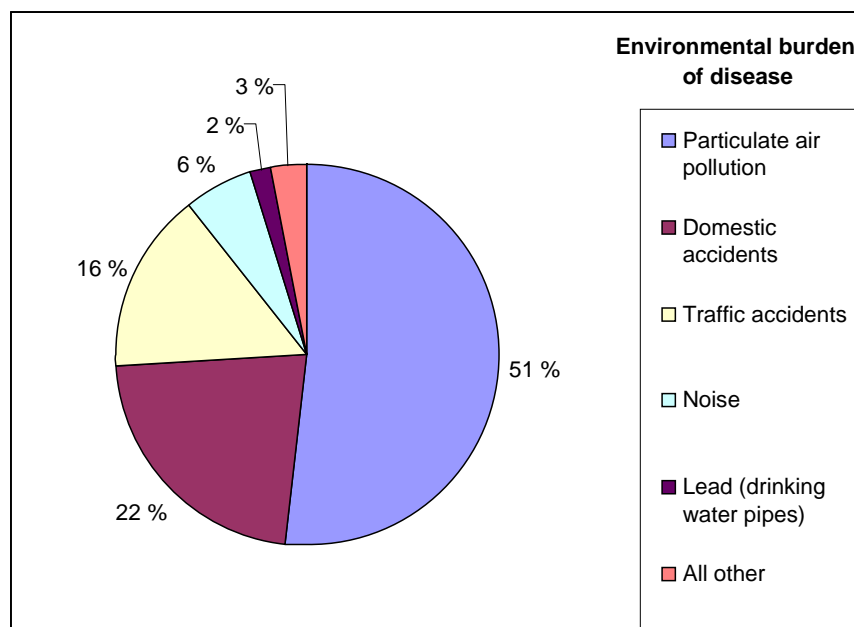**Figure 1:** *Division of the environmental burden of disease in the Netherlands between different sources (de Hollander et al. 1999)*

Although air pollution and noise have often common sources, research on exposure to and health effects of these stressors has progressed almost entirely independently of each other. The other has rarely entered into the study design even as a potential confounder for the other.

According to early (2004) assessment of the EnVIE project team the most important health effects of indoor air pollution are allergy and asthma exacerbation, other respiratory diseases, cancer and cardiac mortality. Odour and irritation from indoor air contaminants may worsen particularly the respiratory effects. The main indoor exposures considered to cause these health effects are tobacco smoke, combustion particles, carbon monoxide, radon, VOCs and moisture induced mould and dust mites. Their main sources are outdoor air, buildings (incl. ventilation and equipment), consumer products used indoors and occupant behaviour.
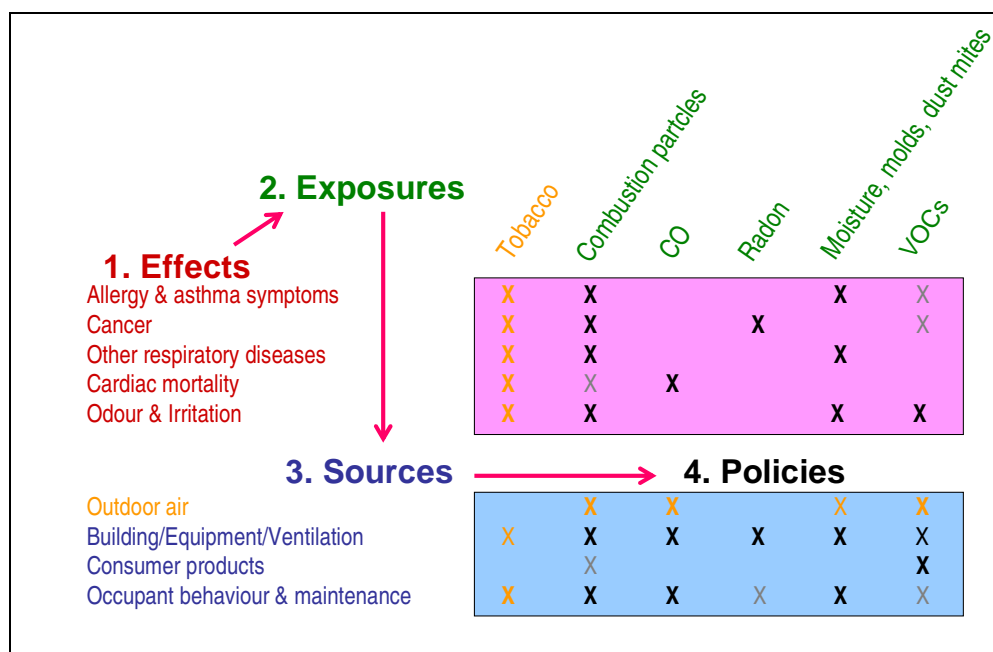
Figure 2: *The EnVIE project approach to the assessment and development of indoor air policies.*

The health effects of noise are twofold: Temporary and permanent hearing loss is caused by damage that prolonged and/or persistent exposures to high noise levels induce in the inner ear. The dose/response characteristics of such effects are well known and fairly independent of the target individual. Stress symptoms, e.g. sleep deprivation and difficulty to concentrate, occur, however, at noise levels, which do not come close to causing hearing loss. They depend both on the information content of the noise (quality) and its energy level (quantity), and both the type and severity of the stress symptoms of noise (or sounds) are quite host specific and variable in time. Severe noise stress symptoms include hypertension and possible contribution to asthma exacerbation. Sources of indoor noise are outdoor activities, of which street traffic is the most common, building functions, such as ventilation and elevators, human communication, music and TV, and noisy work activities, such as building renovation.

Exposures to both noise and air contaminants have been assessed in numerous occupational, residential and SBS (sick building syndrome) studies, but most of the study reports do not try to correlate the exposures with each other. Such studies are not discussed further in this document.

The same individuals are naturally exposed to both noise and indoor air pollution, often at the same time – therefore combined exposures and effects should be of interest, and there is some

published research on these issues. Of particular interest would be noise and air contaminant exposures which correlate with each other both in occurrence and magnitude. Similarly, noise and indoor air contaminant exposures which affect similar health endpoints in a synergistic fashion, one amplifying the effect of the other, should be of particular interest.

Highly correlated noise and air pollution exposures could be expected, when they are caused by the same source. Indoor renovation is an obvious candidate, although a rare nuisance in the course of most lives. Outdoor traffic is the most common. The other significant sources of indoor air pollution and noise are rather independent of each other.

For synergistic health effects to occur, the target organ of noise and air contaminants should be the same. This is not a strict requirement, but for this presentation other possibilities are not considered. Consequently for hearing loss a synergistic effect would require that the contaminant affects the inner ear. Such contaminants exists, they are called ototoxic and are found in indoor air also. Alternatively, noise may affect the target organs of indoor air contaminants. Noise is known to affect hypertension (ie. the heart), that is also affected by exposure to carbon monoxide and combustion particles (e.g. tobacco smoke). It is therefore conceivable that exposure to noise and the named air contaminants may exhibit synergistic cardiovascular health effects.

In the following paragraphs the literature is explored for these potentials. The exposures to noise and indoor air contaminants which are independent of each other are left aside and likewise also the health effects which affect different organs. Also exposures in industrial occupational settings are not considered.

Combined exposures to noise and indoor contaminants

Only two studies were identified, where correlations between indoor noise and air pollution exposures were reported.

Hodgson *et al.* (1991) from University of Pittsburgh analysed symptoms and microenvironmental conditions in non-problem office buildings. Symptoms of 147 office workers in 5 office building areas were assessed by self administered questionnaires. Thermal parameters, light, noise, CO_2, CO, RSP and VOC (TVOC?) were monitored. Noise level did not correlate significantly with any of the air contaminants (it correlated only with radiant temperature!). Noise level was weakly but non-significantly correlated with CO (positive, indicating a common source, probably traffic) and CO_2 (negative, indicating isolation from outdoor noise, possibly due to closed windows). CNS-, mucous membrane irritation, chest tightness and SBS syndromes all correlated significantly with VOC exposure and none with noise level.

Brauer *et al.* (2006) conducted a large (2164 participants), prospective (repeated after one year) questionnaire based study on self reported exposure to indoor air pollution (stuffy air, unpleasant odour, environmental tobacco smoke) and noise index (in room, from other rooms, from outside) at work and SBS symptoms. In this study noise index correlated with stuffy air index (0.30) and with ETS (0.26). In both baseline and follow up studies SBS symptoms increased significantly with stuffy air, ETS and noise indexes, as well as with the self reported draught, temperature, dry air, light, etc. indexes. When, however, the persistence of the symptoms of those individuals who reported SBS symptoms in the baseline were evaluated 1 year later, only the effect of stuffy air index on mucous membrane symptoms remained significant.

Results of the search for combined indoor air pollution and noise exposures (and the health effects thereof) were quite discouraging. It is possible that in spite of many attempts, proper search criteria were not identified. It is also possible that only quite few such studies have been conducted. There exist some additional studies, where both indoor air pollution and noise exposures have been determined, but independently, and not been associated with each other, which would exclude any analyses of combined effects.

Combined effects of noise and indoor contaminant exposures

Ototoxicity of chemicals as well as some other combined effects of chemical and noise exposure have been assessed in a number of experimental animal studies. These have been reviewed by Cary *et al.* (1997) to which one should add an experimental animal study by Morata *et al.* (1998). At least toluene, carbon disulfide, xylene, and trichloroethylene, carbon monoxide, cadmium and lead show combined effects with noise that exceed the summed effects of each agent acting independently. Such effects, however, only occur at levels of chemical exposures that are also independently toxic.

An epidemiological study (Ferrite and Santana 2005) found a combined hearing loss effect of tobacco smoke (active smokers) and noise exposure that was consistent with biological interaction, i.e. ototoxicity of tobacco smoke. The result is actually consistent with the animal studies, because tobacco smoke contains most of the compounds found ototoxic in animal studies, and decades of smoking exposes the smokers to levels of these toxins that are toxic also individually.

Tobacco smoke is such an overwhelming source of air pollution and odour exposure, that Berglund *et al.* (1992) and Berglund and Nordin (1992) argue that if a study method cannot find any effect of active smoking vs. passive or non-smoking on odour or noise detection threshold, "it probably cannot discern any sensory effects caused by indoor exposures." Indeed, they observe increase in both odour (formaldehyde, a component also in ETS) detection threshold and (pink) noise detection threshold among smokers vs. non-smokers.

Pan *et al.* (2003) report a human experimental study finding that in a combined exposure to odour (furfurylmercaptan, a coffee aroma component) and noise, increasing the noise exposure may have a masking effect on the perception of odour, but not vice versa. The observed interaction was, however, statistically insignificant.

An ongoing EU-funded collaborative research project, HYENA (Hypertension and Exposure to Noise near Airports), will assess the combined effects of traffic noise and air pollution, an issue of utmost public health significance (Järup et al. 2005).

Discussion & conclusions

Indoor air pollution and noise exposure cause an overwhelming proportion of the public health impact of all environmental stressors. Combined exposure to and effects of indoor air pollution and noise, therefore, would be of great environmental health significance. It was striking to find that only a few such studies have been reported in open literature.

The two combined noise and indoor air exposure studies that were found reported only low (questionnaire study) to insignificant (monitored exposures) correlations between indoor air pollution and noise levels. Neither reported significant or consisted effects of indoor noise levels on SBS symptoms. The negative findings may indicate that there, indeed, are no such significant effects at the noise levels of typical office buildings.

High exposure levels of some indoor air pollutants, which in non-industrial settings are likely to occur only to active smokers have been shown to interact with noise exposure to affect hearing.

Because exposures to both combustion particles and noise (via hypertension) affect the cardiovascular system, and both exposures are caused by street traffic, both while in transit, and while being exposed along the streets and highways, studies on such combined exposures and effect interactions would be of paramount importance.

The effects of the information content of noise in addition to its level and the effects of the host factors on noise induced stress (and hypertension) are obviously quite challenging to study, but also of utmost importance when the health effects of noise levels below the levels which may cause hearing loss are of interest. Jantunen et al. (2000), however, have published an indoor risks related source – exposure – health effects model, which allows combining the toxic effects of an agent with the sensory and information exposures and respective effects in one model, see Figure 3.
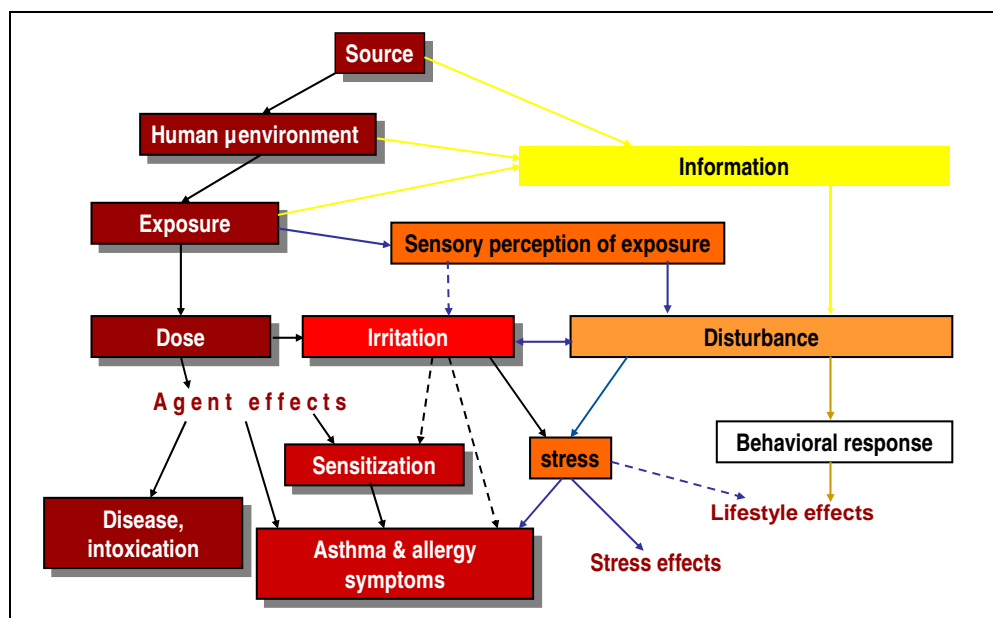

Figure 3: *Environmental health risk model combining toxic, sensory and stress effects of emission(s) from a source (modified from Jantunen et al. 2000)*

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Organic Solvent Ototoxicity – Human Literature Overview

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Organic solvents are frequent contaminants of atmoshperes in industry, including paint and lacquer factories, dockyards, plants manufacturing yachts, furniture, plastic, fibres, rubber tires and several other products. Many types of solvents, like paints and lacquers, are also used in other than occupational procedures – mostly in the household and they may constitute indoor pollution in houses and offices.

The main existing evidence and gaps in knowledge on organic solvents ototoxicity have been recently presented at the International Workshop "Health effects of exposure to noise and chemicals – ototoxicity of organic solvents" held on 15-16 November 2006 in Lodz, Poland (29). As what regards animal studies it has been concluded that several organic solvents, particularly styrene and toluene, are ototoxic in rats and their exposure produces mid-frequency hearing loss along with supporting and hair cell damage in the cochlea. More central (or retrocochlear) hearing damage, although very likely, has not been demonstrated clearly in animals, so far. The lowest concentration of styrene known to increase noise damage is 300 ppm, while for toluene it is 1000 ppm. These have been the lowest concentrations tested in animals but it does not guarantee that lower values are not injuring the cochlea. Styrene was more ototoxic than toluene. Synergistic effects occur in rats exposed to both noise and solvents. It could be explained on the basis of the mechanisms: solvent might modify the membranous structures of the outer hair cells (OHCs) making them more fragile and vulnerable to noise. In combined exposures, the most important factor for inducing hearing impairment is potency of noise exposure (level, impulsiveness); concomitant exposure to organic solvents may induce impairment where the exposure to noise alone may have little effect.

Ototoxicity of organic solvents in occupationally exposed human subjects is more difficult to elucidate. This is because the concentration of chemicals is much lower than this used in animal studies, and the workers are usually exposed to a mixture of solvents at widely varying compositions and concentrations, making unable the assessment of the effect of a single substance. Furthermore, in industrial settings exposure to chemicals often co-exists with an increased level of noise what makes difficult to distinguish solvent effect from noise-induced hearing loss.

Majority of literature data assessing the auditory function comes from industrial workers exposed to one of three following types of solvents: 1/ mixtures of solvents (which are the most common); 2/ styrene-only; and 3/ toluene only. This paper overviews human study evidence for organic solvent ototoxicity in these three exposure categories.

Mixture of organic solvents

Since 1984 fifteen original papers have investigated the relationship between occupational exposure to organic solvent mixture and hearing loss (2, 3, 6, 8-14, 21, 22, 25, 27, 28). The main compounds of the mixtures were xylene, toluene, methyl ethyl ketone (MEK), methyl isobutyl ketone and others (ethanol, ethyl acetate, butyl acetate, ethyl benzene, thinner, cyclohexane, benzene).

All studies, except one, were cross-sectional epidemiological studies (9 papers) or clinical studies (5 papers) from occupational health clinics; one was a longitudinal 20-year follow up study of workers exposed to noise. A total of over 2300 workers exposed to mixtures of organic solvents alone or in combination with noise were examined; among them 642 were exposed exclusively to mixture of organic solvents (noise below 85 dB-A).

The largest groups of workers were: painters, the workers of paint and lacquer industry, dockyards, workers of petroleum refinery, exposed to jet fuel, employees of aviation industry, employed in chemical divisions and others.

Exposure was assessed in 6 out of 15 studies; it comprised the current and/or cumulative concentration of every single solvent and current and/or cumulative exposure index (the sum of fractions of the concentration of a given solvent to its threshold limit value for all solvents in the mixture).

Current exposure concentration in the air of toluene ranged from 0 to 70 ppm, current exposure concentration of xylene ranged from 0–417 ppm, current exposure index ranged from 0.5 to 23 (10,13,14). Mean lifetime exposure (level x time of employment) to toluene ranged from 31-203 ppm, to xylene from 84 to 696 ppm, and exposure index from 10 to 67 (25, 27). The highest exposure was observed in dockyard workers (27), the lowest was in aviation and refinery industry (10, 14). The moderate exposure was observed in painters (13, 25).

No biological monitoring (metabolites in urine) was presented in any of these studies.

Hearing outcome evaluation

Eight studies evaluated risk / odds ratio of hearing loss due to solvent exposure (8, 9, 10, 13, 14, 25, 27, 28). Age, noise exposure, employment time were the most often included variables in the multivariate logistic regression models; in some studies – gender, alcohol consumption, hypertension, diabetes, smoking, noise trauma and family history were also incorporated. The risk of hearing loss was assessed at high frequencies (10, 13, 14), and all frequencies (25, 27, 28) or middle speech frequencies (8, 9).

No additional risk comparing to control non-exposed population was found for solvent mixture-exposed workers when:

- the exposure history was short (up to 4 years) (Fig. 1) (8),

- the exposure level was currently very low (few ppm) (10,14).

Additional risk, comparing to control non-exposed population, was found for solvent mixture-exposed workers when:

- the exposure level was moderate (tens of ppm) (13, 25),

- the workers were exposed to high concentrations of solvents along with noise (up to few hundreds of ppm (27, 28).

With increasing time of employment in exposure to solvents the risk of hearing loss was also increasing (9).

Eleven studies assessed the effect of solvents on audiometric hearing threshold; five papers evaluated central effects to hearing (stapedial decay and contralateral stapedial reflex, interrupted and distorted speech, evoked cortical response, cognitive response. In one study hearing loss was assessed subjectively with a questionnaire.

In the study by M. Sliwinska-Kowalska et al. using the multiple linear regression analysis, the correlation was found between solvent mixture exposure (expressed as lifetime exposure index) and hearing threshold at 8 kHz in dockyard workers (27). The same group of authors has showed similar relationship for 4, 6 and 8 kHz, when the analysis was done for dockyard and paint & lacquer factory workers (respectively high and moderate exposure to solvents) (28).

Central auditory effect has been shown in workers exposed to organic solvents mixture mainly with distorted speech tests and cortical evoked responses (12, 22).

Styrene exposures

Styrene is produced from oil or petroleum and used as an intermediate chemical for polymers in making plastics, resins, coatings and paints. Occupational exposures to styrene occur mainly in the manufacturing of fibreglass reinforced plastic products.

Since 1988 nine studies has been published investigating the relationship between occupational exposure to styrene and hearing loss (4, 7, 16-20, 23, 26). All studies were epidemiological cross-sectional ones or clinical ones, performed in occupational health clinics. More than 1000 workers exposed to styrene alone or in combination with noise exposure were examined.

Exposure was assessed in all of the studies, with current concentrations ranging from 2 ppm to 54 ppm. Two studies assessed whole life exposure with its mean value around 12 ppm (26). Four studies implemented current biological monitoring (mandelic acid in urine) (7, 15, 17, 20).

Hearing outcome evaluation

Out of the nine studies, seven showed some effects on the auditory pathway associated with styrene exposure alone (4, 16-20, 26). These effects were found in different outcome measures such as pure-tone audiometry (16, 26), high frequency hearing loss (17, 18, 20) and central auditory tests (4, 19). It was shown that the exposure to styrene is a risk factor for hearing loss, and that the risk of hearing impairment increases with increasing concentration of mandelic acid in urine (16, 17).

Toluene exposures

Toluene, as a compound of mixture used mostly in the production of paints, lacquers, rubber and glue, dyes, and degreasing agents. The isolated exposures to toluene are present in rotogravure printing plants.

There are only four papers assessing the relationship between occupational exposures to toluene and hearing loss (1, 5, 15, 24). Three of them are positive (1, 5, 15), and one is negative (24). One study has shown an increased risk of hearing loss in workers exposed to toluene at the concentration ranging from 75-365 ppm (15). Moreover, the odds ratio of hearing loss was correlated with an increasing concentration of hippuric acid (metabolite of toluene) in urine. However, another study did not confirm these findings in workers exposed to toluene at the concentration below 50 ppm using the same study protocol (24).

Conclusions

1. There is an increasing evidence derived from epidemiological and clinical studies that organic solvents are toxic to the auditory organ in industrial workers.

2. The most frequent occupational exposures involve solvent mixtures with xylene, toluene, methyl ethyl ketone (MEK) as the main compounds; in some industries styrene-only exposure (glass-fibre reinforced industry) or toluene-only exposure (rotogravure printing) are present.

3. There is no consensus on the lowest occupational exposure limit for solvents in relation to their effect to auditory or vestibular organ. Some studies have shown that styrene at the concentration below 12 ppm (the lowest OEL in the world) could still possibly cause hearing impairment. Another study showed that occupational exposure to toluene below 50 ppm was safe on what regards the auditory (and visual) system. As for organic solvent mixture, very low (few ppm), and very short exposures (less than 4 years) did not cause hearing impairment. Moderate exposure (around and below OELs) were found to significantly increase the odds ratio of hearing loss. For high exposures (above OEL) a correlation between solvent concentration and hearing loss was observed to be linear.

4. Organic solvents have detrimental effects on various levels of the auditory system, including cochlea, retrocochlear and central auditory nervous system structures. Thus, pure-tone audiogram is inadequate in distinguishing between solvent-induced hearing loss and noise-induced hearing loss, and central auditory tests must be implemented.

5. A synergistic effect occurs in case of combined exposure to noise and solvents. This significantly increases the odds ratio of developing hearing loss, although noise-induced hearing loss dominates over solvent one when permanent threshold shift is assessed with pure-tone audiometry.

6. Awareness should be raised among occupational physicians and decision makers that the current limits and hearing conservation programmes might be inadequate regarding exposures of solvents alone or in combination with noise.

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Promotion of Noise-induced Hearing Loss by "Pro-oxidant" Chemicals

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The damaging effects of noise on auditory function can be altered significantly by exposure to additional agents that may or may not, by themselves, be ototoxic. This paper focuses on the ability of chemical asphyxiants and acrylonitrile to potentiate noise induced hearing loss in a laboratory animal model. We will discuss both the exposure conditions that favor such potentiation and also the potential mechanisms for potentiation. The data shows that exposure to low to moderate levels of carbon monoxide (CO) or hydrogen cyanide can potentiate noise induced hearing loss (NIHL). The relationship between such levels and those permitted in work environments is provided. Evidence is presented that free oxygen radicals may be responsible for potentiation of NIHL by chemical asphyxiants: the ability of a free radical spin trap agent, alpha-phenyl N-tertiary-butyl nitrone (PBN), to prevent the adverse effects of CO is demonstrated. Finally, in order to further elucidate the mechanisms involved in the potentiation of NIHL by "pro-oxidant" agents, data is presented on acrylonitrile (ACN), an extensively used industrial chemical that decreases glutathione (GSH) levels and generates cyanide, which in turn, can inhibit Cu/Zn superoxide dismutase. We show that exposure to ACN renders the cochlea much more vulnerable to noise, even for moderate noises close to the human permissible exposure levels. Manipulation of ACN metabolic pathways suggests that GSH is the main intrinsic cochlear defense against reactive oxygen species (ROS). These results suggest that a moderate noise level can initiate the generation of ROS, and that in normal conditions, the free radical buffering system can neutralize these ROS. However, in the presence of ACN, or any "pro-oxidant" chemical, the cochlea can become much more vulnerable, and oxidative stress may occur.

Introduction

Noise-induced hearing loss (NIHL) is the most common occupational disease in the United States (NIOSH, 1996b). Nearly 30 million U.S. workers are exposed to potentially hazardous noise levels in the workplace (Franks et al., 1996). Consequently, the Occupational Safety and Health Administration (OSHA) has adopted a permissible exposure level (PEL) that is designed to prevent NIHL in the Hearing Conservation Amendment (OSHA, 1981) to the U.S. Occupational Safety and Health Act of 1970 (PL 91-596). Nevertheless, NIHL remains a critical occupational concern in the United States and around the world (NIOSH, 1996a).

Noise is estimated to be a significant contributor to hearing loss in roughly 30% of Americans with hearing loss, despite the adoption of exposure standards. The reasons for this epidemic of occupational hearing loss are many. They include substantial individual differences in susceptibility to noise (NIOSH, 1996b), difficulty in quantifying and controlling noise exposure of particular individuals in the workplace (dosimetry) (NIOSH, 1996b), the uncertainty involved in the trade-off between duration of noise exposure and noise intensity that is reflected in the different guidelines recommended by NIOSH and those adopted by OSHA (NIOSH, 1996b), and, probably, the understudied phenomenon of potentiation of NIHL by coexposure to particular chemical ototoxicants (Fechter, 1989). This article focuses on the last of these issues.

Auditory system injury can result from exposure to a wide variety of drug and chemical exposures as well as from the physical agent, noise. In addition, a number of chemical toxicants that do not themselves produce permanent hearing loss can potentiate NIHL. Laboratory animal studies as well as occupational epidemiology studies have identified such chemicals. Several literature reviews have been published previously that focus primarily on ototoxic drugs (Rybak, 1995; Henley & Rybak, 1995). Organic solvents (e.g., Crofton et al., 1994; Campo et al., 1997; Johnson et al., 1988; Crofton & Zhao, 1994; Fechter et al., 1998; Morata et al., 1993, 1994, 1997a, 1997b), metals (e.g., Rice & Gilbert, 1992; Wu et al., 1985; Schwartz & Otto, 1987; Fechter et al., 1992), and chemical asphyxiants (Young et al., 1987; Fechter et al., 1988; Fechter, 1989; Chen & Fechter, 1999; Chen et al., 1999) can all have ototoxic effects. Simultaneous and even successive exposure to certain of these agents in combination with noise can greatly increase susceptibility to NIHL (Johnson et al., 1988, 1990; Fechter et al., 1988, 2002; Johnson, 1993; Lataye & Campo, 1997; Morata et al., 1993; Chen & Fechter, 1999; Chen et al., 1999). It appears that solvents generally have an additive effect to noise in producing hearing loss. Asphyxiants, by contrast, appear capable of true synergistic effects on NIHL. While in most instances the mechanisms responsible for chemical ototoxicity have not been elucidated, there are sufficient data relating oxygen delivery and cochlear function to begin to focus on the process by which chemical asphyxiants and noise interact to permanently disrupt hearing at least in a laboratory animal model. Specifically, evidence showing that intense noise can initiate reactive oxygen species (e.g., Seidman et al., 1993; Yamane et al., 1995; Yamasoba et al., 1999; Lautermann et al., 1997, Henderson et al., 1999) and evidence that both carbon monoxide and hydrogen cyanide may further contribute to oxidative stress (Fechter et al., 1997, 2002) suggest that attention must be paid to other chemical agents which may promote reactive oxygen species generation. Recent evidence with respect to the potentiation of noise induced hearing loss by acrylonitrile (Pouyatos et al., 2005) give increased weight to this suggestion. These findings open the bigger question of whether or not oxidative stress may be a basis by which several chemical agents promote NIHL.

Chemical asphyxiants and promotion of NIHL

The chemical asphyxiants as a class of agents reduce the delivery of oxygen to tissue or the utilization of oxygen by tissues. Clearly, they are chemical contaminants, not agents that have direct commercial benefit. Hypoxia is a state of reduced oxygen delivery that occurs when chemical asphyxiants are applied, but it can also occur under conditions of reduced oxygen delivery per se. Chemical asphyxiants are among the most common chemicals to which workers are exposed.

Cyanides are used in the extraction of low-grade ores, in electroplating, and as chemical intermediates (U.S. Department of Health and Human Services, 1995). Some of the

occupations in which cyanides are used intentionally include steel production, electroplating, mining, metal leaching operations, metal cleaning, and analytical chemistry. Cyanides are used in the manufacture of synthetic fibers such as nylon, plastics, dyes, and pigments. In addition to the inadvertent exposure to cyanide as a combustion product, this toxicant is also a significant breakdown product of acrylonitrile— a compound used in manmade fibers, and in certain plastics. The OSHA PEL for HCN is 5 ppm as an 8-h time-weighted average. Carbon monoxide exposure is ubiquitous, as it is the major combustion-related pollutant in air (U.S. EPA, 1991). All workers whose employment involves vehicles using internal combustion engines have potential exposure to carbon monoxide. These include car, bus, and truck drivers, toll takers, mechanics, garage attendants, and police officers. NIOSH (1972) estimated that nearly 1 million workers are exposed to significant levels of CO in their workplaces. NIOSH has recently reiterated the risk that CO poses in the workplace (NIOSH, 1996). Carbon monoxide is a leading cause of inhalation injuries in the workplace (Henneberger et al., 2000; Valent et al., 2002). It is a prominent factor in ongoing health hazard evaluations conducted by NIOSH (www2.cdc.gov/hhe/hhesearch.html search term = carbon monoxide). In addition to being a major air pollutant and a waste gas generated by incomplete combustion, CO exposure may occur among acetylene workers, steel and coke oven workers, and pulp and paper workers, among others (U.S. EPA, 1991). Carbon monoxide is also produced as a metabolic by-product of the paint stripper methylene chloride. The OSHA 8-h time-weighted PEL for CO is 50 ppm with an instantaneous ceiling of 200 ppm. The ACGIH time-weighted threshold limit value (TLV) is 25 ppm. The NIOSH recommended exposure level is 35 ppm averaged over 8 h with a 200-ppm ceiling.

While exposure standards for noise are of primary importance in protecting against NIHL, it is important to evaluate complex exposures that include chemicals for their potential to injure the ear. The data presented here focus on an approach to risk assessment for combined exposure to noise and the chemical asphyxiants CO and HCN. Figure 1 presents data on the relationship between carbon monoxide concentration and potentiation of noise induced hearing loss. In this experiment, rats were exposed to carbon monoxide concentrations of 300–1500 ppm for 8 h in combination with octave band noise. Comparison groups received either 1200 ppm carbon monoxide for 8 h but with no noise or no experimental treatment. Four weeks following these treatments, auditory thresholds were assessed at a range of tone frequencies between 2 and 40 kHz. This range covers a broad spectrum of the rat's auditory range. Auditory thresholds were measured by recording the tone intensity needed to produce a compound action potential recorded from the round window of the cochlea. The compound action potential represents synchronous neuronal activity generated at the spiral ganglion cell. The abscissa shows the specific test frequencies used, while the ordinate shows the sound level required to obtain a just noticeable compound action potential. The control rats show auditory thresholds that approach 0 dB SPL in the most sensitive frequency range (12–16 kHz). Auditory thresholds are less sensitive at low and high frequencies, although thresholds are readily measurable at all frequencies tested. It is clear from this figure that CO exposure by itself has no persisting effects on compound action potential sensitivity; thresholds for the rats receiving CO alone are comparable to control rats. However, as CO concentration increases for rats receiving combined exposure of CO + noise, there is an orderly increase in the extent of auditory threshold impairment relative to the rats receiving noise by itself. Statistically significant elevations in NIHL are observed with CO exposures of 500 ppm and higher. Benchmark dose analyses have been performed to estimate how much carbon monoxide is necessary before potentiation of NIHL occurs (Fechter et al., 2000; Rao & Fechter, 2000b). Those studies suggest that exposure levels of 200 ppm approach the level at which slight (10% or 5 dB) exacerbation of hearing loss occurs beyond that which can be accounted for by noise. Such an exposure level is far higher than what is experienced even in

highly polluted environments. However, such levels may occur for short time periods in specific industrial settings (e.g., fires and foundries) and may pose some additional hazard for workers.

Histological analysis of cochleae from rats submitted to combined exposure to noise and CO showed that outer hair cells (OHCs) are the cell type most sensitive to this interaction. Surface preparations were dissected from cochleae of rats exposed to 105 dB noise (OBN, 8 kHz) + 1000 ppm CO for 2 days (4h / day). A cytocochleogram showing the repartition of OHC loss along the organ of Corti, and a picture of the organ are presented in figure 2a and b, respectively.

Mechanisms by which chemical asphyxiants may potentiate NIHL

This hypothesis of the involvement of oxidative stress was addressed by investigating the protective effects of the free-radical spin-trap, PBN, against NIHL and its potentiation by CO. The drug was administrated both prior to and following combined exposure and also only following exposure in order to address the potential for this agent to serve in a therapeutic strategy. While both administration strategies reduced the extend of NIHL by combined exposure, PBN given before and after exposure provided significantly better protection against potentiation of NIHL by CO when compared to post-exposure administration alone (Rao et Fechter, 2000a) (Figure 3). Repeated post-exposure administration of PBN within 4 hr of exposure revealed somewhat greater protection than a single administration of PBN. While not providing definitive evidence, such data suggest that free radicals may be generated during the combined exposure leading to cochlear impairment. In this experiment, the disruptive effect of noise by itself on the cochlear action potential (CAP) threshold was quite small and it is not certain whether or not the PBN might serve to reduce NIHL as well as its potentiation by CO.

Estimating cyanide levels that promote NIHL

Unlike the case for hypoxic hypoxia (reduction of oxygen concentration in inspired air typically by the dilution of air with nitrogen), carbon monoxide, and ischemia, the effect of cyanide on auditory function has not been as well studied. Van Heijst et al. (1994) studied twenty patients in Tanzania with sudden onset polyneuropathies correlated with elevated blood cyanide. Hearing loss was identified in nearly half of those cases. The source of cyanide exposure was believed to be increased dietary intake of cassava due to food shortages. Direct experimental evidence that cyanide can produce cochlear impairment is limited to a handful of studies. Konishi and Kelsey (1968) and Evans and Klinke (1982) showed acute impairments in cochlear function due to cochlear perfusion with cyanide salts in experimental animals. Tawackoli, Chen, and Fechter (2001) showed that injection with cyanide salts could also acutely disrupt pure-tone thresholds in rats. This transient auditory threshold loss, seen particularly for high-frequency stimuli, correlated well with an abrupt drop in the endocochlear potential generated by the stria vascularis.

Fechter et al. (2002) investigated the permanent effects of hydrogen cyanide exposure on permanent NIHL. They showed that even low doses of hydrogen cyanide were able to potentiate NIHL in rats. Statistically significant promotion of noise induced hearing loss was observed when noise was combined with 30 ppm HCN. Using a benchmark dose defined as the lower bound to the 95% confidence interval about the benchmark concentration that potentiates NIHL falls between 2 and 16 ppm. If these values are subjected to an 8-h TWA in line with OSHA protocols, then the lower bound to the 95% confidence interval for

benchmark dose would be 0.5 and 4ppm. For comparative purposes, the current PEL for cyanide provided by OSHA is 10 ppm, based on an 8-h TWA with a (Short Term Exposure Limit) STEL value also set at 10 ppm.

Acrylonitrile

There is strong evidence that intense noise can initiate reactive oxygen species (ROS) in the cochlea and that antioxidants may be effective in reducing or blocking. Along with the results obtained with chemical asphyxiants described above, pharmacological studies have documented the ability of antioxidant drugs or prodrugs to block or reduce NIHL (Seidman et al., 1993; Yamasoba et al., 1999; Henderson et al., 1999). Second, genetic studies have demonstrated that laboratory animal models with reduced antioxidant buffering capacity are more vulnerable to NIHL than are wild-type subjects (Ohlemiller et al., 1999a; Ohlemiller et al., 2000). Finally, there are a limited number of reports with direct evidence of oxidative stress or of increased ROS in subjects who have been exposed to noise (Yamane et al., 1995; Ohlemiller et al., 1999b, 2000; Ohinata et al., 2000a, b). Those observations led to the prediction that chemicals that disrupt intrinsic antioxidant defenses hold significant risk for potentiating NIHL. Acrylonitrile (ACN) is one of those chemical compounds.

ACN ranks forty-second on the list of chemicals used in the United States (Anonymous, 1980). Some 3.21 billion pounds of ACN were produced in the United States alone in 1995, with estimated exposure to approximately 125,000 workers (Kirshner, 1995). ACN is used to make synthetic fibers (acrylic and nylon), nitrile rubbers, and plastics and is used as a chemical intermediate in the synthesis of a variety of products including dyes and pharmaceuticals. While NIOSH-recommended permissible exposure level to ACN is quite low (1 ppm), exposure can reach high levels via skin contact in case of accidental exposure (Kirschner, 1995).

The metabolism of ACN (Figure 4) is associated with significant potential for oxidative stress. ACN conjugates glutathione (Benz et al., 1997), depleting this important antioxidant rapidly. A second pathway involves the formation of cyanide as a by-product (Langvardt et al., 1980; van Bladeren et al., 1981). Cyanide, in turn, can inhibit superoxide dismutase and produce oxidative stress through other pathways as well.

Fechter et al. (2003) and Fechter et al. (2004) have shown that ACN (50 mg/kg sc/day) can potentiate permanent NIHL for noise levels ranging from 105 dB for 5 days (4 hours/day) to 108 dB for 8 hours and that this potentiation can be prevented by the administration of PBN. Pouyatos et al. (2005) also showed that combined exposure to ACN and noise yielded pronounced loss of threshold, even for noise levels that did not cause any hearing loss by themselves (95 and 97 dB SPL for 5 days, 4 hours/day). Histological analysis showed that combined exposure to noise and ACN induced massive outer hair cell loss, but no inner hair cell loss (Figure 5).

In a more recent study (Pouyatos et al., 2007) the same authors altered these metabolic pathways pharmacologically (Figure 4) in order to further delineate the role of specific antioxidants in the protection of the cochlea. They investigated the effects of Sodium Thiosulfate (STS), a CN inhibitor, 4-methylpyrazole (4MP), a drug that blocks CN generation by competing with CYP2E1, and L-N-acetylcysteine (L-NAC), a pro-GSH drug, in order to distinguish between GSH depletion and CN production as the mechanism responsible for potentiation of NIHL by ACN. Long-Evans rats were exposed to an octave-band noise (97 dB SPL, 4 hr/day, 5 days) and ACN (50 mg/kg). Separate pre-treatments with STS (150 mg/kg), 4MP (100 mg/kg) and L-NAC (4x400 mg/kg) all dramatically reduced

blood CN levels (Figure 6), but only L-NAC significantly protected GSH levels in the cochlea (table 1). Concurrently, only L-NAC treatment decreased the auditory loss (Figure 7) and hair cell loss resulting from ACN+noise, suggesting that GSH is involved in the protection of the cochlea against reactive oxygen species generated by moderate noise levels. On the other hand, CN does not seem to be involved in this potentiation.

Conclusions

Audiologist, prevention specialists and hearing researchers are acutely aware of the ability of noise to damage hearing; indeed, NIHL is recognized as one of the leading occupational injuries. Recognition that exposure to chemicals in the workplace and in the general environment can also damage hearing directly and make people more vulnerable to the adverse effects of noise is less understood and less recognized. This paper focused attention on a group of specific chemical agents that can impair hearing and has sought to identify both potential mechanisms by which such hearing loss occurs, as well as the cells that are targets for toxic insult. Understanding how chemicals can affect hearing helps audiologists predict other potentially ototoxic agents and to develop therapeutic strategies for increasing recovery from such hearing loss.

The results presented here demonstrate the potential of chemical asphyxiants to potentiate NIHL. CO and HCN, chemical neurotoxic agents, which have only acute effects on hearing, are able to enhance permanent NIHL when both noise and chemical agent are presented together. The data do not fully address the possibility that potentiation of NIHL by CO can occur under noise conditions that produce no hearing loss whatsoever. In all cases where CO potentiation of NIHL was observed, the appropriate comparison group that received only noise exposure did show at least some limited NIHL. However, earlier studies which provided longer recovery periods of up to eight weeks following exposure (e.g. Young et al., 1987; Fechter et al., 1988) did show that CO could potentiate NIHL at noise exposure conditions that had no significant effects on auditory function. In any case, when studying occupational noise exposure, there are a considerable number of individuals who do ultimately develop a threshold shift. The current risk data suggest that these cohorts are at greatest risk for potentiating effects of simultaneous CO exposure.

While several mechanisms are likely responsible for chemical ototoxicity, one mechanism that has received substantial investigation is that of oxidative stress. One can, in fact, hypothesize that chemicals that impair antioxidant pathways in the ear will predispose the hearing organ to injury from subsequent noise exposure. Consequently, using laboratory animal models, it is possible to block or greatly reduce hearing loss from chemicals and noise by administration of antioxidant drugs. Investigations using combined exposure to ACN and noise provided evidence that chemicals that decrease intrinsic anti-oxidant defenses can render the cochlea more sensitive to oxidative stress. Therefore, a noise exposure which is harmless by itself could become harmful in presence of ACN, or any pro-oxidant chemical, including CO and organic solvents. Given the fact that exposure levels to these above-mentioned chemicals are generally very low in the environment, future epidemiological research will have to focus on the workplace to evaluate which professional environments put the workers at risk.

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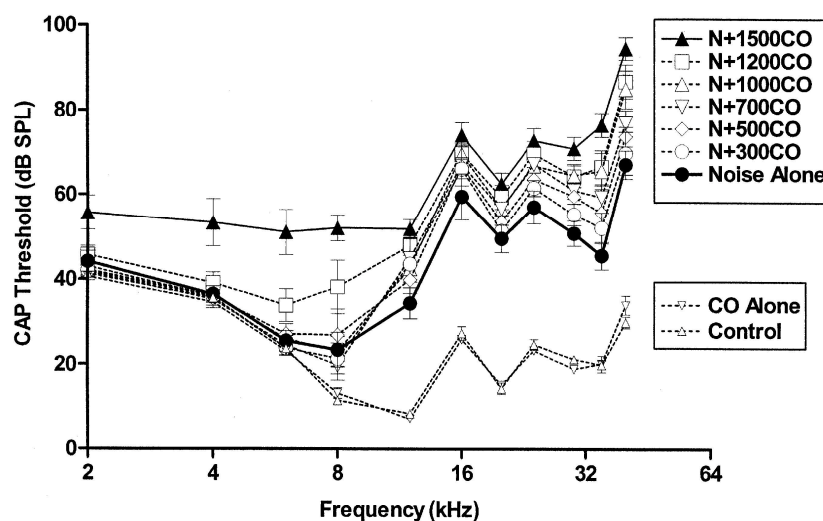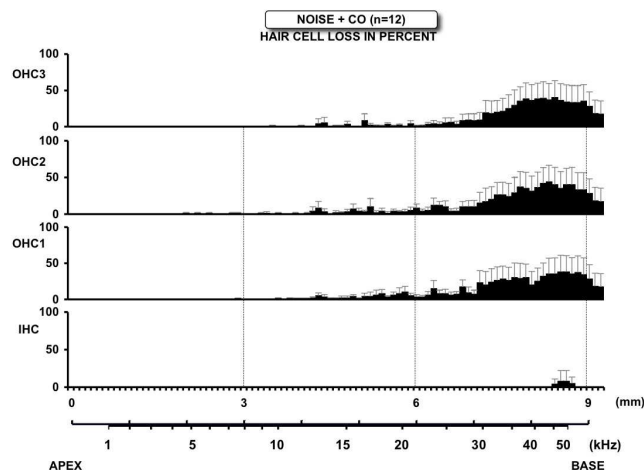
Figure 1. *Effect of simultaneous carbon monoxide (CO) exposure dose on potentiation of noise (N)-induced hearing loss (100 dB OBN 10-20kHz for 8 hours) assessed 4 weeks following exposure. Carbon monoxide levels of 500 ppm and higher produced a significant elevation in noise-induced hearing loss. Adapted from Chen et al (1999).*

(a)

(b)
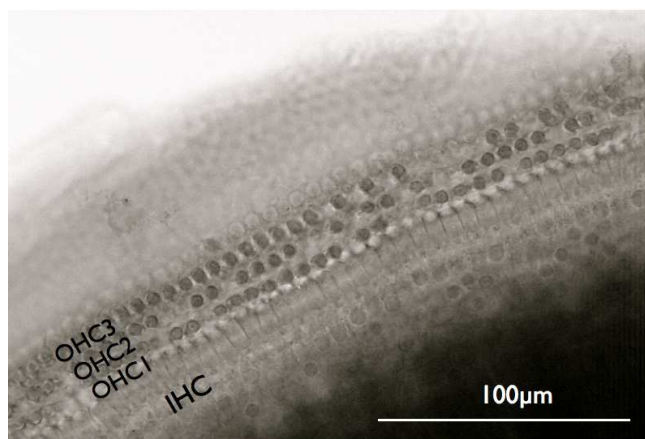
Figure 2. *Average cytocochleogram (a) and microphotograph of the organ of Corti (b) showing hair cell loss in rats exposed to noise + CO (105 dB octave band centered at 8 kHz for 2h + 1000ppm CO for 3.5h). Cochleae from subjects exposed to noise alone displayed very limited hair cell loss. Microphotograph was taken around the 30kHz cochlear location. Cytocochleogram: abscissa - upper trace: length (mm) of the entire spiral course of the organ of Corti from the bottom of the hook. - lower trace : frequency-map according to Müller (1991). Ordinate: hair cell loss in percent. IHC: inner hair cells; OHC1: first row of outer hair cells; OHC2: second row; OHC3: third row. Error bars in the cytocochleogram represent the standard error. The scale bars represent 100 μm.*
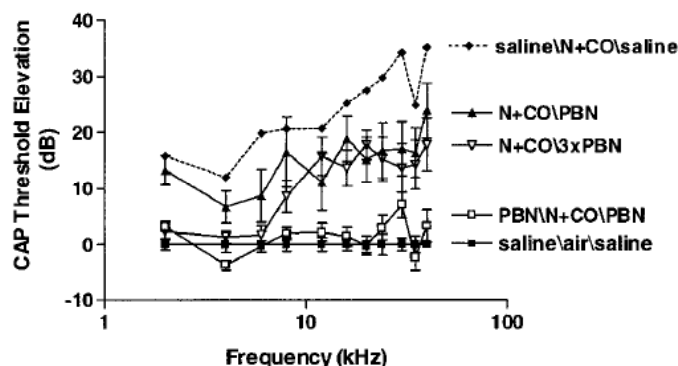
Figure 3. *CAP threshold elevations evaluating protective effects of PBN following the three administration protocols (prior to and following administration with PBN, PBN-N+CO-PBN; single administration postexposure, N+CO/PBN; and repeated administration postexposure, N+CO/3xPBN are graphed. Values presented are means ± SE. Significant protection against the potentiation of NIHL by CO was observed when PBN was given prior to and following combined exposure (100 and 50 mg/kg ip, respectively). In fact, animals given PBN prior to and following noise plus CO exposure were no different from animals injected with saline. The single-dose PBN administration did not protect against potentiation of NIHL by CO, whereas some protection at low frequencies was obtained following repeated administrations of PBN. Adapted from Rao et al (2000).*
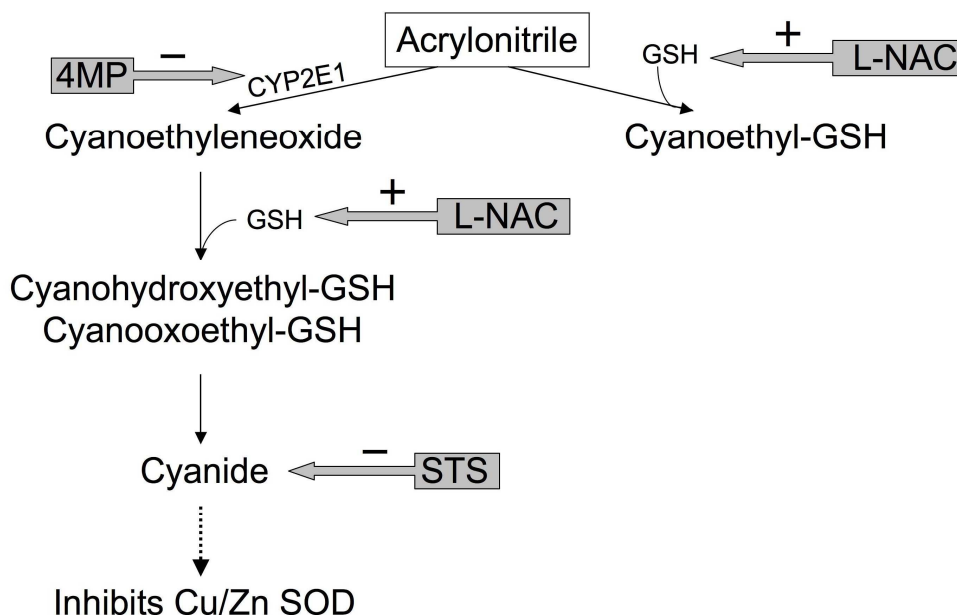
Figure 4. *Simplified acrylonitrile metabolism with the action of the three anti-oxidants used in Pouyatos et al. (2007). ACN: acrylonitrile; STS: sodium thiosulfate; 4-MP: 4-methylpyrazole; L-NAC N-acetylcysteine; GSH: glutathione; CYP2E1: cytochrome P-450 2E1; +: increases; -: decreases. Adapted from Pouyatos et al. (2007).*
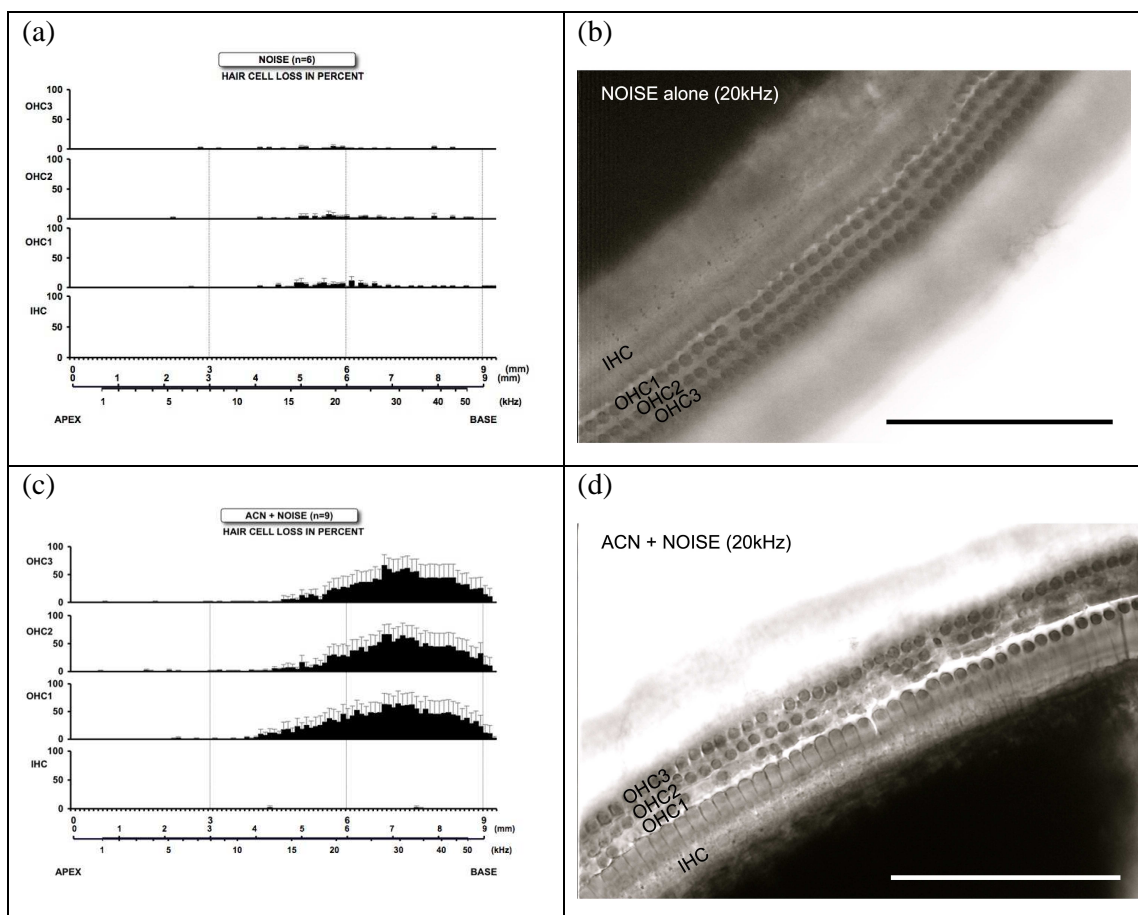
Figure 5. *Average cytocochleograms (left panels) and microphotographs of the organ of Corti (right panels) showing hair cell loss in rats exposed to (a,b) noise alone (97 dB octave band centered at 8 kHz, 4h/d, 5 days), and (c, d) ACN 50 mg/kg + noise. Microphotographs were taken around the 20kHz cochlear location. Abscissa - upper trace: length (mm) of the entire spiral course of the organ of Corti from the bottom of the hook. - lower trace : frequency-map according to Müller (1991). Ordinate: hair cell loss in percent. IHC: inner hair cells; OHC1: first row of outer hair cells; OHC2: second row; OHC3: third row. Error bars represent the standard error. The scale bars represent 100 μm. Adapted from Pouyatos et al. (2007).*
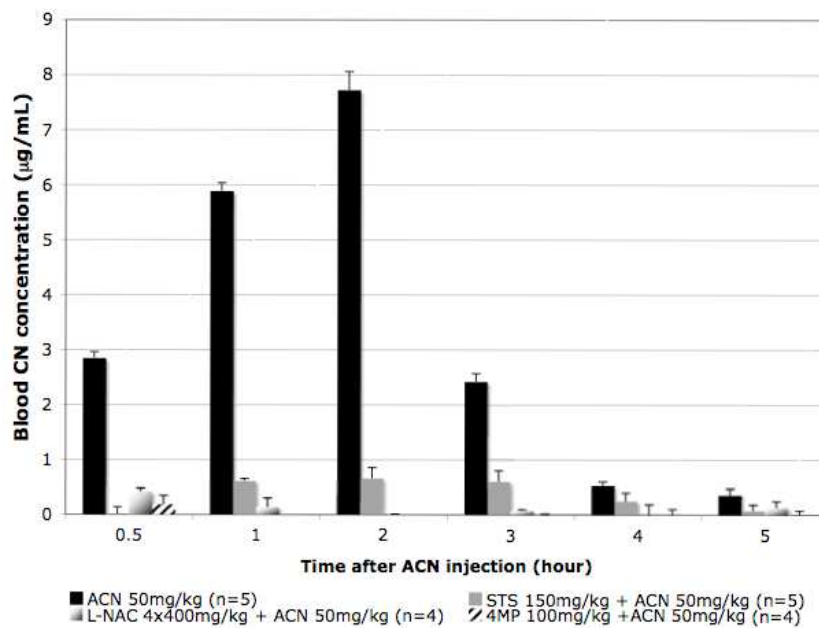
Figure 6. *Accumulation of cyanide in systemic blood following injection with ACN, STS+ACN and L-NAC+ACN. Values at each time point are the mean ± SEM. Adapted from Pouyatos et al (2007).*

Table 1. *Total cochlear glutathione content in control, ACN, 4-MP+ACN, STS+ACN and L-NAC+ACN (n=4 per time point) exposed rats measured 1 and 3h post-treatment. Values at each time point are the mean ± SEM. * significantly different from controls (p<0.05). # significantly different from the ACN-treated group at the same time point (p<0.05). Adapted from Pouyatos et al. (2007).*

COCHLEA		Time after ACN administration			
		1 hour		3 hours	
Treatment	GSH (nmol/mg protein)	GSH (nmol/mg protein)	% change compared to controls	GSH (nmol/mg protein)	% change compared to controls
Controls	7.21 ± 0.54 (n=7)				
ACN		n.d. (n=4)	/	2.82 ± 0.91 * (n=5)	-61%
STS+ACN		n.d. (n=3)	/	n.d. (n=3)	/
4-MP+ACN		3.65 ± 0.81 * (n=3)	-49%	3.89 ± 2.45 * (n=3)	-46%
L-NAC+ACN		24.85 ± 7.59 * (n=4)	+244%	16.40 ± 3.73 # (n=4)	+127%
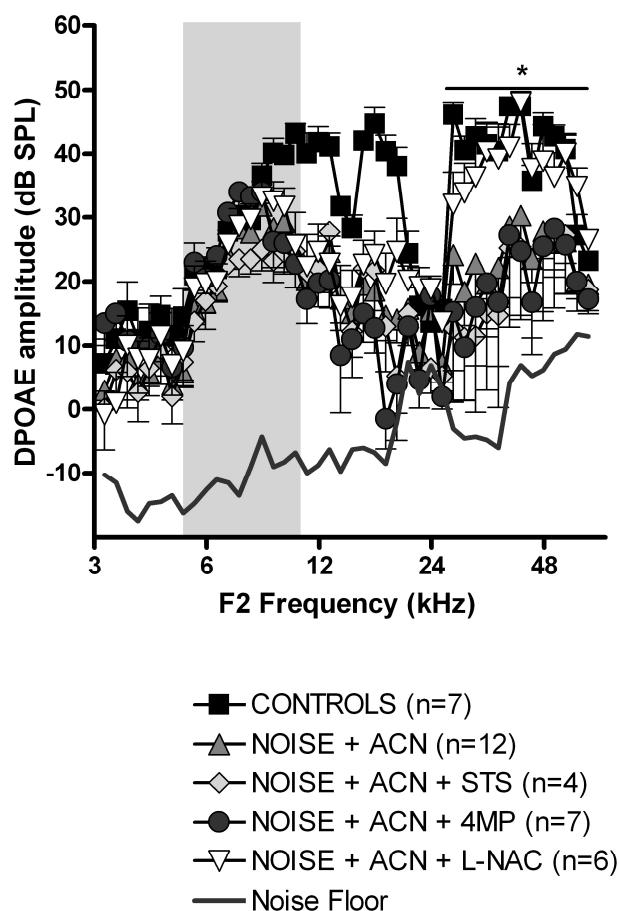
Figure 7. *Effects of sodium thiosulfate (STS), 4-methyl pyrazole (4-MP) and L-N-acetylcysteine (L-NAC) on the potentiation of NIHL by acrylonitrile (ACN). DPgrams were obtained 4 weeks post exposure with the levels of the primaries f1 and f2 set at 75, and with f2/f1 = 1.25. The tested f2 frequencies ranged from 3.2 to 63 kHz (geometric mean frequencies: 2.9 to 56.3 kHz), in 0.1 octave increments. The gray area represents the noise frequency range. Error bars: +/– sem. DPAOE amplitude from rats exposed to noise alone (not shown) were comparable to control values at all frequencies. Adapted from Pouyatos et al. (2007).*

The Interaction of Noise and Pesticides on Human Hearing and Balance

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Presented by Robert W. Keith on 15-16 of January 2007 at the Workshop on "Combined Environmental Exposure: Noise, Air pollution, Chemicals" in Ispra (Italy).

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Introduction

The charge presented by the Physical and Chemical Exposure Unit of the European Commission DG Joint Research Center, of the Institute for Health and Consumer Protection, to the participants of the Ispra meeting was to address several questions related to the health effects of several pollutants and noise on human health. The specific questions are addressed in the following paragraphs.

Question 1: Which health endpoints are affected by noise, air pollutants and other chemicals in ambient air?

Epidemiological studies of pesticides have discovered associations with long-term effects on health in three main areas (Baldi et al., 1998): a) cancer (especially hematological cancer), b) reproductive disorders (for example, infertility, birth defects, adverse pregnancy outcomes) and c) neurotoxic effects (for example, polyneuropathy, neuro-behavioral hazards, Parkinson's disease). Recently, they have also been associated with hearing loss, but knowledge of hearing sensitivity risks associated with prolonged exposure is inadequate.

It is well documented that farmers, who are exposed to noise and pesticides on a regular basis, have a higher prevalence of hearing loss when compared to the general public. In addition, noise-induced hearing loss is the most common occupational hazard, as well as one of the most investigated occupational hazards. Its assessment and effects on the auditory system is well documented (Jones et al., 1968; Thelin et al., 1983; Towsend et al., 1983; McMahon, 1988; Broste et al., 1989; Ejercito et al., 1989; May et al., 1990; Crutchfield et al., 1991; Bean, 1991; Plakke and Dare, 1992; Ehlers et al., 1993; Zeimet, 1993; Knobloch et al., 1998; Beckett et al., 2000; Gomez et al., 2001; Hwang et al., 2001; McCullagh et al., 2002).

A report described a case of profound bilateral hearing loss associated with residual peripheral neuropathy who had acute poisoning from sprays containing a mixture of two organophosphates, 7.5% of malathion and 15% of metamidophos (Harell et al., 1987). Another report indicated that pyrethroid intoxication resulted in acute and chronic symptoms. Most disappeared after the end of the exposure. Impairments such as tinnitus, visual disturbance, and sensori-motor polyneuropathy disorders were observed for more than 2 years after exposure (Muller-Mohnssen, 1999).

More recently, 3 patients indicated they experienced problems with balance - mild-to-moderate sensorineural hearing loss - markedly poor speech discrimination scores and absent auditory-evoked brainstem responses with normal otoacoustic emissions (OAEs) following exposure to pyrethroids. In addition, balance tests (caloric tests and damped rotation tests) were abnormal in each patient with normal, saccades, smooth pursuit eye movements and optokinetic nystagmus (Sheykholeslami et al., 2000).

Peripheral auditory disorders were also observed in a group of 98 farm workers (ages ranging from 15 to 58 years old) who were free from noise exposure. Their hearing losses were found to be associated with combined pesticide (organophosphate) and insecticide (pyrethoid) exposure (Teixeira, Augusto and Morata, 2001). Central auditory system functions were assessed, as well as the more peripheral portions of the auditory system. Fifty-six percent of the exposed workers had hearing dysfunction at the central level and its relative risk was 7.58 for the group with exposure to insecticides (95% CI 2.9- 19.8) when compared to the non-exposed group. The group exposed to insecticides and noise had a relative risk for central disorders of 6.5 (95% CI 2.2-20.0) when compared to the non-exposed group and 9.8 (95% CI 1.4-64.5) when compared to the group exposed only to noise. The finding suggests that exposure to organophosphates and pyrethroid products can induce damage to central auditory system.

Question 2: Which combined exposures occur between noise and pesticides?

In agriculture, farmers are exposed to excessive noise from farm equipment, including tractors, grain dryers, combines, brush hogs, and chainsaws (see Table 1 for examples of farm noise sources).

Table 1. Farm Noise Sources and Their dBA Levels

Noise	Noise Level (dBA)
Lowest audible sound[a]	0
Quiet empty barn[a]	50
Normal conversation[a]	60
Chicken coop area[a]	70
Maximum sound level, tractor with cab[b]	73-90
Tractor or combine idling, barn cleaner, conveyor, elevator, inside acoustically insulated tractor cab[c]	85
Orchard sprayer[d]	85-100
Tractor at 50% load, blower, compressor combine, pneumatic wrench, chopping silage, full throttle lawnmower[a]	90
Pig shed at feed time[d], grinding corn with portable mixture[f]	95
Maximum sound level, tractor without cab[b]	91-99
Tractor at 80% load, power tools, snowmobile, ATV[c]	100
Grain Dryer[h]	102
Tractor at 75% load, no cab[c]	103.5
Self-propelled combine[j], full throttle tractor[c]	105
Average walkman radio half gain[a], older tractors[c]	110
Tractor at full load, bad muffler, old chainsaw[e]	120
Gunshot, engine backfire, dynamite blast[a]	140

[a]Shelly J. and Dennis, M. (1993); [b]Sampson, B.T. (1999); [c]Bean, T.L. (1991); [f]McMahon, K.B. (1988);; [h]; [i]Jones, H.H. and Oster, J.L. (1968); [k]Ziemet, D. et al. (1993).

In a sample of 155 tractors, non-impulsive noise levels of more than 90 dB (A) were measured in 75% of tractors without cabs and 18% with cabs (Holt et al., 1993). Data on noise exposure in farmers have been collected via interviews, self-reported hearing loss, and analysis of noise exposure measurements in large cohorts (Hwang et al., 2001; Gomez et al., 2001; Marvel et al., 1991). Findings indicated that hearing loss was related to farm noise exposures after controlling for confounding variables. This finding is not considered

surprising given the high levels of farm noise exposure. The median lifetime exposure to farm noise above 85 dB (A), 8 hours daily is 4.7 years. Hwang and his colleagues (2001) found that the use of hearing protection was not related to a lower risk of hearing loss when working with noisy farm equipment. This was contrary to health and safety recommendations for reducing noise exposure. A number of epidemiological studies have failed to differentiate between farmers who only have occupational noise exposure and other potential hearing loss etiologies (Plakke and Dare, 1992; Hwang et al., 2001; Gomez et al., 2001; Marvel et al., 1991).

The term "Pesticide" includes insecticides, herbicides, fungicides, rodenticides, and antimicrobials as well as plant growth regulators, defoliants and desiccants (Federal Insecticide, Fungicide and Rodenticide Act, 1947). Pesticides are used worldwide in agriculture, industry, public health and for domestic applications. Consequently, a great part of the farming community is potentially exposed to these compounds. Humans are exposed to pesticides through various routes such as ingestion, inhalation, skin contact and eye contact. For a pesticide applicator, skin absorption is the most common route of exposure (Waldron and Goleman, 2000).

Common pesticides include carbamates, pyrethrin and synthetic pyrethroids, chlorinated hydrocarbons, metals and metalloids, cyanide, anticoagulants, fluoroacetates, dinitrophenols, fumigants, pyridyliums and organophosphates. Organophosphates compounds are one of the most widely used classes of pesticides. They are used as insecticides and, to a lesser extent, as herbicides (Maroni et al., 2000)

Organophosphorous compounds act as an inhibitor of acetylcholinesterase (ACHE), and therefore causes neurotoxic effects or neuropathy (degeneration of the axons of the motor nerves). OP insecticides cause toxic effects through the inhibition of ACHE in the nervous system (Yao and Godfrey, 1995; Chen et al., 1998; Hoya et al., 2001). The effect is failure of physiological transmission of nerve action potentials of neurons of the

- parasympathetic and sympathetic nervous system,

- fibers to effector organs and sweat glands,

- motor nerves to skeletal muscles and the central nervous system, and

- ventral and possible dorsal cochlear nucleus to the olivocochlear bundle of the auditory nervous system.

Question 3: Challenges of studying the effects of noise and pesticides on hearing and balance

There are several reasons why the effect of noise and pesticides on hearing has not been further investigated. Some of these include:

- Difficulty in documenting exposure levels when products are used outdoors under conditions of wind and weather;

- Most users of pesticides apply in uncontrolled situations, with no supervision;

- Itinerant workers are difficult to track in longitudinal studies;

- Unlike industry, no surveillance program exists for agricultural workers; and

- Difficulty in documenting effective use of protection such as clothing, gloves, masks, ear protection devices.

Question 4: What are the data gaps?

There are few controlled studies on effects of combined exposure to pesticides and noise on human hearing and balance, few animal studies on the cochlear and central auditory pathways effects of combined exposure to pesticides and noise on neural pathways, no standard test battery for accessing peripheral and central auditory effects of exposure, and there is no data on difference in susceptibility of auditory effects in younger and older workers.

Question 5: Which approaches are available to study combined exposures and which combinations should be recommended in both environmental and occupational environments?

Currently, when a chemical's toxicity is evaluated, its ototoxicity is not adequately evaluated. The only hearing test required by the Organization for Economic Cooperation and Development (OECD) for toxicity testing when a chemical is to enter the market is the qualitative assessment of the startle reflex (115 dB Sound Pressure Level (SPL) click). This test is not sufficiently sensitive for the detection of ototoxicity (Lund et al, 1997). There must be improvements in the toxicity testing for chemicals in all arenas, both environmental and occupational. Testing for ototoxicity of exposed populations and individuals must be improved, by testing chemicals along with a protocol to evaluate the auditory (and vestibular) system.

Human studies are needed to further understand the ototoxicity of these compounds and the toxicity of mixtures and the interaction between mixture components. Such studies should include documentation of noise exposure (type of noise, intensity and duration), documentation of pesticide exposure, and ideally, biomarkers for measurement of pesticide levels in subjects e.g., urine samples. Epidemiological studies of noise induced health effects in the presence of air pollutants and other chemicals in the air would have to be considered potential confounding variables such as controlling multiple exposures/possible confounders such as age, gender, race and general health indicators (blood pressure, use of medications, etc). Moreover, the distribution of health outcomes (auditory or non-auditory) need to be compared between groups with different exposure conditions. Considerable effort is needed to examine pesticides and characterize their auditory risk; to bring this risk to the attention of workers, public health professionals, and policy makers; to develop specific recommendations and disseminate information addressing hearing loss prevention strategies that are not limited to exposures to excessive noise levels.

In summary, potential implications of the available evidence include:

- Chemical exposures should be monitored and controlled as a part of hearing loss prevention efforts.

- The inclusion of workers exposed to neurotoxic chemicals in hearing loss prevention programs, regardless of their noise exposure, is recommended

- The evaluation of the neurotoxic effects of pesticides requires tests that assess the central functions of the auditory system, in order to complement the information from pure-tone audiometry, the test routinely used in occupational surveillance.

In the meantime is not necessary to wait for additional data in order to institute policies to protect workers by reducing chemical exposures through:

- Engineering controls

- Protective equipment (e.g. respirators, gloves)

- Educating workers to raise awareness of potential hearing hazards

- Testing at risk workers.

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Consumer Heavy Metals and Noise Exposure: Health Effects

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Introduction

"Heavy metals" are chemical elements with a specific gravity that is at least 5 times the specific gravity of water which is 1 at 4°C. The specific gravity may be considered as a measure of density of a given amount of a solid substance when it is compared to an equal amount of water. For example some heavy metal specific gravities are: Arsenic, 5.7; cadmium, 8.65; iron, 7.9; lead, 11.34; and mercury, 13.546 (Lide 1992). These heavy metals are not metabolised by the body and accumulate in the soft tissues or in the bones causing toxic effects. Heavy metals may enter the human body through food, water, air, or absorption through the skin when they come in contact with humans in residential and occupational settings as well as in the general environment. The commonly encountered toxic heavy metals are lead, mercury, cadmium and arsenic.

Lead

Every year industry produces about 2.5 million tons of lead throughout the world, most of which is used for batteries. The remainder is used for cable coverings, plumbing and ammunition. Other uses include paint pigments, PVC plastics, x-ray shielding, crystal glass manufacture, pencils, glazing ceramics, canned foods with lead-solder joints, ethnic foods, herbal remedies, dietary supplements, lead emissions from fossil fuels, metals smelting fuel additives and pesticides.

According to the World Health Organisation's World Health Report, following control measures, lead levels have been steadily declining in industrialized countries but at least 5% of children still have elevated blood lead levels, with even higher rates in children of poorer households. In many developing countries, where leaded gasoline is still used, lead can present a threat to more than half of children. Rapidly increasing traffic loads have the potential to further increase blood lead levels.

The CDC set a limit in the USA in 1991 of 10ug/dL for children based on studies of cognitive deficits. Recently it has been considered that there is sufficient and compelling evidence to lower the limit values as toxic effects have been observed below 10 µg/dL. Gilbert and Weiss (2006) argue for a 2 µg/dL limit.

WHO estimate that worldwide, 120 million people are estimated to have lead levels of 5-10 µg/dl, with similar numbers above 10 µg/dl, and 40% of children have blood lead levels above 5 µg/dl. Overall, 97% of affected children live in developing regions.

Patel et al (2001) reported 50% of children tested had PbB greater than 10µg/dL in India. In a recent study, Jain and Hu (2006) reported that children under 3 years had blood lead levels of between 5-20 µg/dL. In their study low standard of living correlated with a 32% increase in blood lead levels. Children in the 95th percentile for their weight/height compared to below 5% had a higher blood lead by 31%.

Lead affects practically all body systems. Most toxic exposures occur at chronic low levels and can result in reductions in intelligence quotient (IQ), increased blood pressure, and a range of behavioural and developmental effects. The range and extent of adverse health

effects has been appreciated only relatively recently. Furthermore, lead is now understood to be toxic, especially to children, at levels previously thought to be safe. In more severe cases of poisoning, adverse health effects include gastrointestinal symptoms, anaemia, neurological damage and renal impairment. Other adverse effects, such as reduction in IQ levels, behavioural disorders or renal function, can be discerned only through special examinations. These analyses estimate that lead results in about 234 000 (0.4%) deaths and 12.9 million (0.9%) DALYs.

BOX 1: <u>Lead: Toxic Effects</u>
Neuro-behavioural and Endocrine alterations
- Learning disabilities
- Hyperactivity
- Diminished Cognitive Development
- Slowed growth
- Loss of Synaptic Plasticity
- Hearing loss
- Headaches
- Neuropathy
- Renal damage
- Reduced Dermal sensitivity

Lead and Hearing Loss

There are contradictory findings on hearing loss from lead exposure. According to Farahat et al (1997) and Forst et al (1997) lead exposure induces hearing loss but others (Baloh et al. 1979; Otto et al 1985; Counter et al. 1997) have indicated that this is not the case. Some studies have shown a relationship between blood lead levels and hearing loss (Schwartz et al. 1987; 1991 ;Osman et al. 2002) but Counter et al. 1997 were unable to substantiate this in their study. It has also been suggested (Bellinger et al. 1996; Schwartz 1991) that lead exposure results in hearing loss which in turn may be responsible for developmental learning disabilities. Buchanan et al. (1999) have shown that Andean children aged 5-14 years with blood lead levels of 33-118 µg/dL (equivalent to 3-12 times higher than the US limit) had normal hearing thresholds and distortion product otoacoustic emissions (DPOAE) and observed no correlation with blood lead levels. Osma et al (2002) reported delayed wave I of the auditory brainstem response in children exposed to lead. It is clear that there are substantial differences in the current literature on the effect of lead exposure on the auditory sensitivity indicated by pure tone audiometry.

Lead and Noise: Effect on Hearing

There are very few studies exploring the effects of combined lead and noise exposure. Wu et al. (2000) examined 220 workers exposed to lead (56.9 µg/dL) and noise (86dB Laeq) in a lead-battery manufacturing factory. Multi-variate analysis showed a significant correlation between high long-term lead exposure (duration of employment and ambient lead concentration) with hearing threshold at 4kHz but no correlation with short-term exposure was observed. The effect due to lead and noise were not considered separately. No enhancement of hearing thresholds were reported with lead and noise combined. Long-term lead exposure in ceramic glazing workers with mean blood lead level of 45 µg/dL have been shown to have sensori-neural hearing loss in 60% of men and 20% of women. The raised

thresholds between 2 and 8 kHz may be due to combined exposure to lead and noise. Absolute brainstem response latencies were prolonged but the inter-wave intervals were normal indicating a conductive element to the hearing loss. Counter and Buchanan (2002) suggested that environmental exposure must be considered an important factor in occupationally lead-exposed adults.

Lead and Noise: Human Growth

Lead exposure has an impact on Human growth and development (Schell et al 2006) and noise stress is also considered to be implicated in the reduced prenatal growth.

Mercury
The use of mercury is wide-spread as shown in the Box 2 below. The health effects also cover many neurological and psychological symptoms as shown in Box 3.

BOX 2: <u>Mercury</u>
- **Dental Amalgams**
- **Fish- shark, swordfish, tuna etc**
- **Aquatic sediments**
- **Thermometers**
- **Vaccine Preservatives**
- **In the atmosphere**
- **Topical anti-septic**
- **Mercury based skin creams**
- **Fungicides**
- **Gold mining**
- **Chlor-alkali industry**

BOX 3: <u>Mercury: Health Effects</u>

Neurological and Psychological symptoms
- **Tremor**
- **Personality Change**
- **Restlessness**
- **Anxiety**
- **Sleep disturbance**
- **Depression**
- **Hearing Loss**
- **Kidney Damage**
- **Allergy**
- **Paraesthesia**

Mercury: Hearing Loss

Mercury intoxication causes hearing loss in humans and animals. In 1953, a severe neurological disorder was recognised among persons living in the vicinity of Minimata, Japan, where mercury-containing effluent flowing from a chemical plant into the local bay contaminated shell fish. Deterioration in hearing and deafness were reported among other neurological symptoms in the local people after the incident. Findings consistent with Minimata disease have been reported in other instances of accidental mercury poisoning in Japan and Iraq. Early stages of intoxication may result in cochlear lesions, whereas hearing loss in the late stages of intoxication may result from neurological damage.

Methyl mercury is considered more toxic than mercuric chloride. Hearing loss due to Methyl mercury has been reported (rice et al 1998) whilst wave III of the auditory brainstem response has been shown to be delayed and used as a biomarker for prenatal MeHg toxicity from contaminated seafood. Dimethyl mercury, Methyl mercury and Mercuric Sulfide have all been shown to affect auditory brainstem potentials (Counter et al. 1998; Rice and Gilbert 1992; Murata et al 1999; Chua et al. 2001)

Cadmium

It is used in nickel-cadmium batteries, PVC plastics, and paint pigments. It can be found in soils because insecticides, fungicides, sludge and commercial fertilisers that use cadmium are used in agriculture. Cadimium may also be found in reservoirs containing shell fish. Cigarettes also contain cadmium. Lesser-known sources of exposure are denal alloys, electroplating, motor oil and exhaust. Inhalation accounts for 15-50% of absorption, 2-7% of ingested cadmium is absorbed in the gastro-intestinal system.

The health effects range from occupational lung cancer, kidney damage from tubular dysfunction to chronic renal failure, skeletal damage and hearing dysfunction.

Cadmium: Hearing

- Dose-dependent effect on hearing has been shown in rats by Agirdir and Ozcagalar in 2002. Increased blood and renal cortical cadmium levels were associated with high cadmium accumulation in ear ossicles and labyrinth in rats exposed to cadmium. The changes in auditory brainstem responses and otoacoustic emissions in 2-month old male rats exposed to drinking water containing 5 and 15ppm for 30 days shwoed that cadmium –induced nephrotoxicity was associated with signs of defective hearing at a concentration of 15ppm but that 5ppm caused hearing loss without affecting kidney function. The mean latency of ABR wave I, which indicates the function of the cochlea, was 1.335 ± 0.31 ms in the control group and significantly prolonged to 1.641 ± 0.052 and 1.74 ± 0.88 ms in the rats subjected to 5 and 15 ppm, respectively. Non-significant changes in wave III and V latencies were accepted as evidence of unaltered function of the other parts of the auditory system. These results suggest that hair cells are more sensitive to cadmium than kidney tubule cells and that the cochlear component of hearing is more vulnerable to cadmium toxicity than other parts of the auditory system. (Ozcaglar et al 2001).

Cadmium has a dose-dependent deleterious effect on the auditory system in rats. Preventive effect of a zinc-enriched diet on cadmium-induced hearing loss in rats was investigated by Agirdir and Ozcaglar in 2002. The control rats were fed normal rat food and tap water, whilst

the cadmium group was subjected to 15 ppm cadmium-containing water as $CdCl_2$. A third group received 15 ppm $CdCl_2$ and food enriched with 200 ppm zinc as $ZnSO_4$ for 30 days. Hearing function was measured by auditory brainstem response and distortion product otoacoustic emission. Blood cadmium increased from 1.87 ± 1.69 to 6.08 ± 2.62 µg/dL and elevated cadmium contents of ear ossicles and kidney cortex were associated with a decreased glomerular filtration rate in rats subjected to high cadmium. A zinc-enriched diet obviously reduced cadmium accumulation in the kidney and prevented the nephrotoxicity. Cadmium-induced ototoxicity seems to be partially zinc preventable and zinc addition to diet without altering cadmium content in ear ossicles may help to prevent cadmium-induced hearing loss.

Cadmium and Noise: Fetal Malformations

Mice were exposed to a wide octave-band of noise at 100 dB(C) for 6 hours on day 7 of pregnancy and Cadmium sulfate at 1 or 2 mg/kg was intra-peritoneally injected. On day 18 of pregnancy, fetuses were examined for external and skeletal malformations.In the groups exposed to continuous noise for 6 hours, total percentages of malformed fetuses were significantly higher than that in the control group. Although combined treatment with cadmium and noise resulted in an increase of total percentages of malformed fetuses compared to the same dose of cadmium alone, the interactions between cadmium and noise showed no synergistic effect on teratogenicity. The magnitude of teratogenicity due to noise is much weaker than that of cadmium, and is therefore easily masked by that of cadmium in statistical tests of the significance of differences.

Cadmium and Noise: Hearing

DeAbreu and Suzuki (2002) examined the effect of cadmium fumes and noise exposure and showed that 4 kHz and 6 kHz were more severely affected with combined exposure.

Arsenic

Arsenic is released into the environment by the smelting process of copper, zinc, and lead, as well as by the manufacturing of chemicals and glasses. Arsine gas is a common by-product produced by the manufacturing of pesticides that contain arsenic. Arsenic may be also be found in water supplies worldwide, leading to exposure of shellfish, cod, and haddock. Other sources are paints, rat poisoning, fungicides, and wood preservatives. Target organs are the blood, kidneys, and central nervous, digestive, and skin systems.

Arsenic: Hearing

Considerable variability among individual arsenic values in the hair makes group examination a necessity. Hair, urine, and blood samples taken from groups of 10-year-old boys, each numbering 20 to 25 individuals, residing in a region polluted by arsenic and hearing changes were analyzed in a group of 56 10-year old children residing near a power plant burning local coal of high arsenic content. In the case of air conduction, significant hearing losses were found at frequencies of 125, 250 and 8000 Hz. The changes were particularly marked in the low frequency region. The high statistical significance of the hearing impairments found points to very low probability of their being only an "accidental" finding. The possibility of toxic damage to the ear cannot yet be excluded according to Bencko and Symon (1977)

Conclusions

There are inconsistent findings on lead induced hearing loss. It is also not clear whether lead and noise combined exacerbate hearing loss but they do affect human fetal growth. Mercury affects hearing, with central conduction time delay (ABR I-V, III-V) but cochlear function may be unaffected. Cadmium causes dose-dependent loss of hearing in rats, and delay in only Wave I of the auditory brainstem response implies cochlear dysfunction. Zinc-enriched diet reduces ototoxic effect of cadmium. Cadmium and noise show synergistic effect at 4 kHz and 6 kHz, and on Human fetal malformations. Arsenic produces a low and high frequency loss with balance disturbance.

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Combined Effects of Noise and Biological Agents

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General

There is only limited data concerning combined health effects of biological agents and noise. However, simultaneous exposure to these two types of stressors appears to be common, and increased exposures are not infrequent including many work environments, homes and ambient environment. At present, the data on simultaneous exposures to noise and biological agents is limited, and the interactions or combined effects of these factors are seldom discussed.

Exposure to biological agents and their health effects

In indoor environments, there are many types of biological agents present. Viruses, bacteria, fungi and allergens are present in practically all indoor environments, and their concentrations depend on whether there are indoor sources for these agents. There is practically no data concerning simultaneous exposures to the biological agents and noise in indoor environments.

Exposures to environmental microbial material have often been assessed as endotoxin, which is a cell wall component common to all gram-negative bacteria. Endotoxin is generally present in outdoor air and indoor air. Endotoxin exposure is a risk factor for respiratory symptoms and asthma, but it is also considered to have a protective effect against allergy in early childhood (Liu 2004). It is well known for its high inflammatory potential, which probably has importance in both the pathogenesis of endotoxin-associated disease and in its protective effect against allergy. Endotoxin has been used as a surrogate of microbial material in general since gram-negative bacteria are generally present wherever environmental microbial growth takes place. Exposure data to environmental endotoxin and noise that would have been produced, in parallel, is not available.

Cat and dog allergens are common in homes and also in other indoor environments, even in offices where no cats or doges have ever visited. Allergens are carried on people's clothes to wherever they spend their time. Outdoor allergens such as pollen, do enter the indoor environments as do other outdoor particles. There are also important allergens the sources of which are indoors, for example house dust mites and cockroaches. Genetic factors are a major factor, but otherwise the pathogenesis of allergies is not totally known. Indoor factors are assumed to play a role. It has been suggested that pathogenesis of allergies can be stimulated by adjuvant effects such as air pollutants and noise, especially night-time noise through its potential to trigger stress reactions. This was concluded in a study on children 5-12 yrs of age, where relative risks of, both, asthma, chronic bronchitis and neurodermitis increased significantly with increasing traffic load. As data on effects of air pollution did not alone explain the findings, it was evident that night time traffic noise had an adjuvant effect (Ising et al. 2003).

Bacteria in indoor environments are originated either from humans, pets or environmental sources such as outdoor air, soil and wet or moist surfaces where microbial growth takes place. Gram positive bacteria are more common than gram negatives in indoor air, but in any moist or wet microenvironment, gram negative bacteria dominate. Sources of fungi are largely similar to those of bacteria except for filamentous fungi (molds) for which humans do not act as a source. Indoor exposures to these biological agents have often been measured in connection with respiratory symptoms and allergy, but noise exposures have not been taken into account.

Microbial growth on building or furnishing materials is an indoor air problem with many well-documented health effects (Bornehag et al. 2001). These effects are largely those of respiratory tract, and simultaneous assessment of noise exposures or on hearing effects are hard to find. However, one aspect of the microbial (mold) growth on building materials may deserve some discussion. In these specific situations of microbial contamination and growth, there are remarkably many toxigenic species involved, and they have indeed been shown to produce toxic metabolites such as mycotoxins and bacterial exotoxins (Tuomi et al. 2000). Microbial toxins have e.g., immunotoxic and neurotoxic properties. It has still to be revealed if the concentrations of such toxins end up to levels that may have a role in indoor situations. Concentrations of toxic microbial metabolites in indoor air are probably very low, but detectable amounts, up to 1300 pg/m^3 of e.g. macrocyclic trichothecene toxins have been observed in mold-contaminated buildings (Brasel et al. 2005). At present, there is little documentation on the effects of possible toxin exposures in indoor exposure situations, but they should be taken into account in future studies on indoor biological factors.

Exposures to many environmental stressors may be associated with the socioeconomic status. Problems of ear, nose and throat are all common among the population (Hannaford et al. 2005), but the role of housing conditions and especially indoor factors such as noise and biological agents as determinants of these problems needs more clarification. Low socioeconomic status is associated with poor housing conditions and to multiple exposures. Both exposure to noise and to air pollutants (Kohlhuber et al. 2006) have been associated with low household income or socioeconomic status, as well as dampness (Crawford et al. 2006, Lannero et al. 2002) which often leads to higher exposures to microbial contaminants (Nevalainen and Seuri 2005).

Occupational exposure situations

Typical occupational environments where exposure to microbial material takes place are farming environments, wood processing, food industry, biotechnical production chemicals, metal working, waste and wastewater treatment and other environments where wet processing of organic material takes place. In many such occupations, also exposure to noise takes place, although little documentation of these combined exposures is available.

Combined exposures to noise and biological agents have been documented in some occupational settings, such as farming and waste industry. In farming, noise levels of 86.8 dB(A) combined with dust levels of 1.7 mg/m^3 have been reported (Firth et al. 2006). Farming dust contains remarkable amounts of microbes and other biological material; microbial concentrations have typically been 10^5-10^7 spores/m^3. Simultaneous exposure to noise and biological aerosol has been described from waste treatment facilities. Typically, noise levels exceeding 85dB(A) and microbial concentrations exceeding 5 x10^6 biological particles/m^3 have been detected (Tolvanen 2001, Lavoie and Guertin 2001, Poulsen et al. 1995, Tolvanen and Hänninen 2005). In these studies, possible health effects of the combined exposures have not been reported. Gijbels et al. (2006) have also pointed out that dentists

have a simultaneous occupational exposure to noise and vibration and biological factors such as infectious agents and allergens, especially latex.

Findings on ototoxic effects related to biological agents

No studies are available where the combined effects of noise and biological agents would have been investigated in an experimental setting. There are, however, indications that such co-exposures could have health effects since some biological agents or products have been shown to be of ototoxic nature.

Bacterial endotoxin, the common component of all gram-negative bacteria, has ototoxic potential. High exposures to endotoxin may take place in case of infections where large numbers of bacteria actually proliferate locally in the ear region. Endotoxin exposures from environmental sources are much lower although elevated concentrations are observed e.g. in some occupational settings and in damp or moisture-damaged indoor environments. There is, however, no data available if such concentrations would have any importance in inducing inflammation in the ears.

The ototoxic potential of **endotoxin** has been shown in laboratory animals, especially guinea pigs. Auditory brainstem response shifts of 12.5 and 20 dB were observed after exposing guinea pig cochlea to relatively high doses of endotoxin (1000mg/l), with gradual improvement during the following 28 days. Inflammatory infiltrates could be seen histologically (Darrow et al. 1992). The inflammation is probably mediated by iNOS (inducible nitric oxide synthase) -produced high nitric oxide levels (Watanabe et al. 2000). In the experiments of Darrow et al. (1992), the lower dose of 10 µg/ml which corresponds to the human effusions, produced only mild inflammation and no hearing loss was detected. The authors concluded that brief exposure of the cochlea to endotoxin is not sufficient to cause hearing loss, but under chronic conditions, persistent inflammation within the cochlea may result in a sensorineural deficit.

Hearing loss has also been experimentally produced to laboratory animals by injecting lipopolysaccharide (LPS) (endotoxin) to the inner ear (Guo et al. 1994). This exposure caused elevated N1/P1 thresholds and prolonged latencies and the ears had severe strial damage mainly to the cellular organelles. LPS induced strial ototoxicity producing ion imbalance, causing changes in endolymph composition and energy failure in the organ of Corti. LPS exposure was concluded to be responsible for the pathogenesis of inner ear sequelae secondary to otitis media.

These experimental conditions mimic a situation where the ear is exposed to high amounts of bacterial endototoxin. This may take place in case of infections where the gram-negative bacteria actually grow in the ear region. It is not probable, however, that exposure levels to environmental endotoxin would cause such dramatic effects.

It must also be mentioned that many **drugs** have ototoxic properties. A number of such pharmaceutical products, e.g. the aminoglycoside antibiotics such as gentamycin, streptomycin and neomycin, actually are products of microbial secondary metabolism. Use of ototoxic drugs may make an individual unusually susceptible to effects of noise.

While the doses of substances in pharmaceutical usage are of a totally different magnitude than are possible exposures from environmental sources, it must be mentioned that there may be sources of such products in the indoor environments. As presented above, dampness and moisture in the building structures lead to microbial growth which includes a number of organisms that are potential producers of biologically active substances. For example, species

of the fungal genera *Penicillium*, *Stachybotrys* and *Chaetomium* and the bacterial genus *Streptomyces* are known producers of microbial toxins and other biologically active substances, including many antibiotics such as the compounds mentioned above. Toxins have commonly been isolated from building materials where microbial growth takes place (Tuomi et al. 2002, Nielsen 2003). Also streptomycetes are frequently found in moisture-damaged materials and in house dust. There is very limited data about the concentrations of toxic products of microbial metabolism in indoor environments, and very little is known about their possible effects including ototoxicity, but there appears to be growing interest to focus on these potentially very toxic substances in indoor environments.

Conclusions

The present literature offers little for the assessment of the risks of combined effects of noise and biological agents. These environmental exposing factors are different from each other, and they have usually been studied by different researchers and with different study designs. However, it is evident that there are situations where combined exposures take place. Combined health effects could possibly be studied in occupational environments where exposure levels for both these factors are high, such as farming and waste industry. In indoor environments other than occupational settings, the exposure levels may not be high enough that specific effects could be detected. The combined effects should, however, be taken into account in studies on housing and health.

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Review: Noise and vibrations and other interactions with the environment

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Introduction

In their paper given at Internoise 2001, Job & Hatfield (2001) perfectly summarize the issue at stake: "Our understanding of the effects of noise from combined sources on reaction, and other potential consequences of noise exposure (e.g. sleep disturbance, cardiovascular disease), is inadequate, despite an array of theories and data pertaining to this issue. Nonetheless, understanding the interactive effects of noise from combined sources is critical to effective regulation". However, increasing consideration is given to this issue at conferences during the last decade (Internoise 1996, 1997, 2000, 2001, 2006). Unfortunately, not much of this is also published in the peer reviewed literature nor has it found its way into practice with a few exceptions only. While much is written about this topic of effects of mixed noise sources less consensus is about how to deal with it in praxis.

Even less attention was and still is given to combinations of noise and vibration and nearly no information is available on combinations of noise and air pollution. Several experimental studies are dealing with noise combined with other environmental factors (such as odours, radiation, (electric and magnetic fields (EMF), temperature etc.), however, this review focuses on combinations of noise with vibration and air pollution and bring some examples of other contextual factors important in environmental epidemiology.

Furthermore, this short review focuses on studies which are relevant for environmental health impact assessments in transportation or actually originate from this field. The combined or cumulative assessment is required in Environmental Impact Assessment (EIA) (CEC 1985, 1997, Cooper & Sheate 2002) and in Canada, where most regulatory efforts have been taken (Cumulative Effects Assessment Working Group & AXYS Environmental Consulting 1999, Duinker & Greig 2006). In Environmental Health Impact Assessment (EHIA), the cumulative assessment has been largely neglected and interactions are mostly dealt with in a qualitative way (Burris & Canter 1997, Cooper & Sheate 2002).

Before we go into the specific subject it is important to stress at the beginning a few important differences between air pollution and noise (see Table 1 below), which have to be taken into acoount when cumulative effects or interactions are considered. Neglecting of these essential differences may lead to wrong assessments.

Table 1. Core differences between community air and noise pollution

Issue	air pollution	noise pollution
Pathogenetic model	Toxicology	Stress
Measurement of pollutant	objective methods	objective & subjective methods necessary
Propagation of pollutant	less dependence on building structures	strong dependence on building structures
Pollutant mapping*	typically 100-1000m	typically 10-100m
Effects of pollutant	mostly direct	mostly indirect
Context[#] dependency	smaller	larger
Generalizability	good	limited

Especially, the large context dependence of noise (up to 80% variance explanation) - due to its mostly indirect pathway of action (moderation) is of importance.

Moreover, we have to distinguish several more prevalent types of combinations (Table 2).

Table 2. Basic combinations of noise in transportation

Noise/sound	Vibration	Air pollution	Context
Road	+	++	+
Rail	++	+	+
Aircraft	+	+	+
Special*	+	+	+

* low frequency noise and impulse noise

The measurement and assessment of vibrations and low frequency bands is technically demanding – thus, it is done only rarely by modelling (not fully accepted methods) in small sub-samples (like indoor air pollution assessment) but mostly assessed by questionnaire. Only a small number of studies have reported correlations coefficients between exposure indices simply because there was only one or two exposure estimates available.

As expected, there are obvious high correlations between the three considered exposures. Clearly, also substantial variations are to be expected due to the different mix of traffic sources and due to regional context factors that may modify transmission of exposure.

Combined noise exposure ("multi-noise-source"-issue)

In most real-world situations exposure to noise involves more than one source (see Table 3 below).

Table 3. Number of citizens in Germany annoyed by 2 noise sources

noise combination	No in millions
Road and aircraft	13 Mio
Road and railway	11 Mio
Road and industry	12 Mio

Source: Ortscheid & Wende 2000

Based on a simulation the German EPA calculated the following cumulative noise exposure load (see Fig 1 below).
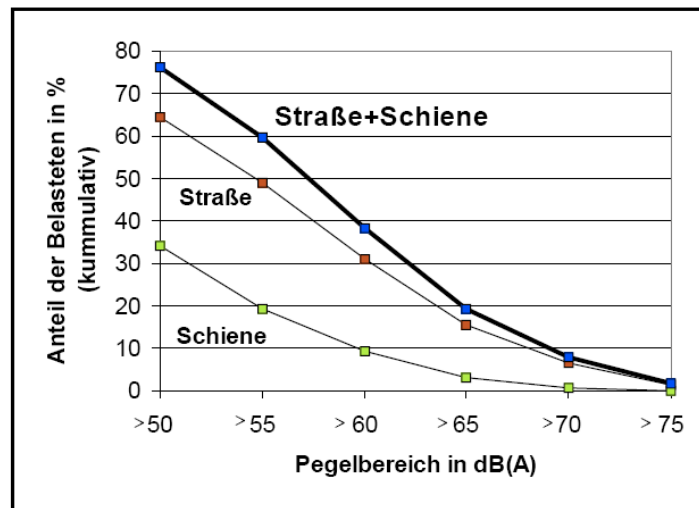

Figure 1. *Cumulative percentage of exposed by road, rail or both (Ortscheid & Wende 2000).*

Furthermore, the concerned people differentiate quite well between the experienced effects (Fig 2). However, it is still standard practice to assess the community response to noise source by source.
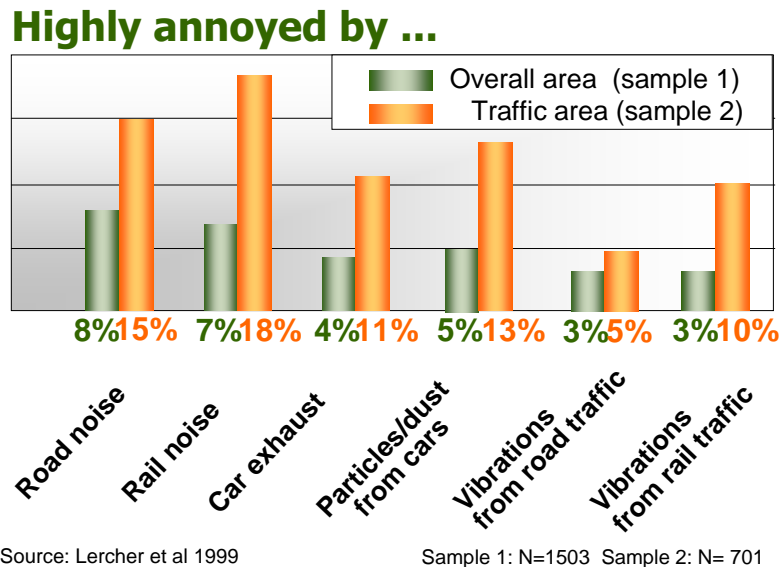
Figure 2. *Percentage highly annoyed by exposure to road and rail traffic.*

This is mainly due to the fact that noise sources show different acoustic characteristics and a simple energetic summation of decibels does not lead to an appropriate equivalent outcome on the human receptor side. To overcome some of these weaknesses, in regulating industrial noises, various corrections and adjustments for annoying sound characteristics (e.g. tonality, impulsiveness etc) were applied and then summed up to get a single number descriptor for comparison.

Unfortunately, in the recently published environmental directive (END 2002) only standard exposure-effect curves for single noise sources are presented. It does not contain any guidance for combined noise situations, simply, because, currently, no commonly accepted method exists to assess the effects of multiple noise sources.

There have been earlier attempts and proposals (Ollerhead 1978, Powell 1979, Berglund et al 1981, Flindell 1983, Izumi 1988, Diamond & Rice 1987, Miedema 1987, Taylor 1982, 1987, Vos 1992) to find a way to deal with noise exposure from multiple sources. In these studies, typically, one or more models were applied to one field data set (with the exception of Vos who used laboratory data) and some, but often little improvement was found in comparison with the most simple model using energy summation. In one review (Schulte-Fortkamp et al. 1996) eight models were tested on a larger data set with various combinations of railway and road noise exposure from Germany. Here, overall, the "dominant source model" did the best job. However, when sources were equally important this approach did not work.

A summary of the most prevalent procedures that have been used or proposed for calculating the total annoyance caused by multiple noise sources can be found in several reviews and conference symposia (e.g. Schulte-Fortkamp et al. 1996, Berglund & Nilsson 1997, Sessions at Internoise 2000, 2001, 2005, 2006, Nilsson 2001). Miedema (2004) has recently tested the two most cited models (energy summation model and dominant source model) and concluded that both models are not consistent with empirical data in important respects. The energy summation model does not take into account the differences among transportation noise sources in their potency to cause annoyance (Miedema & Vos 1998). Based on their field

work, Swiss researchers (Oliva 1998, Oliva and Hüttenmoser 2000) concluded: exposure to noise from aircraft operations is perceived separate from exposure to road traffic noise ("air-versus ground-transportation") and therefore, a energetic summation may not be useful. It is still open whether a cumulative approach based on weighted effect equivalence of noise levels is a way to go.

The dominance model implies that the total annoyance is always equal to the highest single source annoyance while empirical findings also show lower annoyance in a multiple exposure situation (Job et al 2000). This, however, is thought to be a methodologic artifact ("the combined noise paradox"), as it seems extremely difficult for human beings to jugde overall or total annoyance from sources that are qualitatively and quantitatively completely different (Job et al 2000, Oliva and Hüttenmoser 2000). Why this may be so was further investigated by only a few researcher groups (Job & Hatfield 1999, Job et al 2000, Job & Hatfield 2001, Berglund & Nilsson 1999, Nilsson 2001). Scale limits ("ceiling effects"), wording, neglectance of background noises, time pattern of the noise components (simultaneous vs time separated noise components) and differential cognitive assessment strategies contribute to the "combined noise paradox".

As both "exposure intensity" related psycho-physical models and "perceptual models" did not yield satisfactory results, Miedema (2004) proposed – related to similar attempts by Vos (1992) and Delta (1995) – the so-called "annoyance equivalents model" and showed a theoretical proof of this approach. Here, the model first translates the noise from the individual sources into the equally annoying sound levels of a reference source, road traffic, and then sums these levels giving total level L. However, the requirements are strong (independence among others) and seem often difficult to meet in practice in order to be generally applied, as Schomer (2005), pointed out.

Combined exposure of community noise with other agents ("combined effects", "interaction", "cumulative effects")

It is well recognized in the scientific community that the (psycho-social & physiological) reaction toward noise is modified by features of the noise, other accompanying factors of the exposure pattern that contribute to the variance not explained by the physical descriptors of noise. Because noise follows the stress model, consequently, in a recent review Stansfeld & Matheson (2003) pointed out: "Noise effects on health may be augmented by, or in turn may augment, the impact of other stressors on health. Stressors may act synergistically, antagonistically or not at all. Stressors may include physical, chemical, biological, social and work organizational factors".

Due to the high correlation between some of these factors in the environment it is not surprising that cumulative effects but also "masking" may occur. For instance, Wanner et al (1977) and Hangartner (1987) were among the first to report correlations between noise and air pollution related annoyance frequency (0.78 and 0.81). Haider et al (1990), quoting a study from Vienna from 1984, showed even higher correlations (noise & exhaust gases: 0.90, noise and dust/particles: 0.97). Such high correlations clearly could result in multicollinearity problems and caution is needed.

The correlations need not always to be so high. To supplement the results from these urban studies with the ones obtained in rural areas a comparison of correlations is given below for a U-valley and a V-valley (Tables 4a+4b, Lercher 2006 unpublished).

These correlations are very close to the one between rail vibration and rail noise annoyance (r=0.57) which have been reported by Klaboe et al (2003).

Table 4a. Correlations between annoyance indicators: UIT-1998-TEL (U-valley)

	road.noise	rail.noise	road.vibr	rail.vibr	road.exhaust	road.soot
road.noise	1.00	0.40	0.51	0.23	0.57	0.53
rail.noise	0.40	1.00	0.25	0.59	0.29	0.28
road.vibr	0.51	0.25	1.00	0.36	0.49	0.44
rail.vibr	0.23	0.59	0.36	1.00	0.27	0.24
road.exhaust	0.57	0.29	0.49	0.27	1.00	0.69
road.soot	0.53	0.28	0.44	0.24	0.69	1.00

Table 4b. Correlations between annoyance indicators: BBT-2004-TEL (V-valley)

	road.noise	rail.noise	road.vibr	rail.vibr	road.exhaust	road.soot
road.noise	1.00	0.31	0.60	0.22	0.63	0.61
rail.noise	0.31	1.00	0.21	0.27	0.57	0.53
road.vibr	0.60	0.21	1.00	0.61	0.22	0.23
rail.vibr	0.22	0.27	0.61	1.00	0.20	0.22
road.exhaust	0.63	0.57	0.22	0.20	1.00	0.73
road.soot	0.61	0.53	0.23	0.22	0.73	1.00

All correlations based on Spearman rho

Nevertheless, it remains difficult to disentangle combined effects, as regional variations in background variables and exposure combinations have to be taken into account.

Thus, effects may simply surface due to the high intercorrelation between these factors, but may also be triggered by true interaction (one factor sensitizes individuals towards the other factor). However, the biological basis of these interactions is often poorly understood.

However, it has been shown in some studies, that accompanying factors of vehicular or rail traffic such as air pollution and vibrations may substantially modify noise annoyance ratings (Sato 1988, 1994, Howarth and Griffin, 1991; Zeichart et al 1994, Öhrström et al., 1996, 1997; Klæboe, 1998; Passchier-Vermeer, 1998; Passchier-Vermeer & Zeichart 1998, Zeichart, 1998, Lercher et al., 1999; Klæboe et al., 2000; Klæboe et al., 2003; Öhrström et al 2005, Yano et al 2005, Yokoshima & Tamura 2005, Yano et al 2006, Yokoshima & Tamura 2006).

Due to the measurement burden involved, the combined effects of vibrations and low and very low frequency noise are rarely investigated.

Effect modification of community noise in different contexts ("contextual effects")

Even by including physical and chemical factors such as air pollution and vibration the variance explained in reaction is still small. Personal, situational and environmental constraints to cope with the "exposure package" have to be taken further into account (Lercher 1996, Lercher 1998).

It is well known that the presence of multiple stressors reduces the effectiveness of coping efforts which depends on the expenditure of coping resources in the presence of other stressors (Lepore & Evans 1996). Thus, the conditions of living and the surrounding environment are potential moderators of any noise effects (see Table 5).

Table 5. *Selected examples of contextual factors potentially influencing response to noise (Source: Lercher 2007)*

Climate	Geography/Architecture	Environment	Social ecology	Culture
Cold, hot or moderate	Nature/Topography: flat, hilly, valley, lake, sea	Vibration, air pollution/odours	Land use: residential/mixed	Habits and life style
Seasonality	Area layout: the built environment	Visual appearance	Neighbourhood relationships	Meaning of living
Prevailing winds	Housing: type of house, Common green, garden	Density, room design	Infrastructure, Safety	Meaning of place

A study in the Netherlands has found a high clustering of other environmental risks with noise exposure at local levels while risks due to radiation or chemical substances were more evenly distributed across the country (Pruppers et al., 1998). In a different context, a longitudinal study found reported ambient noise exposure to be associated with a loss of physical function in older adults (Balfour and Kaplan, 2002).

Evans & English (2002), Evans (2003) and Evans & Marcynyszyn (2004) have shown that multiple environmental stressor exposure is more prevalent in a poverty sample of children compared to a middle-income sample.

In Japan, noise researchers try to understand, why they do not find a "rail bonus" in their studies (Kaku & Yamada 1996, Yano et al 1998, Ma & Yano 2005) and why people show a steeper noise-annoyance curve at the same noise levels with the "Shinkansen-express" (Yano et al 2005, Yokoshima & Tamura 2005, Yano et al 2006, Yokoshima & Tamura 2005).

Effects on annoyance

Annoyance by noise from multiple sources

Some older lab studies (e.g. Yano & Kobayashi 1990) have suggested that when high level, dominant sources such as aircraft or rail noise are combined with road noise as background noise the contribution to total annoyance is negligible. Fields (1993) has reviewed the effect of ambient noise on the source specific annyance and did not see a significant effect. It is, however, questionable, whether the mix of "ambient" noise of many field studies is a reasonable basis to prove this. Rather, the mix of studies will blur the picture

In a recent series of thorough experimental studies more detailed analyses have been carried out by Nilsson (2001) for his dissertation. His experiments showed that total loudness of simultaneous traffic sounds do not follow an arithmetic summation rule: total loudness is rather influenced by the louder sound to a greater extent than implied by arithmetic summation, whereas, for combination of equally loud sounds total loudness is less than the complete arithmetic sum of source specific loudnesses.

An interesting field approach was used by Klæboe et al (2005). They tested for the effect of the larger neighbourhood soundscape as potential effect modifier for the general noise annoyance. This idea is based on the fact that noise exposure is usually calculated for the most exposed façade. However, noisy or unsafe roads and sideways may have an extra effect.

They found such an "neighbourhood soundscape effect" and conclude that exposure-effect relationships may be misleading without considering the neighbourhood soundscape.

Recent field studies dealing with rail and road noise in combination (Moehler et al 2000, Joncour et al. 2000, Botteldooren et al 2001, Cremezi et al. 2001) have analyzed this combination more in detail. Overall they found that the kind of combination of the two sources (both, dominant or dominant/non-dominant combination) plays an important role. They differ, however, in their results.

Botteldooren et al 2001 analyzed four categories of dBA-differences between the rail and road and observed a stronger annoyance response at higher noise levels (>55dBa), when the dBA-difference between the sources was larger than 3 dBA (Figure 3).
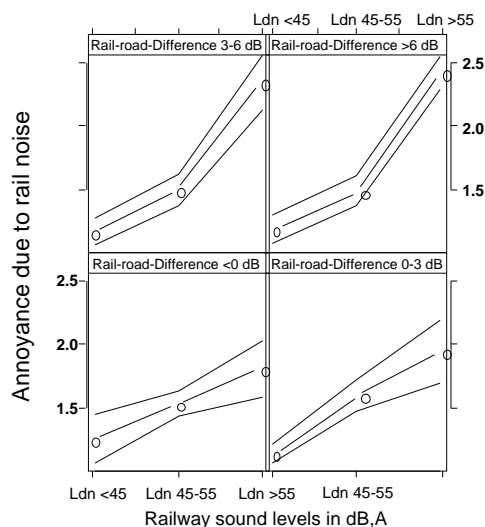

Figure 3. *Exposure-response curve for railway noise stratified by rail-road noise difference (Botteldooren et al. 2001).*

In Figure 4 below the results of Cremezi et al (2001) are described: here the lowest exposure-response is seen when the road exposure is below 55 dBA and the highest, when road exposure is between 60-65 dBA. However, these areas with road exposure between 55-60 dBA and above 65 dBA deviate.
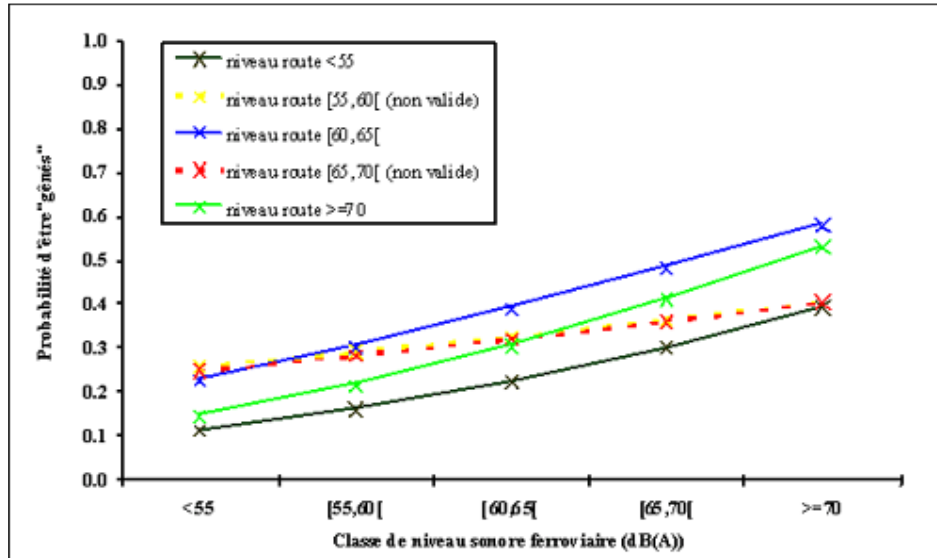
Figure 4. *Exposure-response for rail noise stratified by exposure to road noise.*

Recently, Öhrström et al (2005) found in areas exposed to high sound levels (at sound levels above $L_{Aeq,24h}$ 55dB) both from road traffic and railway noise, an interaction effect for noise annoyance (Figure 5). The difference in annoyance increases from 6 % at 48-51 dB, through 10 % at 56-60 dB and to about 20 % in the highest sound exposure category.
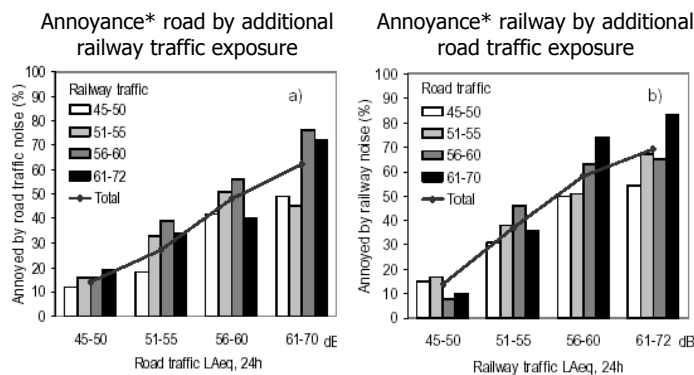
Figure 5. *Exposure-response for road traffic noise by railway noise (left) and railway noise stratified by exposure to road traffic noise (right).*

Annoyance by noise & vibration

Some studies have dealt with the effect on annoyance by a combination of noise and vibrations in a laboratory context (e.g. Meloni & Krüger 1990, Howarth & Griffin 1991,

Paulsen & Kastka 1995). Field studies carried out in Austria, Germany, Japan, Sweden, Norway. Sato (1988) was among the first to report a carefully designed field study (see group definitions in Figures 6a) with measured noise and vibration indices. He did show that residents exposed to both noise and vibration exhibited higher annoyance responses (see Figure 6b). In a later path analysis Sato (1994) tried to determine the factors that affect most total *annoyance*. He found strongest *direct effects* for annoyance due to vibration, the noise level, interference with communication, irritation and problems with falling asleep, while the vibration level showed up as *indirect effect* in size above the noise level. Overall, the noise level (due to both direct and indirect effects) made a larger contribution. The annoyance due to vibration made a similar large contribution to the *total annoyance*.
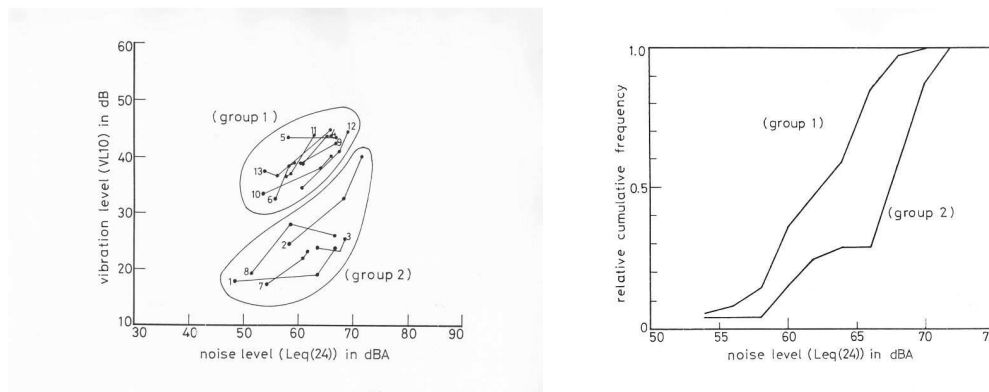

Figure 6a. *Study group definitions by noise and vibration levels (Sato 1988)*

Figure 6b. *Cumulative annoyance response by simultaneous exposure to noise and vibration (group 1) or predominantly noise exposure only (group 2).*

Then the German field study was conducted, where objective measurements of noise and vibration were done for most houses (Knall 1996, Zeichart 1998, Passchier-Vermeer & Zeichart 1998). The sample size for these analyses were N=417. They found an interaction between noise and vibration exposure only on daytime noise annoyance. Noise exposure explains 8% of the variance in the overall annoyance data, vibration exposure 5% and the interaction 3%. They also compared S-trains (short travel trains) with F-trains (long travel trains) and found for situations with equal vibration and noise exposure annoyance scores for S-trains to be about half of these for F-trains. Based on their exposure-response curve they calculated the equivalent dBA-levels that are responsible for the excess annoyance due to the additional vibration exposure. Figure 7 below shows the resulting overall noise level for several grades of vibration intensity (KBr from 0-0.2).
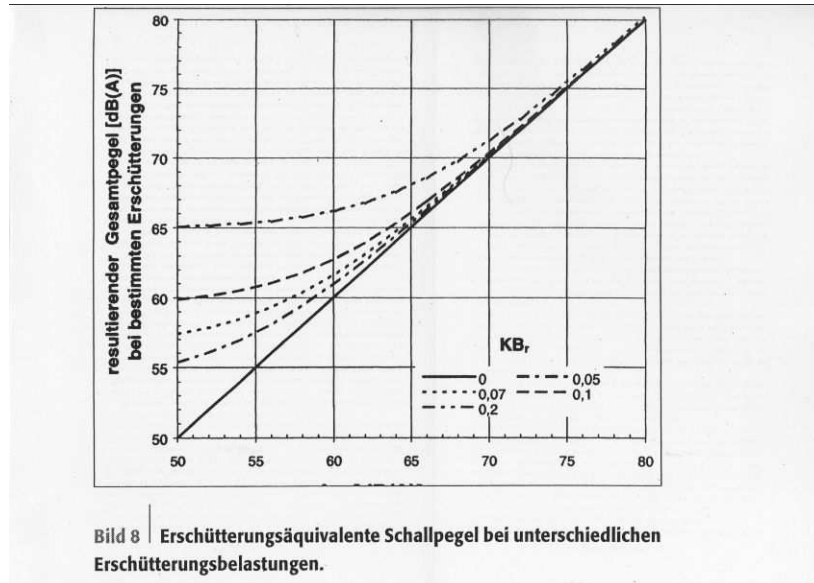
Bild 8 | Erschütterungsäquivalente Schallpegel bei unterschiedlichen Erschütterungsbelastungen.

Figure 7. *Resulting overall noise level when the excess annoyance due to additional vibration exposure is accounted for (based on several grades of vibration intensity: KBr from 0-0.2). (Source: Zeichart 1998).*

The resulting curve indicates that additional vibration affects mainly areas with mid to lower rail noise levels, while above 70 dBA the effect diminishes. The results of Öhrström et al. (1996, 1997) in Figure 8 show that railway noise is experienced as more annoying in areas in which there is simultaneous exposure to vibration from railway tracks. From their large field study (2883 persons between 18 and 75 years of age), they concluded that in areas with simultaneous exposure to strong vibrations (2mm/s) either action against vibration or a greater distance between the houses and the railway line is needed, corresponding to a 10 dBA lower noise level than in areas without vibration.
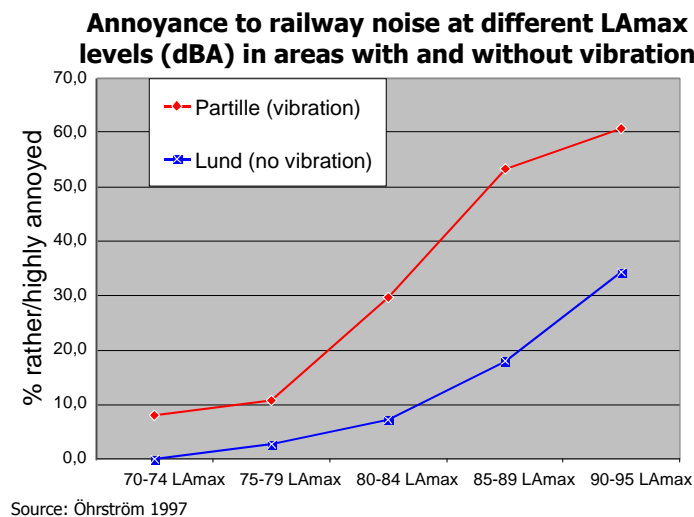

Source: Öhrström 1997

Figure 8. *Percentage annoyed (rather/highly) due to railway noise (LAmax, dBA) in areas with (Partille) and areas without (Lund) additional vibration exposure.*

The Austrian study (Lercher et al 1999) was conducted within the framework of a EHIA for a new rail track (N=2007, age range 18-70 yrs). Vibration exposure was assessed by questionnaire as pilot case studies have shown quite difficult and unpredictable vibration propagation pattern. The result (Figure 9) combines the result from Zeichart and Öhrström: the curves shows already a strong effect of additional perceived vibration at lower levels (like Zeichart) which follows up further to the higher levels (like Öhrström).
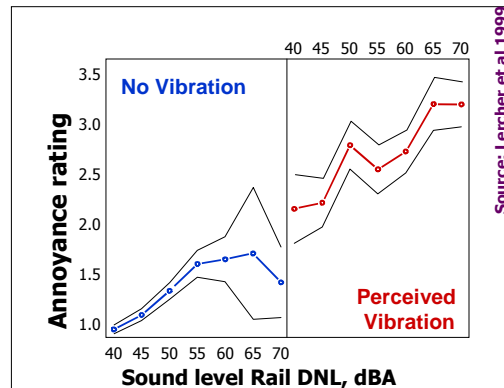

Figure 9. *Railway noise - annoyance (4 grades: 1 to 4) relationship with (right panel) and without (left panel) perceived vibration exposure (Lercher et al 1999)*

The discrepancies between the two large field studies (Öhrström and Lercher et al) and the study by Zeichart are not well understood. Most Japanese studies (Yano et al 2005, Yano et al 2006, Ota et al 2006) did notice some excess annoyance at some points of the exposure effect curve. A full interaction was, however, not demonstrable, as the sample sizes were not sufficient to prove this. However, Yokoshima & Tamura (2005) found significant interactive impacts of noise and vibration annoyances on each other only in detached houses but not in apartment homes. What should not to be forgotten here is the specific field of low frequency noise. It can also produce vibrations and rattles as secondary effects. A study by Yamada et al (1991) showed a very complex effect pattern which is probably modified by masking. As this is a highly specialized area not many community studies did deal with it (Fidell et al 1999, 2002, Persson-Waye 2004). However, health effects due to low-frequency components may be more severe than for community noises in general (see review by Berglund et al 1996, Schust 2004, Persson-Waye 2004). E.g. In the small Swedish study by Persson-Waye, persons having a sleeping room exposed to low frequency noise were more annoyed then those having the sleeping room expsoed to road traffic noise. A combined assessment was not possible due to the small sample size.

Annoyance by noise & air pollution

There are only three groups that have addressed this combination in major field studies (TOI 1991, Clench-Aas 1991, Lercher 1992, Lercher et al 1993, Lercher & Kofler 1995, Lercher et al. 1999, Klæboe et al. 2000, Job & Hatfield 2004). The interdisciplinary effort from the Norwegian transport economic institute (TOI) together with the Norwegian Institute for Air research was one of first to investigate cumulative effects of both air pollution and noise exposure in different community settings. While the results in the left panel are obtained from a diary study, the results in the right panel are obsevd in a cross-sectional community study by asking for average annoyance during the last year.
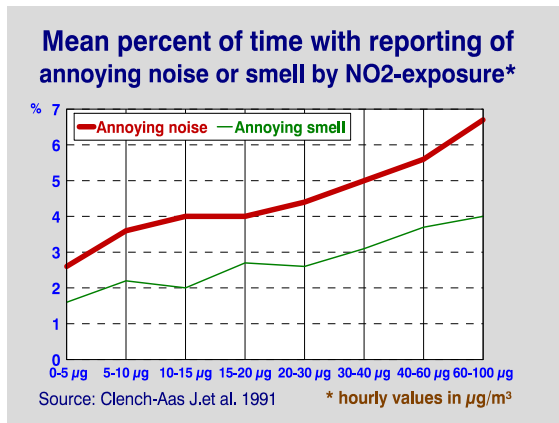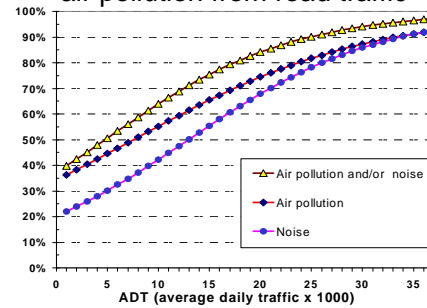
Figure 10a. *Percentage of time with reporting of annoyance due to noise or smell by hourly levels of NO2-exposure (Source: Clench-Aas et al 1991)*

Figure 10b. *Percentage of highly annoyed due to single noise or air pollution experience or in combination by average daily traffic volume (Source: TOI 1991)*

The Tyrol studies (Lercher et al 1995 & 1999) further demonstrate the mutual dependence of the annoyance response towards combined exposure (Figures below). The left panel presents the main determinants of the perception of traffic exhaust: Noise annoyance is by far the most important determinant. Also noise sensitivity is significant, while odour sensitivity and weather sensitivity were not. The right panel graph shows a stronger exposure-response in noise annoyance when additional annoyance due to traffic exhaust is considered. Overall, there is a shift toward the left with a stronger effect in the higher noise exposure levels.
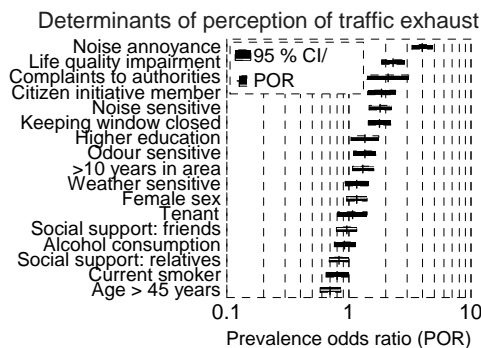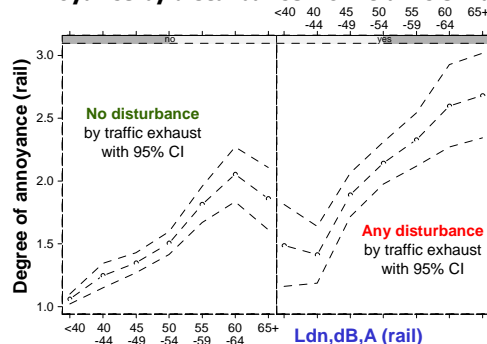
Figure 11a. *The main determinants of the perception of traffic exhaust (Source: Lercher et al 1995).*

Figure 11b. *Railway noise – annoyance relationship with (right panel) and without (left panel) perceived traffic exhaust (Lercher et al 1999)*

Klæboe et al 2000 have analyzed the relationship between noise and air pollution annoyance in more detail with a 3-step procedure. They applied various sensitivity tests. By omitting sensitive persons they tested against bias due to negative affectivity. They adjusted for other sensitivities, socio-demographic varibiables and mobility and received the same result: both noise and air pollution annoyance depends in a highly significant way on both the NO2-
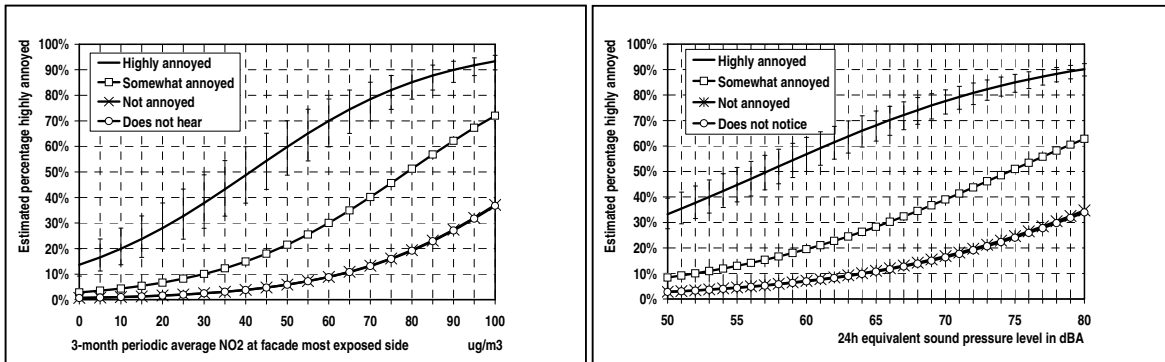
Figure 12a. *Estimated probabilities of people being highly annoyed with exhaust/odour right outside their apartment by NO2-levels. Separate curves for people differing in their degrees of noise annoyance (left panel).*

**Figure 12b.** *Estimated probabilities of people being highly annoyed with road traffic noise by 24h equivalent sound pressure levels. Separate curves for people with different degrees of annoyance with exhaust/odour (right panel). Pooled data. N=2990.*

indicator and the noise indicator (Figure 12a and 12b).

Conclusion: "Exposure-effect models for noise and air pollution annoyance only including noise and air pollution indicators, respectively, will give misleading results".

Klæboe et al (2000) see a need for "more robust exposure-effect relationship assessment" by integrating air and noise pollution modelling to better assess the combined impacts and to assess the effects of traffic measures. They recommend multistage modelling tools such as structure equations models to identify the different causal pathways involved.

In a further attempt to analyze the effects of coping on both noise and air pollution annoyance (Botteldooren & Lercher 2004) two main results were drawn: First, with increasing annoyance (both: air and noise) coping activities increase in the population. Second, the actual prediction whether the respective annoyance response is due to noise or air pollution is, however, difficult, as some coping activities (e.g. closing windows) overlap. Furthermore, different annoyance distributions for air and noise annoyance in terms of severity also may contribute to uncertainty.

Annoyance by noise & context
The mutual influences of context variables are of great importance in noise effects research as the moderational potential is large (see Lercher 1998, Job & Hatfield 2001). The number of variables is large and not for all is sufficient evidence available (Job 1991, Fields 1993, Lercher 1996, Miedema & Vos 1999, Miedema & Vos 2003, Miedema & Fields 2005).

Furthermore, the context dependence makes it difficult to generalize the observed results in individual studies. Nevertheless, the neglection of these factors in the framework of an EHIA could result in wrong assessments at regional levels. To show the importance the moderation effect is sometimes expressed in dB-equivalents (Fields 1990, Job 1991).

Effect size of Moderator variables

Moderator	dB-Equivalent
Fear of crashes	6 dB
Noise sensitivity	9 dB
Belief: noise harms health	14 dB
Satisfaction with life	10 dB
Attitude to the source	8-15 dB
Neighbourhood has complained	9 dB
Satisfaction with neighborhood	13 dB
Reduction in rates	15 dB
Sight of the noise source	10 dB
Dust, air pollution, loss of privacy	26 dB

Source: RFS Job 1991 (based on various sources)

Annoyance Meta-analyses of moderators

▣ **Miedema & Vos 1999: 34 surveys (25 EU)**

▶ 10 factors studied

▶ Effect size in dB,A-equivalents (DNL)
  - fear — up to 19 dB
  - sensitivity — up to 11 dB
  - age — up to 5 dB
  - dependent on source — up to 3 dB
  - others — below 2 dB

Figure 13a. *Effect size (in Leq-dBA-equivalents) of important annoyance moderators from various sources.*

Figure 13b. *Effect size (in Ldn-dBA-equivalents) of selected annoyance moderators based on 34 surveys (25 from EU-countries)*

In one of the rare annoyance studies with children, the largest moderation of the reported noise-annoyance curve came from satisfaction with the living area ("I like to live here") and from opportunities "to act out" and "have fun in the neighborhood" (Lercher et al. 2000).

The effect of visual settings on the perception of noise has been demonstrated in laboratory and field studies (e.g. Kastka & Noack 1987, Carles et al 1992,1999, Abe et al 1999, Fyhri & Klæboe 1999, Suzuki 2000, Viollon et al 2002).

A Swedish research programme "soundscape for health" is investigating the potential of "quiet courtyards" with respect to health and well being (Kihlman et al. 2001; Berglund & Nilsson 2002, Kihlman et al. 2002, Skanberg & Öhrström, 2002).

Verkeyn & Botteldooren (2002) found an effect of some land use variables on the reported noise annoyance keeping sound level constant: reported traffic density and degree of urbanization made significant, separate contributions in a Ldn based model. And people living in an environment with rather uniform land use were found to report less frequently high annoyance by road traffic noise than people living in a mixed environment or at an edge, compared with what is expected based on an Ldn based model.

As far as mixed sources are concerned (**see chapter 2.1 above**): recent research has confirmed a variety of possible context combinations with considerable moderation of dose-response relationships (Moehler et al 2000, Joncour et al. 2000, Cremezi et al. 2001, Botteldooren et al 2001).

Effects of combined exposures on selected health outcomes

Respiratory diseases and allergies

Ising et al 2003, 2004, 2005 observed in a small (N=68) and midsized study (N=401) with school children (age 5-12yrs) a combined effect of noise and air pollution using a 3-grade "traffic exposure index". Adjusted for age, sex, education, persons/household, animals, ETS they found significantly higher odds ratios in the highest exposure category for diagnoses of asthma, bronchitis, and atopic dermatitis in a children's sample from pedriatic offices (N=401). In a selected subsample (N=68) physician contacts over the past five years were taken from physician records: contacts due to chronic bronchitis did show a dose-response dependent increase with the 3-grade "traffic exposure index" (Figure 14 below).

An extended analysis including cortisol excretion in urine (first half of night) did result in a significant increase in variance explanation (7%) of the physician contact model.
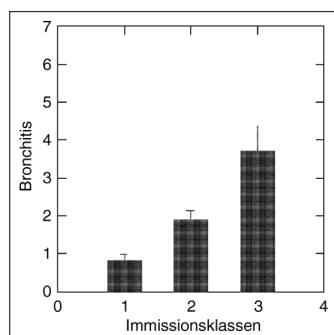
Figure 14. *Physician contacts due to bronchitis/year by combined traffic exposure (Source: Ising 2005).*

Sleep

Only recently, experimental studies were designed to assess the effect of multiple noise source exposures. E.g. Basner et al (2006) presented first results of a study performed by DLR: 72 subjects (40+/-13 years, 32 male) were polysomnographically investigated during 11 consecutive nights in the laboratory. During these nights they were exposed by playback to realistic single (either air, road, rail), double (air-road, air-road, road-rail) and triple source exposure (air-road-rail) at 5 levels of noise exposure (maximum SPL 45, 50, 55, 60 and 65 dBA). The results on sleep quality (see Fig below) show on the extreme points: only 22% of the subjects experienced good/very good sleep with triple source exposure while percentages with single noise exposure varied between 51 and 35%, and the reference without noise exposure stayes at 61%.
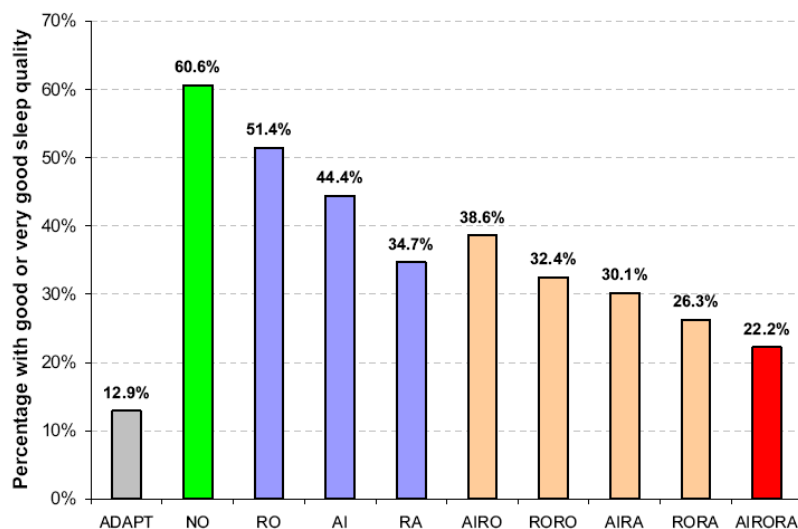
Figure 1: Sleep quality depending on traffic noise pattern (ADAPT = adaptation night #1, NO = noise free night, AI = air traffic, RO = road traffic, RA = rail traffic).

Source: Basner et al, Internoise 2006

Figure 15. *Single, double and triple noise source exposure and reduction in sleep quality*

Cardiovascular health indicators

In a cross-sectional analysis of a subsample of the Caerphilly cohort study, 255 men exposed to both traffic noise at home and work noise were studied for potential effect moderation (Babisch et al 1990). It could be shown (Table 6a, 6b) that the impact on both blood pressure and cholesterol levels was more pronounced in traffic noise exposed subjects who also experienced a high noise load at the worksite. The occupational noise exposure was obtained by personal dosimetry.

Table 6a. Combined effect of noise[+] on blood pressure		
Systolic blood pressure*		
Noise exposure	Work noise < 90 dB	Work noise > 90 dB
	Mean (95 % CI)	Mean (95 % CI)
Traffic noise < 60 dB	141.2 (137.4,145.0)	137.5 (133.6,141.4)
Traffic noise > 60 dB	141.0 (136.5,145.5)	145.1 (137.4,152.8)
* mmHg		[+] Adjusted for wearing hearing protectors
		Source: Babisch et al. 1990

Table 6b. Combined effect of noise[+] on total cholesterol		
Total cholesterol *		
Noise exposure	Work noise < 90 dB	Work noise > 90 dB
	Mean (95 % CI)	Mean (95 % CI)
Traffic noise < 60 dB	5.44 (5.13,5.75)	5.86 (5.51,6.21)
Traffic noise > 60 dB	5.84 (5.63,6.05)	6.36 (5.80,6.92)
* mmol/l		[+] Adjusted for wearing hearing protectors
		Source: Babisch et al. 1990

Cohen et al (1986) did provide an interesting example how tricky combined effects can be:. In this study of schoolchildren exposed to aircraft noise during schoolhours the importance of the home environment was studied as a potential modifying variable for blood pressure responses at school. The surprising result (see Table 3) shows higher mean blood pressure readings during schoolhours for the children coming from low-noise home environments. The interpretation given - based on the adaptation level theory of Helson (1964) - assumes that children residing in noisier areas may have established a higher adaptational level and therefore exhibit lower arousal in noisy classrooms.

Table 7. *Systolic/Diastolic Blood Pressure[§] as a function of home noise levels*

	Systolic*		Diastolic*	
Home Noise[§]	Mean	SD	Mean	SD
Low				
Noisy classroom	92.58	14.52	49.90	10.73
High				
Noisy classroom	86.99	10.56	46.67	8.91

[§] **Home Noise Effect, p < 0,01**   * **in mm Hg**

Source: Cohen et al. 1986

As the focus of this summary is on environmental effects it should be mentioned that there are also examples of combinations of effects between physical factors (noise, low frequency noise, vibrations) and psycho-social factors (demands, night-shift work, work satisfaction) at the worksite (e.g. Melamed et al. 2001, Lercher et al. 1993), which may not be covered by the specialist group who talks about interactions between physical and chemical factors.

Conclusions: noise and vibration

Short summary:

As estimations from Germany have shown (Ortscheid & Wende 2000), about 11 Mio persons are exposed to road and rail noise. This combination is the most likely producer of noise and vibration interactions, predominantly in the vicinity of the sources.

The potential interactions between aircraft and road noise with vibration exposure has been poorly studied. As potential health outcomes only annoyance has been studied in environmental field studies.

In the 4 larger field studies higher annoyance responses have been observed among those with either measured or perceived vibrations. There is some indication about stronger annoyance responses in areas below 55 dBA,Leq, but the larger studies see a continuous effect up to the highest noise exposure. On average this additional effect due to the combination would correspond to about 10 dBA, when areas with and areas without vibration are compared at the same noise levels.

These "hidden" additional effects are currently not considered in legislation and EHIA and will therefore lead to underestimations of annoyance in areas

with additional vibration exposure, when the noise maps that will be produced by member states in the course of the request by the Environmental Noise Directive are taken as basis for the annoyance assessment.

Research needs:

In addition to annoyance, sleep disturbance and cardiovascular endpoints should be considered in environmental studies. On the technical site the issue of the potential effects of low frequency noise components (which often accompany vibrations) should be investigated further.

Legal issues:

Currently only the Swedish and the Norwegian government have considered the additional effect of vibrations in their legislation. There is a need to set a European initiative to integrate this issue into legislation and make it mandatory in EHIA-procedures.

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Epidemiological Methods and Risk Assessment Models of Combined Effects: An Approach to Complexity

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Introduction: Challenges in studying combined effects of Environmental Exposure to Noise, Air Pollution and Chemicals

Health can be impacted in many ways by exposure to chemicals. The respective contributions of a number of factors to every disease/health outcome have to be assessed. The possibility of effects latency only adds to the complexity of epidemiological health investigations. Most studies concern health effects of single chemical and few studies address combined exposure to several chemicals and the possibility of synergetic or antagonistic effects. Until recently, standards were essentially derived from observations in occupational exposure or subjects selected from the general population of "average" adults. Additional bodies of information are involved in the case of vulnerable groups, e.g. fetuses, babies, young children; the elderly, people with diseases or medical problems, people in deprived - socioeconomic, housing, nutritional, ... - , status, etc. As an additional burden upon such already complex analyses, exposure to noise is a widespread environmental problem. Noise levels in vulnerable subgroups have been reviewed for specific environments (*in utero*, incubator, home, school, etc.) and for specific lifestyles (listening to loud music through headphones, or at discotheques and festivals; motor cycling, etc.). (Bistrup, 2001).

The exposure to one or several chemicals may be concomitant to exposure to physical agents such as noise and vibrations and such combinations are rarely addressed. Potentially, even small risks are important because a large number of persons are currently exposed or likely to be exposed in the future to noise or air pollution levels able to induce changes in the population mean. These changes can reflect large changes in susceptible subgroups of the population.

The purpose of this contribution is to address methodological issues related to the multiplicity of factors involved in connecting environmental contaminants, noise and human health, with an emphasis on vulnerable groups and to contribute to disentangle various layers of complexity.

1. Ambient noise rarely occurs in isolation of other social and environmental problems

Ambient noise exposure rarely occurs in isolation of other social and environmental problems. Noisy environments frequently co-exist with crowding, substandard housing, poverty and pollution. Examples are given below with regard to pollutants and noise exposure in lower socio-economic status.

In the United Kingdom, cities and towns have become 10 times noisier in the last decade (based on acoustic noise measurements since 1991 in Sheffield), and 66% of outdoor noise is estimated to come from motor traffic (Rimmington, 2006). Children living near busy roads had a 50% increased risk of suffering from respiratory diseases (WHO, 2004b). Ponce et al (2005) found that traffic-related air pollution exposure especially impacted lower socio-economic neighborhoods resulting in increased susceptibility during the winter amongst women with known risk factors in Los Angeles County, California. Indicators studied were birth records from 1994-1996, traffic counts, census data, and air pollution measures and related the effects of traffic-related air pollution on pre-term births. In England, Walker et al (2003) found that the most deprived wards were those with the highest pollutant concentrations, and that people in deprived wards were exposed to NO_2 concentrations 41% higher than those of wards of average deprivation. Their study found that "the number of people resident in wards above high pollution thresholds increases progressively with

increasing deprivation" and that "of the 10% of the population resident in wards with poorest air quality, half reside in wards that are amongst the 20% most deprived in the country." They underline "the general recognition that deprived communities are likely to experience disproportionate levels of pollution and other forms of environmental degradation", with empirical evidence. They examined the distribution of "environmental bads (such as pollution) and goods (such as access to green spaces)" within society. Brunekreef and Holgate (2002) suggested that the effects on life expectancy of exposure to particulate matter could be greater for more disadvantaged groups. Jerrett et al (2001) noted a "triple jeopardy" in that disadvantaged groups suffered from increased risk due to social and behavioural determinants of health, from worse air quality in deprived neighbourhoods, and from exposure to air pollution that causes disproportionately large health effects (effect modification) as compared with advantaged groups. An integrated approach involved the examination of several routes of exposure to lead and particulate matter both in adults and children in dense urban and industrial environments. The intensity and number of sources of exposure indoors and outdoors, the lead body burden, the quality of the built environment and the conditions of housing, the rate of renovation over time; traffic density etc. were all among the factors that explained the different health outcomes of white- and blue-collar employees (Steenhout, 1987a,b; 2001).

2. Which combined exposures occur via inhalation, where do they occur? Examples

In addition to exposure to ambient air contaminants and occupational exposure to chemicals, exposure also occurs to a number of toxicants penetrating buildings and/or emitted in the indoor environment. Indoor air pollutants emitted from construction materials, products and articles and during human activities such as cleaning products, air fresheners, pesticides, furnishings, heating and cooking appliances. Pollution from outdoor sources also penetrates into buildings. Ventilation rate and insulation play a role in the circulation and fate of chemicals (SCHER, 2005, 2006). In kindergartens and schools, noise levels have been measured that sometimes exceed the limits promulgated for occupational noise. Headphones, as well as certain toys, toys guns and fireworks are important sources of impulse noise are. High noise levels also occur in discotheques, at outdoors concerts, from some motorized sports and leisure activities and in dwellings, depending on the distance to sources and/or on lifestyle (Bistrup, 2001).

Chemicals present in environmental tobacco smoke (ETS) compose a complex mixture including irritants and systemic toxicants such as hydrogen cyanide and sulfur dioxide (SO_2), mutagens and carcinogens such as benzo[*a*]pyrene, formaldehyde, and 4 aminobiphenyl, and the reproductive toxicants nicotine, cadmium, and carbon monoxide (CO) (Jenkins et al. 1992). Nicotine is neurotoxic with lasting effects on neurological function after fetal exposures. Picone et al (1982) reported that infants born to smokers score significantly lower at 2, 3, and 14 days postpartum than unexposed infants. Hearing seemed to be particularly affected. Exposed infants were able to adapt to sounds normally but were less able to orient toward the source of the sound. This finding persisted at 2 weeks of age. Disorders of the middle ear were measured in children of smoking parents and indicate more frequent middle ear effusions (Reed and Lutz 1988; Strachan et al. 1989),

Sexton et al (2005) studied the occurrence of combined VOC exposure in childen. The study measured blood concentrations of 11 volatile organic compounds (VOCs) up to four times over 2 years in a random sample of more than 150 children from two poor neighborhoods in Minneapolis, Minnesota. Children blood levels of benzene, carbon tetrachloride, trichloroethene, and m-/p-xylene were comparable with those measured in selected adults

from the Third National Health and Nutrition Examination Survey (NHANES III, 1988-1994). Blood levels of styrene were more than twice as high, and for about 10% of the children 1,4-dichlorobenzene levels were ≥ 10 times higher compared with NHANES III subjects. The concentrations of ethylbenzene, tetrachloroethylene, toluene, 1,1,1-trichloroethane, and o-xylene were two or more times lower in the children.

Two-day, integrated personal air measurements explained almost 79% of the variance in blood levels for 1,4-dichlorobenzene, approximately 20% for tetrachloroethylene, toluene, m-/p-xylene, and o-xylene and 0.5 to 8% of the variance for trichloroethene, styrene, benzene, and ethylbenzene. A strong statistical association occurred between numerous pairwise combinations of individual VOCs in blood (e.g., benzene and m-/p-xylene, m-/p-xylene and o-xylene, 1,1,1-trichloroethane and m-/p-xylene, and 1,1,1-trichloroethane and trichloroethene). Between- and within-child variability were approximately the same for ethylbenzene and 1,1,1-trichloroethane. Between-child variability was higher than within-child variability for 1,4-dichlorobenzene and tetrachloroethylene while it was lower than within-child variability for the other seven compounds. For siblings living in the same household, a strong statistical association was found between measured blood VOC concentrations.

Sources of organic compounds in the indoor environment include furnishings. They release organic gases and vapours, some of which contain formaldehyde. New building materials may contribute substantially to the indoor air concentrations of VOCs (Hodgson et al., 2000). Temporarily high concentrations are also obtained during human activities such as cleaning (Nazaroff and Weschler, 2004; Wolkoff, 1995; Wolkoff et al., 1998). The hazards of selected categories of cleaning agents used in Denmark and their classification as irritant, harmful to health or corrosive have been listed.

Gas and wood stoves are other common sources indoors. Natural gas combustion emits NO_2 and CO. Smoke results from cooking or heating with wood. Gases such as NO_2 and SO_2 also occur. The aerosol mixture includes fine liquid droplets in suspension. Particles in the inhalable range [PM_{10} = particles <10 μm in aerodynamic diameter] are also present (Lambert et al, 1996) Oxidation of alkenes and unvented combustion produce radicals in indoor environments (de Kok et al., 2004; Sarwar et al., 2002; Weschler and Shields, 1997a,b). For example, alkenes, like monoterpenes react with ozone to produce the hydroxyl radical (Atkinson and Arey, 2003; Weschler and Shields, 1997a). Monoterpenes are common and relatively abundant compounds indoors emitted from wood (furniture), plant and fruits and their extracts (e.g. citrus and pine oils). In addition, monoterpenes and monoterpene derivatives are common fragrances used in cleaning agents, household products, including personal care products (Nazaroff and Weschler, 2004). The abundance of and hence the exposure to terpene oxidation products indoors depends on the identity and concentration of the reactants (e.g. limonene and ozone), their reaction rate and the air exchange rate, both of which determine the build-up of reaction products (Weschler and Shields, 2000).

3 Confounding variables for consideration in epidemiological studies of noise induced health effects in the presence of air pollutants and other chemicals

3.1. Confounders

Confounders include population characteristics, ethnicity, age, gender, education, health or disease status and medication, weight and body mass index (BMI), nutritional status, tobacco and alcohol consumption, conditions of housing, time-use patterns, physical activity, socio-economic/professional status, occupation and leisure activities, etc. Some additional variables are discussed below with more details in the examples of several outcomes (non exhaustive list).

3.2. Confounders in noise-induced hearing loss studies

Air pollution or chemicals may induce susceptibility to infections that can reduce hearing and balance. Additional factors of interest when evaluating possible noise-induced hearing loss in the presence or other stressors include the following.

3.2.1. Medical drugs: Canlon et al (2003) showed that prenatal glucocorticoid treatment increased the susceptibility of the inner ear to acoustic noise trauma in adult life. These data support the hypothesis that alterations in the intrauterine environment may modify the developmental program of the cochlea, inducing dysfunction later in adult life. Excessive prenatal exposure to dexamethasone decreased the potential for recovery of the cochlea to oxidative stress induced by acoustic trauma; this decreased recovery potential can be counteracted by treatment with antioxidants.

A number of anticancer drugs, such as *cis*-dichlordiammine platinum (II), or cisplatin, and vincristine, can cause temporary and permanent hearing loss. Cisplatin is used in chemotherapy of ovarian, lung, and testicular cancer. The hearing loss affects the high-frequency range; severity of hearing loss depends on peak blood plasma levels. The pattern of damage to the organ of Corti is similar in many respects to that of the aminoglycosides, with similar progression of hearing loss. Disturbances of epithelium within the stria vascularis are also seen (Lang, 1994).

3.2.2. Ear infections: In the first ten years of life children experience about 100 infections. Many of them are upper respiratory infections. Bacteria in the nasopharynx easily migrate up the E-tube and cause infections of the middle ear. Children under six with persistent or frequent middle ear effusions undergo hearing loss and suboptimal development of language skills. Bennett and Haggard (1998), concerned with middle ear disease and conflicting evidence arising from small and incompletely controlled studies, examined a large UK birth cohort for which parent-reported data were available on health and social factors including data on two markers for middle ear disease: the occurrence of purulent (nonwax) ear discharge and suspected or confirmed hearing difficulty of children at the age of 5 yrs. The three main risk factors predicting reported hearing difficulty up to age 5 are maternal smoking, day care attendance, and male sex. A child having all three risk factors (attends day care, a mother who smokes, and male sex) is 3.4 times more likely to have problems with hearing than a child who has none, based on cumulative risk. This study called into question the importance of breast feeding as a protective factor in middle ear disease.

3.2.3. *Immunosuppressive compounds and increased risks of respiratory infections*:

Prenatal exposure to ETS affects fetal growth and is associated with low birth weight and increased infant mortality and morbidity, including higher risk because of the small diameter of their airways and their higher breathing rate compared to adults (McConnochie and Roghmann 1986; Ogston et al. 1987). The highest risk seems to occur below 3 months of age (Wright et al. 1991) but a lower than normal pulmonary function also occurs in childhood (Cullinan and Taylor 1994; Cunningham et al. 1994; Wang et al. 1994). More frequent middle ear effusion is found (Reed and Lutz 1988; Strachan et al. 1989) as well as chronic respiratory problems (cough, phlegm, or wheezing) (Mannino et al, 1996). Asthma is more likely and in turn, more severe diseases occur in asthmatic children (Chilmonczyk et al. 1993; Martinez et al. 1992; Weitzman et al. 1990).

Exposure to polycyclic aromatic hydrocarbons - especially benzo[a]pyrene, a known carcinogen -can cause immune suppression and increase the risk of infection and disease (Mishra, 2003).Prenatal exposure to polychlorinated biphenyls (PCBs) and dioxins was associated with changes in the T-cell lymphocyte population in healthy Dutch infants (Weisglas-Kuperus et al (2000); Weisglas-Kuperus N (2001). A group of 207 healthy mother/infant pairs had been examined to see whether these changes persist into later childhood and whether background exposure to PCBs and dioxins is associated with the prevalence of infectious or allergic diseases and humoral immunity at preschool age. Adjusted for confounders, prenatal PCB exposure was associated with less shortness of breath with wheeze. Current PCB body burden was associated with a higher prevalence of recurrent middle ear infections and of chickenpox and a lower prevalence of allergic reactions. Higher dioxin TEQ was associated with a higher prevalence of coughing, chest congestion and phlegm. Effects of perinatal background exposure to PCBs and dioxins were found to persist in preschool children and associated with a greater susceptibility to infectious diseases.

An Inuit cohort was investigated for PCBs and dichlorodiphenyldichloro-ethylene (DDE) effects of perinatal exposure on the incidence rates of upper and lower respiratory tract infections, otitis media, and gastrointestinal infectious in infants (Dewailly et al., 2000) and preschool children (Dallaire et al, 2006). For what concerns children from 0 to 5 years of age (Dallaire et al, 2006), compared to children in the first quartile of exposure (least exposed), children in fourth quartile (most exposed) had rate ratios of 1.25 ($p < 0.001$) and 1.40 ($p < 0.001$) for acute otitis media and lower respiratory tract infections, respectively. The incidence rates were positively associated with prenatal exposure to PCBs. In both studies, no association was found when postnatal exposure was considered. Prenatal exposure to PCBs could be responsible of a significant portion of respiratory infections early in life in this Inuit population.

Higher concentrations of specific phthalates were associated with persistent allergic symptoms in children, i.e. BBP (butylbenzyl phthalate) with rhinitis and eczema and DEHP (Di(2-Ethylhexyl)-Phthalat) with asthma (Germolec (2005). Exposure to both particles <10 μm (Lambert et al, 1996) and allergens of house dust mites, cats, and cockroaches (Cullinan and Taylor 1994) occurs, inducing irritation and inflammation of the respiratory tract, with rhinitis, cough, wheezing, and asthma. Moulds or dampness may increase the risk of respiratory symptoms among children (Dales et al. 1991; Delfino et al. 1997; Verhoeff et al. 1995). A recent ILSI/HESI workshop acknowledged that there are a variety of techniques available for assessing immunosuppression in adult animal models but emphasized that there is uncertainty about how to apply these approaches to a developing animal, especially if the

goal is to have some standard procedure(s) that could be applied for regulatory risk assessment (Holsapple 2001).

BGVV (2001) and Moeller (2001) noted that pesticides and other chemicals could have effects in relatively new areas of toxicity that deserve special consideration with respect to toxicity to infants and children, and that these areas may not be adequately assessed by the core toxicology data set: e.g., developmental neurotoxicity, endocrine disruption and immunotoxicity. Rodent models are used to study the susceptibility of the developing immune system to environmental or new chemicals. Drugs treatment during pregnancy, neonatal period and childhood are based on data from rodent studies. While the aim is to identify discrete windows of immune development where differential immunotoxic risk is likely to exist in humans, the exact time windows for the fetal, neonatal and juvenile immune system of man and rodents in developing sensitivity or resistance to chemicals and drugs remain to be determined (Dietert et al, 2000; Althoff, 2001). Maturation of the human immune system in the early postnatal period provides a balanced Th1/Th2 state facilitating resistance to infections. As infections and vaccinations that may influence the Th1/Th2 balance have been shown to impact the maturation of the immune system, the post-natal period is likely to be another vulnerable period in addition to in utero development of the immune system, during which immunotoxic chemicals may have relatively pronounced consequences (Van Loveren, 2001).

3.2.4. Single or multiple exposure to other ototoxic agents:

Studies focusing on noise from traffic often poorly or omit to characterize traffic-related exposure to air pollutants. Given the ubiquity of noise exposure both at work and at home, possible interactions may occur with ototoxic agents in the occupational or the living environment. Other examples include lead exposure of children (Schwarz and Otto, 1987;1991) and arsenic exposure in children living around a power plant burning coal with high arsenic content (Bencko and Symon (1977). Exposure to methyl mercury was studied by Rice and Gilbert (1992) using developmental models, in young primates and by Murata et al (1997) on Madeira newborn/mother pairs and follow-up testing (Grandjean et al, 1997; Murata et al, 2004)).

A series of chemical contaminants with the potential to disrupt intrinsic antioxidant pathways or to enhance reactive oxygen species (ROS) generation were shown to produce permanent hearing loss in the presence of noise. These agents include carbon monoxide, hydrogen cyanide and acrylonitrile. There is evidence that intense noise can initiate ROS generation, resulting in cochlear damage. It has been shown that even moderate noise levels, including noise close to permissible workplace exposure levels can initiate oxidative stress leading to the death of sensory receptor cells for sound, the outer hair cells, and subsequent permanent impairment of auditory function (Fechter et al. 1987,1988, 2000, 2002, 2003; Fechter and Pouyatos (2005).

Hearing loss was observed in 63.8% of workers exposed to pyrethroid insecticides spayed in vector control campaigns and in 66.7% of these exposed to both noise and insecticides. The median exposure time necessary to detect high-frequency losses was 7.3 years and 3.4 years, respectively. Hearing thresholds were poorest among workers exposed to both agents. Noise exposure can potentiate the ototoxic effects of insecticides (Fernandes Teixeira et al, 2003). Solvents such as trichloroethylene (TCE) and toluene can induce auditory deficits in both animals (Crofton et al, 1993, 1994; Fechter et al, 1998) and humans (Morata et al (1994). Recent data provide evidence for a cochlear origin (Fechter et al, 1998). An atypical and persistent mid-frequency hearing loss has been identified in rats after inhalation exposure to

TCE and other volatile organic solvents such as styrene, toluene, and mixed xylenes TCE was associated with vestibular and auditory nerve impairment. Length of exposure was associated with increased likelihood of abnormal audiograms. Young rats are more severely affected by toluene than older rats: weanlings tend to be more sensitive than adults (Pryor et al, 1984). Organic solvents (toluene, xylene, styrene, *n*-hexane, trichloroethylene, carbon disulfide, petroleum) and mixtures produce auditory system abnormalities including speech discrimination problems, increased latencies of brain stem auditory evoked potentials and hearing loss (Morata et al, 1993, 1995; Lang, 1994); Morioka et al., 2000; Chang et al., 2003). Toluene, for example, primarily affects the central nervous system. The loss of auditory sensitivity related to toluene was found most pronounced in the middle frequencies, the severity depending on exposure duration (Johnson et al, 1990; Chang et al, 2006). Multiple peripheral and central nervous system toxic effects result both from acute and chronic low level exposures. Vestibular disturbances are common in exposed workers. Dose-response relationships need to be established for early detection of vestibulo-toxicity (Aylott and Prasher, 2002). Lead for example is also affecting the vestibular/proprioceptive system and balance.

Studies of combined effects require knowledge on mixture components and adequate exposure assessment.

3.3. Confounders in noise-induced blood pressure and hypertension studies

In a meta-analysis of more than fourty epidemiological studies, the relation between occupational or environmental noise exposure and blood pressure and/or ischemic heart disease remained inconclusive (Van Kempen et al., 2002), in relation with unadjusted important confounders and poor exposure characterization.

Studies of blood pressure and hypertension might include additional variables of interest such as:

3.3.1. Stress: Physical and psychological stress is thought to affect blood pressure via multiple mechanisms. It activates the hypothalamus-pituitary–adrenal axis (HPA), the rennin -angiotensin system, and the sympathetic-adrenal-medullary axis (Black and Garbutt 2002). The relationship between noise exposure and blood pressure has been assessed in normal vs. deaf children from two elementary schools. Deaf children had significantly lower blood pressure than those with normal hearing after adjustment for confounders (age, BMI, hearing ability, sex). Noise exposure is associated with higher systolic and diastolic blood pressure. A substantial degree of vascular change occurs in those who have lived in an acoustic environment for a long time. It was considered that the difference in the level of noise exposure between the two groups exceeded 50 dB(A) at least, given that the environmental noise levels of the two schools ranged from 60 to 75 dB(A) (Wu et al., 1993).

3.3.2. Stress and lead: Psychological stress has been associated with hypertension in various populations. Animal studies suggest that, when stress co-occurs with lead exposure, effects may be exacerbated due to interaction (Vyskocil et al. 1990; Vyskocil et al. 1991a; Vyskocil et al. 1991b). Lead exposure heightens the harmful impact of other types of stressful situations on neurotransmission and behavior (Cory-Slechta et al., 2004) as well as on the function of the hypothalamic- pituitary-adrenal axis (HPA) (Virgolini et al. 2005). Low lead exposure interfered with sodium transport, affects the rennin-angiotensin - aldosterone

system, stimulated the HPA, increased sympathetic activity and catecholamines, and elevated the level of reactive oxygen species in other studies (Gonick and Behari 2002; Schwartz 1991; Vaziri and Sica 2004).

3.3.3. Traffic exposure and sleep disturbance: Traffic-related air pollution has been found associated with increased mortality, both in children and adults, especially with proximity to major roads. Links with cardiovascular problems are increasingly recognized. Effects such as annoyance, sleep disturbance, ischaemic heart disease and impaired performance by school children have been described (WHO, 1999). Clear associations have been reported between both daily and long-term average concentrations of air pollutants and effects on the cardiovascular system, reflected by a variety of outcome measures including risk of death and of hospital admissions. In a systematic data assessment in support of air pollution policy development in Europe, and in particular the European Commission's Clean Air for Europe (CAFE) programme, WHO (2004a) quoted that short-term changes in PM_{10} at all levels lead to short-term changes in acute health effects, included lung, respiratory symptoms, adverse effects on the cardiovascular system and increases in medication use, hospital admissions and mortality. Of greater significance are long term effects including increases in lower respiratory symptoms and chronic obstructive pulmonary disease, reductions in lung function in children and adults, and reduction in life expectancy, due mainly to cardiopulmonary mortality and probably to lung cancer. Increased $PM_{2.5}$ concentrations increase the risk of emergency hospital admissions for cardiovascular and respiratory causes. $PM_{2.5}$ shows the strongest association with mortality, indicating a 6% increase in the risk of deaths from all causes per 10-$\mu g/m^3$ increase in long-term $PM_{2.5}$ concentration.1 The estimated relative risk amounts to 12% for deaths from cardiovascular diseases and 14% for deaths from lung cancer per 10-$\mu g/m^3$ increase in $PM_{2.5}$ (Pope et al, 2002; 2004). Studies on large populations have been unable to identify a threshold concentration below which ambient PM has no effect on health.

3.3.4. Exposure, timing vs. duration: The role of exposure duration has been investigated separately for noise and for lead. A cross-sectional study in the Paris area gathered noise exposure of workers and length of exposure. Workers were exposed to levels at or above 85 dBA. Their BMI was higher and their job characteristics different from those of other subjects, with assembly line, shift-work and job under time pressure being more frequent. Blood pressure was higher among the exposed subjects (but not after adjustment for age, body mass index and alcohol intake). Taking length of exposure into account, blood pressure and the prevalence of hypertension increased for durations > 25 years. This relationship was still significant after adjustment for confounders. These results suggest that a long exposure to occupational noise is a risk factor for high blood pressure (Lang et al., 1992).

In a longitudinal 4-year study in current and former employees of a United States chemical-manufacturing facility with a previous occupational exposure to inorganic and organic lead, Glenn et al (2003) aimed at determining whether reported associations of both blood lead or bone lead with blood pressure indicated effects that were acute or chronic in nature. These authors considered that if blood lead is more strongly associated with blood pressure change compared to tibia lead, the effect of lead was likely to be acute, requiring its continuing presence at the target site for toxicity. If tibia lead was more strongly associated, then the effect on blood pressure change more likely would reflect a cumulative, perhaps irreversible effect. Tibia lead at year three averaged 14.7 ± 9.4 μg/g of bone mineral. Mean age at baseline was 55.8 years with a mean of 18 years since last occupational exposure to lead.

Blood lead at baseline of the study averaged 4.6 ± 2.6 µg/dl. Changes in systolic blood pressure (SBP) during the study were associated both with blood and tibia lead. The authors concluded the data supported an etiologic role for lead in the elevation of SBP among adult males and were consistent both with acute and chronic components or modes of action.

Martin et al. (2006) analyzed data in men and women aged 50–70 years (40% African American, 55% White, 5% other race/ethnicity) in Baltimore, Maryland, to evaluate associations of blood lead and tibia lead with systolic and diastolic blood pressure and hypertension while adjusting for a large set of potential confounding variables. Blood lead averaged 3.4± 2.3µg/dl in African Americans and 3.5± 2.4µg/dl in white Americans and tibia lead, respectively 21.5±12.6 µg/g and 16.7 ±11.9 µg/g of bone mineral. Blood lead was significantly associated with both systolic blood pressure and diastolic blood pressure without or with adjustment for socioeconomic status and race/ethnicity. In contrast tibia lead is not associated with systolic or diastolic blood pressure. The magnitude and statistical significance of this association was reduced after adjustment for race/ethnicity and socioeconomic status but propensity score analysis suggested that standard regression analysis may have exaggerated the attenuation. Blood lead was not associated with hypertension status but tibia lead was. The authors concluded that lead had both an acute effect on blood pressure via recent dose and a chronic effect on hypertension risk via cumulative dose.

The blood lead levels appearing in both studies were suggestive of low present exposure. Both, Glenn et al. (2003) or Martin et al. (2006) studies addressed the issues of the duration of exposure but did not question the combination of factors in exposure history nor the meaning of indicators of exposure.

Whether psychological stress modified the impact of cumulative lead exposure on hypertension and blood pressure has been examined in a subset of the Normative Aging Study (Peters et al., 2007), Aldwin et al. (1996). Self-reported stress was found to modify the effect of lead on blood pressure and incident hypertension in a Boston area community sample of older exposed men. After adjustment for age, BMI, family history of blood pressure, education, smoking, alcohol consumption, physical activity and nutritional factors, there was a significantly stronger association between lead levels and systolic blood pressure among men with higher levels of self-reported stress, compared with those with lower levels. Additionally, in prospective analysis, baseline self-reported stress modified the effect of baseline bone lead on the risk of developing hypertension. Those reporting high stress had about 2.6 times the risk of developing hypertension per standard deviation increase in bone lead. However, this study did not address the issue of the timing of exposures. Individuals who were exposed earlier in life may have experienced more lasting physiological changes that may have then made them more prone to judge experiences as distressful. Older subjects also have a higher probability of a history including higher exposure in the past during critical developmental stages or in adulthood, of a higher bone lead pool source and of a release of lead to blood and soft tissues putting them at greater risk for hypertension.

3.3.5. *Lead kinetics and time-related significance of indicators of the effective dose*:
Integrated studies in both adults and children have quantified the contributions to hard tissues lead or to blood lead that result from external variations in exposure and have distinguished these contributions from those related to internal circulating lead, age, release of lead stored in hard tissues etc. (Steenhout, 1987; Steenhout and Pourtois 1989).

*3.3.6. **VDR genotypes***: Blood pressure and hypertension risk may be influenced independently by lead and by genes for vitamin D receptor (VDR) and delta-aminolevulinic acid dehydratase (ALAD). These genes can modify the toxicokinetics of lead. Lee et al. (2001) reported relations among ALAD and VDR genotypes, blood pressure and hypertension status and three lead measures in Korean lead workers vs. controls without occupational exposure to lead. 9.9% of lead workers were heterozygous for the ALAD(2) allele, and there were no ALAD(2) homozygotes; 11.2% had at least one copy of the VDR B allele, and 0.5% had the BB genotype. On average, lead workers with the VDR B allele, mainly heterozygotes, had higher systolic and diastolic blood pressures vs. workers with the bb genotype. Larger elevations in systolic blood pressure with increasing age and a higher prevalence of hypertension occurred in VDR genotype B allele compared to the VDR bb genotype. In contrast to VDR, ALAD genotype was not associated with the blood pressure measures and did not modify associations of the lead dose measures with any of the blood pressure measures. These data suggest that the common genetic polymorphism in the VDR is associated with blood pressure and hypertension risk The BsmI polymorphism might be in linkage disequilibrium with another functional variant at the VDR locus or with a nearby gene.

3.4. Pulmonary function studies

Health outcomes that may be associated with air pollution- or chemicals exposure may also be investigated within the noise - induced stress scheme. Variables for consideration include:

*3.4.1. **Susceptibiity***: Effects of air pollution on the lung function account for a few per cent of the deficit on average. Nevertheless, the effects can be cumulative over a 20-year growing period, and there is uncertainty over whether the chronic effects are reversible. Furthermore, even a small shift in average lung function can yield a substantial increase in the fraction of children with "abnormally" low lung function, that is, small changes in the population mean can reflect large changes in a susceptible subgroup of the population (WHO (2005).Air pollution in childhood reduces maximum functional capacity of the developing lungs, leading to enhanced susceptibility in adulthood to the effects of ageing and infection, to tobacco smoke and occupational exposure. Airway defence to inhaled oxidants are interacting systems. Lung function growth declines following exposure to elevated levels of air pollutants A number of host and genetic factors may contribute to the response of fetal and children's lung function to air pollutants. Asthma and other respiratory conditions are important determinants. A growing number of susceptibility genes have been identified as participants in the pathogenesis of persistent lung damage. Genotypes that result in a higher-intensity oxidative stress, inflammatory responses or altered tissue response to damage appear to be associated with increased susceptibility to respiratory effects from acute and chronic exposure to air pollution.

*3.4.2 .**Indoor and traffic-related air pollution***: Air exchange and ventilation, humidity, etc are playing a role in the concentration and fate of pollutants and chemicals indoors. Bodies of information related to release of organic gases and vapours, oxidation and reaction products indoors are needed. As people spend much more time indoors than outdoors, and indoor air may contain over 900 chemicals at concentrations higher than in the outdoor environment, all relevant sources that are known to contribute should be evaluated (SCHER, 2006), including tobacco smoke, any open fires including candles, building materials, furniture, pets and pests,

use of household products, as well as conditions that lead to the growth of moulds. Data on combined and mixture effects of indoor air pollutants are scarce. Methodology developments are needed.

Outdoor particles are measured by PM_{10} and $PM_{2.5}$ and until recently also as TSP, total particle mass per cubic metre). The relative contributions from different types of sources are site specific. There are a number of hypotheses available, linking the health effects, for example, to the mass, the number of particles inhaled, or to their surface area or to the mass of trace components they carry. A number of mechanisms of cardiopulmonary responses to particle inhalation and different particle properties could be causal of different health effects. Little is known on the health impact of ultra fine particles or the surface of particles.

Vehicle exhausts are considered to effect foetal development and affect respiratory and cardiovascular health in childhood and later life (Kaiser et al. (2004), Gilboa et al. (2005). Burr et al. (2004) applied repeated questionnaires in an area where the construction of a by-pass has occurred, leading to lower the road traffic. Rhinitis and rhino-conjunctivitis reduced and a great improvement was found for chest symptoms. WHO (2004a) quoted that PM increases the risk of respiratory death in infants under 1 year, affects the rate of lung function development, aggravates asthma and causes other respiratory symptoms such as cough and bronchitis in children. PM_{10} affects respiratory morbidity, as indicated by hospital admissions for respiratory illness. WHO (2004b) found sufficient evidence to assume a causal relationship between air pollution exposure (especially particulates, ozone and nitrogen dioxide) and aggravation of asthma in children, and a causal link between particulate exposure and cough and bronchitis.

Therefore, the inclusion of indicators of air pollutant concentrations, vehicle distance travelled per day per square km, number of vehicles, traffic density in local areas, personal exposure is appropriate. Humans are normally exposed to PM from several different sources. The PM-exposure for an individual is the concentration of particulate matter (PM) with specified characteristics that exists in a person's breathing zone over a specified period of time.

3.4.3. Activity patterns and physical activity: Time-activity patterns may also be involved in the effects of air pollution on lung function growth and development. Children who spend a significant amount of time outdoors in polluted environments or those with poor nutrition may be more strongly affected by air pollution. Children are especially vulnerable to the effects of poor air quality because their lungs, metabolic and immune systems are still developing. 821 schoolchildren were examined In Hong Kong. Children from high pollution areas had lower lung function, even those who undertook regular physical exercise, suggesting that exercise in a polluted environment may not be beneficial for lung function. Physical exercise was associated with greater lung function in children from low pollution areas (Yu et al., 2004). In communities with high ozone concentrations, the relative risk of developing asthma in children playing three or more sports was 3.3 compared with children playing no sports. Sports had no effect in areas of low ozone concentration.

Gauderman et al. (2004) followed 12 communities of southern California over 8 years to measure the lung function of children during the period of rapid development and examine possible adverse effect of exposure to air pollution. They measured the forced expiratory volume in one second, or FEV_1, and other parameters in 1759 children aged 10-18 years (average age of 10). Lung development was impaired where children had been exposed to NO_2, acid vapor, $PM_{2.5}$ and elemental carbon. For example, 7.9% of 18-year olds exposed to the highest levels of $PM_{2.5}$ observed had a low FEV_1, compared with only 1.6% of those

exposed to the lowest levels. A cohort of 3535 children with no history of asthma was recruited from schools in 12 communities in southern California and followed for up to 5 years (McConnell et al., 2002). Air pollution (ozone) and outdoor exercise was found to be an increased risk for new-onset asthma in children with no previous history of wheezing. Whereas sport exercise had no effect in areas with low ozone concentration, under high ozone concentrations, the relative risk of developing asthma in children playing 3 or more sports was 3.3 compared with children playing no sports. For Venn et al. (2001), testing 6147 primary school children aged 4-11 and 3709 secondary school children aged 11-16 in Nottingham in 1995-96, the risk of wheeze increased with proximity to the main road, particularly living within 90 m of a main road. Among primary school children, the effect of road traffic pollution on asthma was higher in girls compared to boys.

3.5. Chemicals and sensory processes

The number of chemicals that disrupt sensory processes, including the auditory system is not precisely known.. Crofton (1994) estimated that 44% of reported neurotoxic chemicals affect some aspects of sensory functioning and that the percentage of all known chemicals with neurotoxic effects range from 3% to 28%. From these admittedly crude estimates, one can presume that 1.5 % to 16% of all chemicals may be sensory toxicants (Crofton, 1994). Table 1 gathers the body of information on learning or behavioural effects of toxicants or physical impairments that lead to them. An additional source of vulnerability in fetuses and young children is that the blood–brain barrier is not fully developed, and therefore xenobiotics may be more easily able to enter the central nervous system (Rodier 1995).

Table 1. *Neuro - developmental toxicants effects on learning or behavior*. *From Schettler et al. (2000)*

	Inorganic	D, PCBs	Solvents				Pesticides			ETS
							OC	OP	PT	
Learning disabilities	Cd,Pb,Mn,Hg	D; PCBs	EtOH	Toluene		Xylene				ETS
Decreased IQ	Cd,Pb,F									
Decreased ability to draw familiar objects							MX			
Attention deficit	Pb,Mn,Hg	PCBs	EtOH							
Memory impairment	Mn, Hg	PCBs	EtOH 1			Xylene	MX			
Psychomotor dysfunction	Pb	PCBs								
Decreased coordination							MX			
Brain damage	Mn									
Motor dysfunction	Cd,Mn,Hg			Toluene		Xylene		OP		
Visual impairment	Hg									
Speech deficits				Toluene						
Behavioral disorders	Pb		EtOH					OP		
Hyperactivity	Cd,Pb,Mn,F	PCBs		Styrene	TCE		DDT	OP	PT	ETS
Increased exploratory behav					TCE					
Decreased activity				Styrene						
Decreased avoidanceBehav.¥				Styrene						
Hypoactivity	Cd									
Decreased stamina							MX			
Impulsivity	Pb									
Violence	PbT									
Aggression	Pb									
Compulsive behavior	Mn									
Eating & sleeping disorders			EtOH							
Developmental delays Cognitive function	Pb		EtOH					OP		ETS
Brain smaller size/weight	Hg		EtOH	Styrene		Xylene				
Cellular distortions in brain	Hg									
Mental retardation	Pb,Hg		EtOH							
Craniofacial,limb & cardiov. abnorm. #			EtOH							

Craniofacial abnormalities				Toluene						

Notes and abbreviations: ¥ : In conjunction with dietary protein deficiency; # : associated with various growth & developmental delays ;
D: Dioxins ; PCB : Polychlorinated Biphenyls ; OC; Organochlorines; OP: Organophosphates (including DFP, chlorpyrifos (Dursban), diazinon) ; PT: Pyrethroids (including bioallethrin, deltamethrin, cypermethrin) ; ETS Environmental Tobacco Smoke ;MX: Mixture; TCE Trichloroethylen; EtOH: Ethanol; Underlined Items: Studies on animals ; Learning disabilities include dysfunctions in listening, speaking, reading, writing, spelling or calculations

3.6. Deficits in learning performances: the example of reading acquisition

The risks of noise exposure to human development include disturbance in cognitive processes, attention and performance by school children. Non-auditory effects of noise may occur far below the levels responsible for auditory damage. Lead affects learning, behavior and threshold in children (Schwartz and Otto, 1987, 1991 even below 10 µ(mu)g/dl blood (Osman et al., 1999).. Variables of interest in studies of combined effects of noise and lead or other neurotoxicants include

3.6.1. Age-related competencies: Reading acquisition for example depends upon the development of certain language competencies (e.g., phonological awareness) that are age dependent (Mann and Brady, 1988; Evans and Maxwell, 1997). Noise- or chemical exposure prior to- , or following, the development of phonological awareness may not affect reading acquisition in an identical way than if exposure occurs during the critical period of phonological awareness learning. For example, effects of auditory distractors are contingent upon noise exposure history, with children exposed to ambient noise levels for longer periods of time being less resistant to the distracting properties of noise compared to shorter exposure (Cohen et al., 1981). This could result in an attempt to filter out noise in the first periods of exposure and a loss of motivation at the longer term. The ability to filter out aircraft noise versus white noise or irrelevant speech may be a function of duration and type of noise exposure

3.6.2. Noise exposure assessment: Studies on reading acquisition and noise refer mostly to qualitative or semi-quantitative evaluation of noise or to community values. At the contrary, Lukas et al. (1981) studied the math and reading performance of schoolchildren in relation with overall noise exposure (traffic and street noise, 75 dB(A) peak and ambient classroom noise, 45 - 75 dB(A)). Reading scores were lower in 3rd and 6th graders in noisier classes. Math scores were lower in pupils in noisier 3rd grade classes. Inverse correlations between community noise and math and reading scores were similar but less consistent than these between classroom noise and performance scores. There also was a synergistic effect of home and school noise exposure on reading. The period of exposure is critical for learning and whether cumulative adverse impacts in later childhood or adolescence may occur from longer need further investigation.

The RANCH (Road traffic and Aircraft Noise Exposure and Children's Cognition and Health) cross-national epidemiologic study confirmed the consistency of the exposure-effect relations between aircraft and reading comprehension. It examined this outcome in pooled data for children aged 9–10 years from schools around Amsterdam Schiphol, Madrid Barajas, and London Heathrow airports vs. noise exposure from aircraft and road traffic. Aircraft noise exposure at school was linearly associated with impaired reading comprehension and the association remained after adjustment for socioeconomic variables, aircraft noise annoyance and other cognitive abilities (episodic memory, working memory, and sustained attention). Aircraft noise exposure at home was highly correlated with aircraft noise exposure

at school and demonstrated a similar linear association with impaired reading comprehension. Road traffic noise exposure at school was not associated with reading comprehension in either the absence or the presence of aircraft noise (Clark, et al., 2005).

3.6.3. Stress, annoyance, blood pressure: The level of annoyance to children created by noise has been evaluated. Road-traffic noise has been associated with impaired concentration amongst schoolchildren and lower achievement levels, raised blood pressure and lower psychological well-being. Children are more vulnerable with regard to cognition and adults with regard to annoyance. Evans et al. (2001) and Lercher et al. (2002) studied 2 cross-sectional samples of 1280 and 123 Austrian primary school children aged 8-11. In the noisier areas the blood pressure was higher even when not under stress and children had elevated heart rate during reading tests. They scored themselves as having higher stress levels. Girls showed lower motivation levels but boys didn't.

3.6.4. Social factors: It seems useful to include social factors together with outdoor and indoor exposure to pollutants as well as noise in studies on possible combined effects, as socially excluded communities are hit by both higher air pollution and higher traffic- and school noise and poorer housing conditions. It is also possible that subgroups of children who grew up in impoverished physical and social circumstances are more vulnerable in various ways and potentially at higher risk for negative combined effects. The co-occurrence of noise with other adverse social factors and environmental exposure makes it difficult to isolate the effects of noise on children.

4. Considerations on chemical mixtures and noise in combination

Mixtures of chemicals occur in air, water and other environmental media and people are seldom exposed to single chemicals. Due to the time spent indoors, the mixtures encountered indoors play an important role in total exposure. Some species inhaled indoors are of outdoor origin, other come from materials, products and articles used indoors. Chemicals present in indoor air can react with one another, either in the gas phase or on surfaces. Both the concentrations of reactants and products are modified. Indoor environments include major source of free radicals and other short-lived reactive species (Weschler et al., 2006).

Consideration of interactions of chemicals in mixtures and their variation with time adds layers of complexity (Table 2, DVFA, 2003). Such an area may lead to further investigation of exposure standards as the majority of them are still for single compounds. Combined effects due to concomitant exposure to different chemicals through different routes may request a case-by-case approach. Interactions may also occur in toxicokinetics, with absorption, distribution, bio-transformation and with excretion.

Table 2. *Combined actions of Chemical Mixtures*

Interaction of compounds	Type of action of compounds	Type of association between effects
No interaction	Simple similar action (dose addition, Loewe additivity)	Positive correlation. Components differ only in their potencies. The correlation of tolerances is completely positive (r = +1) and each chemical contributes to the toxicity of the mixture in proportion to its dose
	Simple dissimilar action (Response or effect additivity, Bliss	• Positive correlation between effects of two chemicals: the individuals most susceptible to one toxicant are also most susceptible to the other. The proportion (P) of individuals

independence)		responding to the mixture is equal to the response to the most toxic compound in the mixture • Negative correlation: the individuals most susceptible to one toxicant are least susceptible to the other. This is the simplest form of response additivity. The proportion (P) of individuals responding to the mixture is equal to the sum of the responses to each of the components: • No correlation/Bliss independence: individuals responding to one constituent cannot react to the other as well: The proportion (P) of individuals responding to the mixture is equal to the sum of proportions of individuals responding to each of the toxicants
Interactions	Complex similar action; Complex dissimilar action	Synergism (and conversely, antagonism) is when the combined effect of two chemicals is greater (lower) than the sum of the effects of each chemical given alone. Potentiation is a form of synergism when the toxicity of a chemical on a certain tissue or organ system is enhanced when given together with another chemical that does not have toxic effects on the same tissue or organ system.

Most of the toxicological results published refer to single chemicals. The ability and validity of information from single chemicals for assessing risks from mixtures restrain to circumstances where substances act independently and the effect of each mixture component is not influenced by the presence of the others. Some authors (see e.g. Cassee et al., 1998 and other work of the Dutch group of researchers around V. Feron (Reference needed)) reported that interactions of concern start around the LOAEL and are unlikely to occur before the NOAEL, whereas concentrations of each single component below or approaching the individual NOAEL value were pointed in studies on mixtures of hormonally active chemicals or pesticides (Cavieres, 2002; Welshons, 2003). The independent approach is not applicable on a general basis and there is no general approach for assessing risks of chemical mixtures.

Risks of a mixture can be tested by considering it as a whole. Such a strategy has been applied in the case of simple, defined chemical mixtures where the toxicological properties of the individual components are also investigated (Mumtaz et al. 1993). .Dose-response curves obtained in correspondent range of concentrations are necessary to address the possibility of combined actions and/or interactions between the individual components of the mixture.

A non interactive process is this of simple similar (joint) action (dose addition) where each component differs only in its potency (expressed as the percentage of the dose of that chemical alone that would be required to obtain the given effect of the mixture) but acts on the same biological site, by the same mechanism of action.

 "Toxic equivalency factors" (TEFs) describe for example the combined toxicity of isomers or structural analogues as species of the same toxic agent, and their relative potencies are assumed to be constant throughout all dose levels, on the implication that no threshold exists for dose additivity, a linear dose response curve occurs. Differences in toxicokinetics can be ignored due to the derivation of TEFs often from short-term in vitro experiments. The approach has been used to organochlorine compounds such as 'dioxins' and mixtures of PCBs, interacting with the Ah-receptor as the reference compound 2,3,7,8-TCDD (van den Berg et al., 1998). Coplanar PCBs, however, are not Ah-receptor-mediated (Seed et al., 1995).

Risks of groups of organo-phosphorous pesticides have been considered with the Relative Potency Factor approach in the framework of the Food Quality Protection Act, for chemicals inhibiting AchE (USEPA, 2001b). RPF is of similar nature as the TEF, the mixture is treated as a single chemical and the relative contributions of components are calculated with

reference to the inhibition power of chorophos (used as the 'index' chemical) and summed. However, beyond similarities in pesticides mechanism of action, interactions occur in vivo and the sequence exposure to chlorpyrifos and other organophosphorous pesticides could markedly impact the toxicity, due to the depletion of esterases involved in detoxification reaction (Karanth et al., 2001, 2004).

Another approach is the Hazard Index (HI) approach, related to the reference dose (RfD). As RfD is derived by using NOAELs and uncertainty factors, summing ratios between the exposure level and the RfD of each component present limitations. Revised modes of HI derivation include the introduction of a numerical factor (weight of evidence, WoE) or e, when separate hazard indexes can be estimated for all endpoints of concern, the use of the target-organ toxicity dose (TTD) method, incorporating interaction data (US EPA, 2001a; ATSDR, 2004).

A point of departure (POD) is traditionally a NOAEL or a point in the dose-response curve at which a change in response can be reliably said to be due to dosing with the chemical. It can be a point estimate on the index chemical's dose-response curve that is used to depart from the observed range of empirical response (or incidence) data for extrapolating risk to the exposure anticipated in the human population, to derive a benchmark dose (BMD) that estimates a pre-specified level of response. The benchmark response (BMR) quantifies that level of response (US.EPA, 2002). Wilkinson et al. (2000) considered the point of departure (POD) based on doses causing a particular biological response (ED_{10}, ED_{20}) in preference over the NOAEL.

The MOE approach is the ratio of the POD (e.g. NOAEL, ED_{10}) to the level of exposure. It is often used to determine the acceptability of acute risks for single chemicals and MOEs of >100 or >10 are usually considered acceptable when derived from toxicological data from animal or human studies, respectively. The US EPA favours this concept for performing aggregate and cumulative risk assessments (Whalan and Pettigrew, 1997). The combined MOE is the reciprocal of the MOEs of each compound in the mixture. The Cumulative risk index (CRI) or aggregate risk index (ARI) has been developed by Whalan and Pettigrew 1997) to combine the MOEs for chemicals with different uncertainty factors The risk index (RI) of a chemical is the MOE divided by the uncertainty factor or simply the reference dose divided by exposure and is the reciprocal of the hazard quotient (HQ). The POD fractions (PODF) are reciprocals of the individualMOEs of each compound. This approach sums the exposures to the compounds in terms of their relative potencies.

Non interactive processes also include simple dissimilar action. In these cases, the modes of action of the constituents in the mixture will always differ and possibly, but not necessarily, the nature and site of action among the constituents as well. Rather than the average effect of a mixture on a group of individuals, the sum of the responses of the subjects to each toxic chemical in the mixture is recorded and the correlation of susceptibility of individuals to the toxic agents are taken into account.

In assessing occupational hazard, for mixtures of two or more hazardous substances that act on the same organ system, the ratio of the exposure concentration to the threshold limit value (TLV) for each component was summed (ACGIH, 2000). If independency of the chief effects is expected and a hazard quotient exceeds unity, the hazard index for the mixture would be the highest hazard quotient of that component, as in the case of response addition with completely positive correlation. ACGIH stated that synergism or potentiation should be evaluated on a case by case basis as such interactions are characteristically exhibited at high concentrations and are less likely at low. In the case when a process emits a number of harmful dusts, fumes, vapors, or gases, ACGIH states that frequently it may be feasible only

to measure a single substance in order to evaluate the hazard. In this circumstance, the threshold limit for this substance should be reduced by a suitable factor, the magnitude of which takes into account the number, toxicity, and relative amounts of the other components typically present. This appears to be a combination indicator chemical/uncertainty factor approach.

The magnitude or the type of toxic effect may be altered as a result from chemicals interaction, with either weaker (antagonistic) or stronger (synergistic) combined effects compared to assessment based on individual compound and their modes of action. Compounds such as these identified as co-mutagens or co-carcinogens may result in potentiation, i.e. the toxicity of a chemical on a certain tissue or organ system is enhanced when given together with another that does not affect the same target.

5. Which approaches are available to study combined exposures?

5.1. Examples of interactions and implications for hearing protection standards

Long-term occupational exposure to toluene often includes exposure to other solvents with effects on memory and concentration deficits and disturbance of emotional and psychomotor functions. Other interactions occur. For example, toluene-induced loss of auditory sensitivity was shown permanently potentiated by simultaneous exposure to acetylsalicylic acid. (Johnson, 1990).

Morata et al. (1993) explored the effects of occupational exposure to noise, to noise and toluene, or the case of an organic solvent mixture on hearing in rotogravure printing and paint manufacturing workers. The risk of hearing loss was greater for the exposed groups than for the unexposed group. Audiometric testing revealed a relative risk for high-frequency hearing loss 4 times greater for the noise-exposed group, 5 times greater for the solvent-mixture group, 11 times greater for the noise and toluene group. The findings suggest that exposure to the studied solvents had a toxic effect on the auditory system and that an interaction between noise and toluene took place.

Morata et al. (1997) explored the effects on the hearing of rotogravure printing Brazilian workers of occupational exposure to noise and to an organic solvent mixture of toluene, ethyl acetate, and ethanol. The findings also suggest that exposure to toluene has a toxic effect on the auditory system. Chang et al. (2006). observed a much greater prevalence of hearing loss of ≥25 dB in the toluene plus noise group (86.2%) in workers at an adhesive materials manufacturing plan than that in the noise-only group (44.8%) and in the administrative clerks (5.0%). The prevalence rates were 67.2, 32.8, and 8.3%, respectively, when 0.5 kHz was excluded from the estimation. Multivariate logistic regression analysis showed that the toluene plus noise group had an estimated risk for hearing loss ≥25 dB, 10.9 times higher than that of the noise–only group. The risk ratio dropped to 5.8 when 0.5 kHz was excluded from the risk estimation. Hearing impairment was greater for the pure-tone frequency of 1 kHz than for that of 2 kHz. However, the mean hearing threshold was the poorest for 6 kHz, and the least effect was observed for 2 kHz. These results suggest that toluene exacerbates hearing loss in a noisy environment, with the main impact on the lower frequencies. Such data questioned the possibility of a synergism, of an interactive-additive type of potentiation between noise and solvent exposures. This has implications for hearing protection standards.

Since noise is so prevalent in almost every industry, in earlier studies, the hearing loss often blamed on the noise and not on other factors. Unless the nature of exposure was known effects of chemicals versus noise from animals studies, both audiometrically and even at the cellular level, appeared very much the same. Pure-tone audiometry, the test commonly used for occupational studies could not distinguish between noise-induced hearing loss and other sources of hearing loss (Dunn and Morata, in Lang, 1994). These authors suggested that adequate protection of workers from hearing loss might need to be looked beyond the sole responsibility of noise. There was no indication how to make a guideline or propose a guideline for safe exposures to the combination of chemicals and noise at the same time. Some studies showed that a combination of noise and solvents have an effect on hearing even at low threshold exposures, Dunn stated. "We really won't be able to say that if we are below the level considered safe for the chemical or below the level considered safe for the noise, then the combination will be considered safe" (Lang, 1994).

Schwela et al. (2005) further insisted that most studies of health impacts of physical and chemical agents in the environment considered the health effect as being solely due to the air pollutant(s) under investigation, for example, air pollution without due regard for the simultaneous presence of noise pollution whereas both have an impact on the cardiovascular system; or noise without investigating the contribution of solvent, asphyxiant or metal exposures whereas they can have an impact on hearing impairment. The stringency of the available evidence of epidemiological studies in both fields can be questioned. This warrants the consideration of air pollutants and chemicals as confounding or aggravating factors in studies of specific effects due to noise (and vice versa). The influence of other factors, which can confound noise studies but are currently not included in the analysis also need to be weighted with the existing evidence on the association of noise and air pollutant exposure and associated health impacts .

5.2. Integrated Environment and Health approach and policy issues

Consumers are exposed to numerous substances through various routes indoors/outdoors. Recognition that integrated strategies are necessary to handle environment and health issues is recent in European policy and Action Plans (EEA, 2003a). The generation of data compatible with the concept of integrated monitoring beyond the collation of data, needs to ensure their types and modes adequately address the link between environmental indicators, exposures, biomarkers, and effects. Combined, complex, exposure occurs to a series of contaminants. The sources and routes are multiple. The level of exposure and its duration and its occurrence and "windows of vulnerability" need concomitant attention for improving the theoretical basis of the strategy towards a high level of protection vs. combined risks. Working papers of the European Environment Agency as well as baseline reports of the SCALE initiative (see e.g. SCALE-TWG HM, 2004) underlined that exposure is a key component. A number of parameters are interrelated. The rational approach shall assess relevant factors for each toxicant/stressor and exposure from all pathways in order to avoid misclassification in exposure classes.

The level of protection to children of existing regulation on lead was shown insufficient when questioned within such an integrated approach. The need to further reduce the maximal admissible concentrations of the toxicant in several media beyond existing limits was demonstrated (Steenhout, 1987, 1987b, 2001).

IPCS (2000) highlighted exposure in the context of an environmental health paradigm. Exposure is a necessary component in a sequence of events having potential health consequences. The release of an agent into the environment, its ensuing transport, transformation and fate in various environmental media and its ultimate contact with people are critical events in understanding how and why exposures occur. EEA (2003c) stressed that if the objective is to improve our knowledge of causal links between environmental factors and health, it is not sufficient to just monitor environmental factors (emissions, concentrations etc.) and health (morbidity, mortality, well-being), even if that is well-coordinated. Central in this context is exposure. The environment can influence genes, and genes can influence lifestyle choices, which, in turn, affect both the host state and the stressors that it receives. EEA (2003b) addressed these issues at the interface between assessment and policy-making, Multi-causality scheme provides many obstacles to understanding the mechanisms and factors in the causal chain but it also provides many opportunities for removing links in the chain and thereby preventing harm, particularly where there are inter-dependencies between causal factors.

5.3. Accounting for all pathways and sources of exposure to stressor(s)

Human behaviour varies greatly among populations. Exposure involving one or more routes occurs via a variety of activities such as work, leisure and sports activities indoors and outdoors, consumption of drinking water, food and consumer products. Sensitivity may be higher in children, pregnant women, the elderly, and vary with health/disease status, race, and gender. The assessment of consumer exposure involves descriptors of lifestyles and living conditions, taking account vulnerable groups. The complex, aggregated, exposure in the daily life in a chemical requires time-consuming enumeration and quantification of many factors often beyond current indicators. Data gaps for certain types or levels of information and the lack of harmonization of "exposure language" and metrics occur. A holistic approach can address issues such as the origins of variations, the understanding of which having important consequences in establishing standard, quality measurements methods and sampling strategies.

Exposure may occur to ambient pollution, to household contaminants and indoor chemicals with relation to a number of activities, consumption and product uses, time spent indoors by children, either at home or at day care, school, etc. Children have specific activity patterns. The breathing zone for a child is close to the floor. Gases of higher densities than air may occur at their breathing level. Droplets from sprayed products may reach the floor before total evaporation and increase the concentrations to which children are exposed to. Air circulation indoors may also result in more dust deposited on ground or furniture surface. Owing to hand-to-mouth or pica behaviour in young children, and frequent contact with soil and indoor surfaces, higher re-ingestion may occur of dust particles adhering on wet fingers, and the ingestion of house dust may significantly raise total exposure to toxicants. Lifestyle, behaviour, time-activity patterns, physical activity, nutritional or health statuses and other determinants of exposure prior to the absorption of chemicals are of importance to exposure assessment and may vary, according to age, gender, socioeconomic and occupancy status, housing and social characteristics, time, etc. Scenarios of exposure have to be taken into account in exposure estimates to assess whether some or the aggregation of risk factors may lead to higher exposure to chemicals in certain groups of population such as children, the elderly, etc. or in various European regions (Steenhout, 2005, 2005b).

Determinants of exposure may be especially of importance in assessing combined exposure to several stressors. An increasing number of exposure models are being built and need validation tests.

5.4. More factors of variation and windows of vulnerability

Some evidence suggests relation between low birth weight in babies, psychiatric disorders and noise (Medical Research Council, 1997). Children have more years of life ahead than adults and may develop diseases with long latency periods that may be triggered by early environmental exposure.

Due to differences in absorption, distribution, metabolism and excretion, the way xenobiotics are handled and the response may differ significantly between adults and infants (US.EPA, 2001) or children Tamburlini (2002). There is also evidence that sensitivity to chemicals differs in adults and in infants with relation to the immature metabolic capabilities of infants up to 6-12 months of age and to some extent, in children, leading to a longer period with higher blood levels for many compounds. The influence of polymorphism in population variability in susceptibility to environmental contaminants receives increasing attention. (Scheuplein et al., 2002). The human being might also face novel compounds for which it simply might not possess the enzymes to metabolize them (WHO and EEA, 2002) Possible detoxification mechanisms and the relative reactivity of the metabolic intermediates and end-products need also to be accounted for.

Respiratory volume is twice per unit of body weight in the resting infant compared to adult. The development of various organs may have different rates and the effective target dose of the substance may vary with growth (Steenhout, 1987; 1990_91; NAS, 1993). Pulmonary absorption of chemicals may also be affected by postnatal structural lung development and changes of membrane properties with children age. Age-related changes in the extent and rate of oral or dermal absorption may also alter the internal dose of a chemical when this route is involved. Additional uptake may result from other routes and conditions.

Physiologic change occurs in the respiratory function during pregnancy. Pulmonary tidal volume increases by about 40%, from about 500mL to 700 mL, and minute ventilation from about 7.5 to 10.5 L/min. These features are likely to raise the rate of absorption of volatile agents and gases (Lehmann and Fabel (1973), quoted in Scialli and Lione, 1998).

Xenobiotics may be more easily able to enter the young central nervous system as the blood–brain barrier is not fully developed (Rodier 1995).

Physicochemical properties of compounds affect their distribution within the body. Distribution of reported bioavailability factors may be affected by a variety of factors, including analytical methods, types of vehicle and chemical forms and other difference in experimental designs, exposure duration and frequency, species, age, gender, health, nutritional and smoking status, genetic disease (Hrudey et al., 1996). Information of bioavailability of xenobiotics in infants and children is available for some substances and routes but rather scarce for most chemicals.

Hepatic xenobiotic metabolism can be modulated by many factors (Kitani, 1988;; Schmucker et al., 1990). Depending on the chemical, aging can result in either an increase or a decrease in the metabolizing capacity of different organs and tissues (liver, kidney, gastrointestinal tract, lungs and skin). The elevation or reduction in metabolism can both lead to higher and lower toxicity, depending on the relative reactivity of the metabolic intermediates and end-products. Thus, studies on the effect of ageing on metabolism should be considered case by

case (ICPS, 1993). Decreases in gastric motility in older rats (Lin & Hayton, 1983) can prolong the transit time of chemicals in the gut, thus enhancing their potential for absorption. Age-related alterations in GI absorption and a decrease in gastric acid secretion are commonly seen in the elderly (Bender, 1968). The resulting increase in pH can alter the ionization of compounds, enhancing or retarding their ability to diffuse passively across cellular membranes. Maturation of enzyme activity occurs during the first 2 years of age. Higher gastric pH and intestinal motility vs. adults affects the absorption of drugs and chemicals. The increased gastric emptying time and the decreases intestinal motility during pregnancy may also raise the absorption of xenobiotics owing to longer retention of chemicals in the GI tract (Klaassen, 1996).

As lipophilic molecules readily pass across cellular membranes and accumulate in lipid-rich tissues, changes in body composition such as an increased size of the fat compartment in older, sedentary animals would be expected to increase the body burden of lipid-soluble substances and reduce the overall rate of elimination from older animals (IPCS, 1993). Since adipose tissue volume increases but blood flow decreases with age, lipophilic compounds tend to show greater retention in the elderly. This has been shown for polychlorinated biphenyls in rats (Birnbaum, 1983) and halogenated solvents in rats and mice (Schumann et al., 1982a,b). Changes in blood concentrations of lipids, free fatty acids, hormones and total body water content with pregnancy may also influence the distribution of chemicals in the body.

A decrease in binding of drugs to red blood cells has also been reported to occur during aging (Chan et al., 1975), again leading to a higher level of free drug. The changes in the physiology of the kidney in ageing have been known for many years (Schmucker, 1979, in ICPS,1993). A slower or a more rapid clearance in children vs. adults is reported by Renwick (1998) and Renwick et al. (2000).Decreases in renal function can result in a decreased rate of renal clearance, leading to a greater potential for elevated and/or persistent levels of chemicals in the body which could lead to toxicity. Decreased renal clearance in the elderly has been demonstrated for many drugs, including the aminoglycosides, tetracyclines, lithium, digoxin, procainamide, methotrexate, and phenobarbital (Kampmann & Hansen, 1979, in ICPS,1993). Although the total plasma protein content does not change dramatically with age, there is a small but significant reduction in albumin in both animals (Rodgers & Gass, 1983) and humans (Bender et al., 1975). For drugs or xenobiotics that can be bound, such a decrease in albumin enables a higher concentration of free drugs or xenobiotic to reach the target site. Reduction of plasma albumin concentration by about two thirds during pregnancy may increase the risk for transfer via the placenta. The renal blood flow and glomerular filtration rate are increased during pregnancy, which may result in enhanced renal clearance of certain xenobiotics.

5.5. Accounting for time-sequenced exposure to chemical(s) and/or to noise: examples (solvents, lead)

Rats were exposed to toluene, or noise, or toluene followed by noise. A high-frequency auditory impairment was observed after exposure to toluene alone and noise alone. Toluene followed by noise resulted in a higher threshold at all frequencies. The threshold shift exceeded the summated loss caused by toluene alone and by noise alone, particularly at 3.15 and 6.3 kHz (Johnson et al., 1988). With the reverse sequence - noise followed by toluene exposure (Johnson et al., 1990) - the sensitivity loss was greater than that after exposure to noise alone or toluene alone, but did not exceed the summated loss caused by noise alone and toluene alone at any frequency. These results suggest an additive effect when noise exposure

preceeded and a potentiation when toluene exposure sequence preceeded noise exposure. Lataye and Campo (1997) concluded that the nature of the cochlear damage induced by noise alone (injured stereocilia) or by toluene alone (outer hair cells loss) is different. In another study, a predominantly noncochlear site of damage, perhaps with central auditory pathway (brainstem) involvement is suggested in both to noise and toluene (Morata et al., 1993).

Physiologically Based Pharmacokinetic/Pharmacodynamic (PBPK/PD) modelling can be used for the assessment of joint action of chemical mixtures (Haddad et al., 2000; ATSDR, 2004; De Rosa et al., 2004) and may be very useful for the evaluation of metabolic interactions. Interactions may take place in the toxicokinetic phase and/or in the toxicodynamic phase. Transfer rates of lead from blood to tissues were shown higher in young children compared to older children and adults in a large range of exposure. The amounts of lead circulating in the body were quantitatively explained as combined functions of exposure and kinetics. The times needed to reach critical levels of lead have been assessed for various scenarios of constant, variable or peak exposure. This holistic approach seems interesting to pinpoint windows of vulnerability and the emergence of effects (Steenhout (1991; 1990_91; 1992) and covers combined metals exposure (Steenhout, 1992_94).

The use of indicators with reference to human quantitative toxicokinetic and toxicodynamic data and the understanding of occurrence and extent of physiological variations are important for avoiding bias, for example in the classification of the subjects in exposure categories.

5.6. Epidemiological approaches and priority issues for future research and policy making

The interest of using epidemiological data in the health impact assessment relates to the advantage of epidemiological measures to approximate the required information under "true life condition" of human beings and contributes to limit the use of uncertainty factors. Epidemiology studies the relations between characteristics of groups of population or their environment, and health or disease states. The reasoning and the level of statistical significance of such association give insight into causes which may apply to other populations. Assessing the effect of a single parameter at the time would be ideally simple but parameters may not occur in isolation. Demonstrating that an association occurs and does not reflect chance relies on study design and the ability to avoid selection or measurement biases and to adequately account for confounding factors.

It seems essential to gather data on the emergence of various effects in the growing child and detailed exposure assessment, not only for protecting children, but also for better understanding possible latencies in disease in adulthood.

Especially in the case of combination of agents, the larger number of parameters as well as confounders involved may preclude a proper assessment or the identification of effects itself. There may be events of exposure to single agents or simultaneous exposure to several, and the occurrence or intensity of effects might be different according to previous exposure and at which age or development stages exposure to a variety of stressors has occurred. As some chemicals may not exert effects during pregnancy, but may do so during other, later, vulnerable periods, it seems useful that predictive testing approaches examine perinatal and postnatal exposure in addition to prenatal exposure. How the target stressor will be handled at certain developmental stages need to be delineated. Even cohorts may miss the critical window of interest.

The data available for many pollutants are yet limited to perform risk assessment. Research on effects of long-term exposure to air pollutants or to chemicals in daily activities or in the working environment and on the possible latency in developing disease needs to be developed. Validated biomarkers are needed to establish the dose-response relationships. The contributions of single agents or factors embedded in the complex combinations occurring in real situations remain difficult to establish. Difficulties may be encountered for performing exposure estimates for multiple sources and pathways, for each component of a mixture and for noise. The need exists for indices of fine and ultrafine particles, for examination of the comparative effects of aerosols of different composition and further time-series studies designed to look at associations between PM and effects, for example on the cardiovascular system..

It is also difficult to take into account the multiplicity of chemicals present together in the composition of products and articles. Some combined exposures leading to concern may be neglected. Effects that are common across various stressors, such as cardiovascular or neurological effects, may be considered for combined studies, with adequate examination of confounding variables and noise. Few data are available on interactions among more than two chemicals and they usually do not address issues of chronic toxicity at concentrations representative of actual human exposure.

Many data gaps and uncertainty remain, indicating the need of strengthening the basis of integrated approach and a step by step building. Priority can be given to study effects of combinations of known compounds for which bodies of information are already available, such as metals or solvents and include studies of possible synergic or antagonist effects and crossed effects with noise.

A list of recommendations for the evaluation and use of environmental epidemiology studies for health risk assessment set by WHO (2000) set and how they are met by an existing epidemiological and risk assessment approach (Steenhout, 1987) is provided in Table 3. Such recommendations can be extended to cover combined exposure to noise and air pollutants and chemicals in future studies.

Table 3. *Ten recommendations from WHO (2000)'s evaluation and use of epidemiological evidence for environmental health risk assessment and how there are met by an existing integrated approach (Steenhout, 1987 and more developments beyond).*

WHO's recommendations	*Brief overview of an existing integrated approach validated in the case of lead and other metals, with principles applicable to other types of combined exposure.*
Specify the purpose and framework of the impact assessment	Purpose is to improve causal analysis, using emidemiology, field measurement and modeling and to provide help decision tools in support to policy preparation or evaluation, addressing risk assessment and risk management
Specify the method to deal with uncertainty	The approach builds frameworks and links to direct epidemiological studies and quantifies uncertainty
Specify exposure	All exposure sources investigated and quantified.
Specify the range of exposure to be considered	No limit in the level or sequences of exposure examined
Derive the population exposure distribution	Done for each source and pathway

Specify the time window between exposure and effect	Allows to assess the times to reach various indicators levels. Critical times and time windows are a result
Select appropriate health outcome(s)	The connections that are made between various levels of analysis allow flexible selection of the outcome(s) and analysis of critical factors
Specify the exposure-response relationship	It distinguishes toxicokinetics and toxicodynamics Identifies vulnerable groups. Can also establish links between dose and biomarkers values
The exposure-response function is, in fact, the key contribution of epidemiological studies to Health Impact Assessment. The function may be reported as the slope of a regression line, as a relative risk measure for a given change in exposure or comparing "exposed" with "unexposed". Due to the many sources of uncertainty in observational science, different epidemiological studies may lead to different exposure-response functions. Thus, for the Health Impact Assessment, the process used to derive an exposure-response function (or functions) must be defined. The following issues have to be considered:	Slopes provided. Total exposure or contribution from various sources quantified, comparison "exposed/unexposed" made as well. Validation exercises successful on other data sets, indicating possible use of the included predictive tool for assessing efficiency of risk management measures
Obtain information on reliable exposure-response relationships for every selected health outcome. The hazard identification process normally will provide an inventory of the relevant studies that are considered of acceptable quality. All studies with quantitative information on exposure or which allow linkage to such information should be considered for the exposure-response evaluation	It provides quantitative information on exposure and exposure-response relations. The approach quantitatively links exposure, the effective dose and health effects in an integrated way and the contributions linked to physiological components are distinguished from these resulting from pathways and sources (including indoor air).
The process of combining studies for deriving an overall exposure-response relationship may be based on formal meta-analytic methods, pooled analyses, or on expert judgment. Published meta-analyses may also be useful, provided they are based on studies that are considered to be eligible for Health Impact Assessment purposes. Measures of uncertainty around central point estimates should be derived and information on heterogeneity between studies (for example from published meta-analyses) should be considered.	It addresses heterogeneity between studies , provides eligibility criteria and an analysis framework It simultaneously improves both the specificity and sensitivity (avoid types I and II errors)
The studies selected during hazard identification may need to undergo an additional selection process and may have to be weighted for the purpose of evaluating the exposure-response relationship for Health Impact Assessment, on the basis of the following aspects: (a) The quality of exposure measurement needs to be considered..	Quality of exposure measurements is investigated Harmonization issues and sampling strategies are addressed.
(b) Studies based on the same exposure metric as that used in the population for which the impact assessment is required will have highest priority; studies based on different metric, but for which it is possible to convert results to the selected metric, will be given less weight	Metric issues are accounted for. Metric-related uncertainty also quantified within the framework.
(c) Studies will also be evaluated on the basis of whether or not the estimated risks might apply to the population for which the Health Impact Assessment is being conducted (i.e. generalization from one to another population). E.g. information on the possible presence of effect modifiers, such as local socioeconomic factors, or the importance of susceptible subgroups, such as asthmatics, that may drive	Quantification of the contribution of parameters of variation and modifiers. The presence of susceptible subgroups is underlined. Socio-economical factors and series of possible confounders also considered with reference to precaution and sustainable development.

the observed effects is valuable and should be taken into account. It is possible that the body of evidence will provide an estimated exposure-response relationship for a medium range of exposure levels, while Health Impact Assessment is required for a population mainly exposed to much lower or much higher levels. Projecting exposure-response relationships beyond the range of exposure observed in the underlying studies normally involves uncertain extrapolations. The arguments for and the limitations or potential impacts of extrapolations ought to be carefully addressed in the Health Impact Assessment. Knowledge of the biological mechanisms underlying the specified effect may support the decision to extrapolate. In any case, allowance for additional uncertainty should be made.	The framework allows to examine Bradford Hill criteria and checks for consistency, underlines the origins of the discrepancies observed in epidemiological studies, etc Approach tends also to identify groups at most risks. Plausible biological explanation provided for the higher vulnerability of children. Limitations or potential impacts of extrapolations also addressed within the framework. Framework flexible for introduction of additional variables in the analysis.
The shape of the exposure-response function should be specifically evaluated in all available studies. Particularly, the possible existence of threshold levels ("no effect level") may be very important for the Health Impact Assessment.	Shape of exposure functions and origins of the discrepancies observed in epidemiological studies addressed within the framework.
Derive population baseline frequency measures for the health outcomes under consideration. Calculate the number of attributable cases	Population baseline frequency measures obtained for all parameters under consideration. Frequency estimates of population with various characteristics and exposure and the % at risk of excessive exposure. Health outcomes examination possible within the framework.

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APPENDIX 1

Agenda for International Workshop on
"*Combined Environmental Exposure: Noise, Air Pollutants and Chemicals*"
15-16 January 2007, Joint Research Centre, Ispra (Italy).

Final Agenda

Monday, 15 January 2007		
08.30-09.00	Registration	
09.00-09.45	Welcome and introduction to JRC/IHCP/PCE activities	*D. Kotzias*, JRC-PCE Unit Head
09.45-10.00	Main findings of FP5 and FP6 projects for air quality health effects and plans for FP7	*T. Karjalainen*, TG RTD (presented by *S. Kephalopoulos*)
10.00-10.10	Introduction to the Workshop	D. Schwela, University of York (UK)
10.10-10.15	Introduction of participants	
10.15-10.30	Preliminary Findings of WHO Study of Environmental Burden of Disease from Noise: Are We Seeing Combined Effects?	*R. Kim*, WHO (Germany)
10.30-10.45	Assessment Possibilities and Data Availability	*A. Bäckman,* European Environmental Agency (Denmark)
10.45-11.00	Coffee Break	
11.00-11.45	Cardiovascular Noise & Outdoor Air Pollutants (particulate matter, sulphur dioxide, nitrogen dioxide, carbon monoxide)	*L. Jarup*, Imperial College (UK)
11.45-12.30	Cardiovascular Effects of Road Traffic Noise with Adjustment for Air Pollution	*F. Pierik*, TNO (The Netherlands)
13.00-14.00	Lunch Break	
14.00-14.30	Mechanisms Controlling the Interaction between Noise and Particles	*C. Maschke*, FBB-Maschke (Germany)
14.30-15.00	Noise and Indoor Air Pollution: Combined Exposure and Interaction	*M. Jantunen,* KTL (Finland)
15.00-16.00	Organic Solvent Ototoxicity – Human Literature Overview	*M. Sliwinska-Kowalska,* NOFER (Poland)
16.00-16.15	Coffee Break	
16.15-16.45	Promotion of Noise-induced Hearing Los by "Pro-oxidant" Chemicals	*B. Pouyatos*, Loma Linda Va Medical Centre (USA)
16.45-17.15	The Interaction of Noise and Pesticides on Human Hearing and Balance	*R. Keith,* University of Cincinnati (USA)
17.15-17.45	Consumer Heavy Metals and Noise Exposure: Health Effects	*D. Prasher,* University College (UK)
17.45-18.15	Combined effects of Noise and Biological Agents	*A. Nevalainen,* KTL (Finland)
18.15-18.45	Noise and Vibrations and other Interactions with the Environment	*P. Lercher,* Innsbruck University (Austria)
18.45	Transport to hotel	

20.00-22.00	Dinner	Ristorante "Nettare di Giuggiole", Angera

Tuesday, 16 January 2007		
09.00-09.30	Review: Epidemiological Methods and Risk Assessment Models of Combined Effects: An Approach to Complexity	*A. Steenhout, Bruxelles University (Belgium)*
09.30-09.40	Definition of Workgroups A and B	
09.40-10.30	Working in workgroups	
10.30-10.45	Coffee Break	
10.45-13.00	Working in workgroups	
13.00-14.00	Lunch	
14.00-15.00	Working in workgroups	
15.00-16.00	Report of WG A & Discussion	
16.00-17.00	Report of WG B & Discussion	
17.00-17.30	Way forward and adjourn	

APPENDIX 2

List of Participants of the International Workshop on
"*Combined Environmental Exposure: Noise, Air Pollutants and Chemicals*"
15-16 January 2007, Joint Research Centre, Ispra (Italy).

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APPENDIX 3

Questions answered by the two Working Groups A and B

Group A

1. Which health endpoints are affected by:

- *noise and indoor air pollutants (environmental tobacco smoke)?*
- *noise and outdoor air pollutants (particulate matter, sulphur dioxide, nitrogen dioxide, carbon monoxide)?*
- *noise and asphyxiants (carbon monoxide, hydrogen cyanide)?*
- *noise and solvents (occupational, environmental)?*
- *noise and heavy metals (lead, mercury)?*
- *noise and pesticides?*
- *noise and variables related to housing (biological agents)?*
- *Noise and vibrations?*

2. Which confounding variables have to be considered in epidemiological studies of noise-induced health effects in the presence of air pollutants and other chemicals in the air?

3. What are the data gaps to be covered?

4. Which are the priority issues to be considered for future research and policy-making?

Group B

1. Which combined exposures occur, where they occur, which are the risks of the different pairs of combined exposures in occupational or non-occupational environments between:

- *noise and indoor air pollutants (environmental tobacco smoke)?*
- *noise and outdoor air pollutants (particulate matter, sulphur dioxide, nitrogen dioxide, carbon monoxide)?*
- *noise and asphyxiants (carbon monoxide, hydrogen cyanide)?*
- *noise and solvents (occupational, environmental)?*
- *noise and heavy metals (lead, mercury)?*
- *noise and pesticides?*
- *noise and variables related to housing (biological agents)?*
- *Noise and vibrations?*

2. Which approaches are available to study combined exposures and which combinations should be recommended in either/both environmental and occupational environments?

3. Which are the priority issues to be considered for future research and policy-making?

APPENDIX 4

**Outcome of Group A in the International Workshop on
"Combined Environmental Exposure: Noise, Air Pollutants and Chemicals"
15-16 January 2007, Joint Research Centre, Ispra (Italy).**

Proceedings of the International Workshop on "*Combined Environmental Exposure: Noise, Air Pollutants and Chemicals*", 15-16 January 2007, Ispra (Italy)

The first column on the left presents the health effects of noise ('*auditory*', '*non-auditory*' and '*cognitive effects*'). Such health effects that are not outcomes of noise exposure alone, but occur only together with other stressors are listed at the end of the first column (i.e, '*combined effect outcomes*'). The second column summarises the subpopulations (adults (*A*) and/or children (*C*)) that are affected by that specific health effect. In the case of non-auditory effects, it also presents if they occur only when one is sleeping (*Sleep*) or in both cases when being awake and when sleeping (*+Sleep*). The next eight columns describe the level of current knowledge of the combined effects of exposure to noise and the specific stressor in that column. The level of the current knowledge is categorized as follows: *P= possible, D= some data available* and *G= data gap*. Finally, a prioritisation was given for research and policy needs for the combined effects of noise with each stressor (see numbers between 1 and 5, 1 having the highest priority and 5 having the lowest).

Exposure to noise and… {P=possible, D=data (A=animal, H=human), G=gap, A=adults, C=children}		indoor air pollutants ETS, CO	outdoor air pollutants PM, CO, SO₂, O₃, NOx	asphyxiants CO, HCN	solvents Mix, Tol, Sty, Xyl	heavy metals Pb, Hg, Cd, As	pesticides OP, OC	indoor biological agents MOULD, ENDOTOXIN, MITES	vibrations
Health effect	Research priority	5	1	5	2	3	2	3	4
	Policy priority (X), not enough knowledge (?)	?	?	?	X	?	?	?	?
Auditory	Population affected								
Speech understanding	A C			P D	P D (H)	P D (H)	P D		
Hearing loss	A C	P G	P G	P D (A)	P D (A+H)	P D (A+H)	P G		P D
Tinnitus	A C				P G	P G	P G		P D
Non auditory / Physiological									
Cardiovascular disease	A +Sleep	P D	P D		P D	P D	P G	P G	P D
Sleep disturbance	A C Sleep	P G						P G	P D
Immune dysfunctions	A C +Sleep	P D	P G		P G	P D	P G	P G	P D
Cognitive / Psychological									
Cognitive function	A C				P G	P D (H)	P G		
Annoyance	A C	P D	P G		P G				P D
Performance	A C	P G	P G			P D (H)			P G
Accidents & injuries	A C								
Stress	A		P D						
Mental health / illnesses	A C				P G	P G			
Combined effects outcomes									
Respiratory disorder		P G	P D		P G		P G	P G	
Human growth		P G				P D			
Balance disorders					P D	P G	P G		P G

Health endpoints affected by:	
Noise and indoor air pollutants *(environmental tobacco smoke, VOCs)*	There may be exacerbation of effects of ETS on hearing, cardiovascular health, immune function, sleep, annoyance and performance
Noise and outdoor air pollutants *(particulate matter, sulphur dioxide, nitrogen dioxide, carbon monoxide)*	There may be exacerbation of effects on hearing, cardiovascular health, immune system function, annoyance, performance and stress
Noise and asphyxiants *(carbon monoxide, hydrogen cyanide)*	There may be worsening of speech perception and hearing
Noise and solvents *(occupational, environmental: xylenes, styrene, toluene, benzene, etc)*	There may be interaction effects on hearing, speech perception, tinnitus, cardiovascular disease, immune system function, cognitive function, stress, and balance function
Noise and heavy metals *(lead, mercury)*	There may be interaction effects on hearing, speech perception, tinnitus, cardiovascular disease, immune system function, cognitive function, stress, balance function, mental health
Noise and pesticides *(organophosphates)*	There may be interaction effects on hearing, speech perception, tinnitus, cardiovascular disease, immune system function, and cognitive function
Noise and variables related to housing *(biological agents)*	There may be interaction effects on, cardiovascular disease, immune system function, and cognitive function
Noise and vibrations	There may be interaction effects on hearing, tinnitus, cardiovascular disease, immune system function, sleep, performance, and accidents and injuries

Factors which may have confounding or aggravating effects on the results of noise or air pollution studies are listed below. These factors should therefore be taken into account in forthcoming studies

Confounding Factors
Age
Gender
Smoking
Obesity
Alcohol
Socio-economic status
Occupation
Education
Family status
Military service
Hereditary disease
Medication
Medical status
Race and ethnicity
Physical activity
Noisy leisure activities
Stress reducing activities
Diet & nutrition
Housing condition (crowding)
Residential status

Research priorities for the future

The future needs for research in the field of combined effects of noise, air pollutants and chemicals were prioritised. The highest priority was given to issues related to research on noise and outdoor air pollutants. This is due to the fact that it may concern the largest population compared to the other stressors in this analysis and there is some evidence of serious health outcomes such as cardiovascular effects. The next priority was given to the research on the effects of noise and solvents in occupational settings and to research on noise and organophosphates.

APPENDIX 5

Outcome of Group B in the International Workshop on
"*Combined Environmental Exposure: Noise, Air Pollutants and Chemicals*"
15-16 January 2007, Joint Research Centre, Ispra (Italy).

1.   Combined exposures

The essential results of the deliberations of Group B on
- Which combined exposures occur;
- At which locations; and the
- Risks of different pairs of combined exposures are compiled in Table 1.

Table 1: Combination of noise with contaminants, the likeness of exposure, the locations of exposure and the estimate of potential risks related to combined exposures.

Combination	Exposure	Location	Risk
Noise and indoor air pollutants (ETS)	Unlikely	Smokers' Homes	Low
Noise and outdoor air pollutants (PM)	Yes	Traffic areas; Industrial areas	High
Noise and outdoor air pollutants (SO$_2$)	Likely	Industrial areas	Low
Noise and outdoor air pollutants (NO$_2$)	Yes	Traffic areas ; Industrial areas	Medium
Noise and outdoor air pollutants (CO)	Yes	Traffic areas	High
Noise and asphyxiants (CO)	Yes	Workplace; Smokers' homes	High
Noise and asphyxiants (HCN)	Yes	Workplace	Medium
Noise and solvents (occupational)	Yes	Workplace	High
Noise and solvents (environmental)	Unlikely	Homes	Low
Noise and lead (occupational)	Likely	Workplace	Medium
Noise and lead (environmental)	Unlikely	Urban areas	Low
Noise and mercury (occupational)	Likely	Workplace	High
Noise and mercury (environmental)	Likely	Urban areas	Medium
Noise and pesticides	Likely	Agricultural areas	High
Noise and biological agents	Not known	Homes	Low
Noise and biological agents (endotoxins)	Likely	Industrial workplace	Medium
Noise, low frequency noise and vibrations	Yes	Homes; workplace; leisure activities	High

2.   Approaches

In order to answer the question on which combinations of noise-chemical interactions should be recommended and which approaches are available for this purpose, the Group focussed on really established combinations (high risk) and interactions (known effects), and where the Group can make the largest contribution.

Environmental

Table 2 is extracted from Table 1 for high risk estimates of certain combinations of environmental noise and other environmental contaminants. It shows the established combinations of high risk exposure and related potential effects**.**

Table 2. Established combinations of high risk environmental exposure and related potential effects**.**

Combination	Location of exposure	Effects
Noise and PM	Traffic areas; Industrial areas	Cardiovascular; annoyance
Noise and CO	Traffic areas	Cardiovascular; annoyance
Noise and asphyxiants (CO)	Smokers' homes	Cardiovascular
Noise, low frequency noise and vibrations	Homes; Industrial workplaces, Offices; Schools; Leisure activities	Cardiovascular; vibroacoustic disease, annoyance; speech interference; sleep disturbance

The dependent variables are the effects – cardiovascular and annoyance for the combination of noise and PM/CO exposure and cardiovascular; annoyance, speech interference, and sleep disturbance, for noise and vibration exposure. Independent variables are characteristic parameters for noise and PM exposure, noise and CO exposure, and noise and vibrations exposure. Confounding variables include age, social status, location of homes, duration of potential exposure (time living at a certain place), crowding, frequency of disco visits (potential hearing loss), use of earphones (potential hearing loss), ETS, active smoking, drug treatment

Assessment of noise and PM/CO/vibrations exposure should be performed in microenvironments (home - work/school, other) and for time activity pattern (exposure factors; night - day exposure). Behavioural reaction may modify exposure through adaptation ("active coping").

Methodological caveats

The following issues should be considered in planning epidemiological studies on noise air pollutant interactions:

- o Confounder list depends on the selected health endpoint ("a priori selection");
- o The number of confounding variable should be limited to a minimal set in order to avoid "overadjustment";
- o Sample size should be determined to provide most power;
- o Noise characterising parameters should include frequency band analyses in addition to levels (e.g. tonality, low frequency bands);
- o Effect modification may occur as a consequence of
  - dispositional factors (e.g. perinatal factors such as low body weight or genetic factors);
  - specific sensitivities; and
  - drugs;
- o Effects may be related to exposures in a linear or a non-linear way. Therefore regression equations based on both linear and non-linear models;
- o Selected models should be as simple as possible, e.g. multiple but not multivariate regression.

Occupational

Table 3 is extracted from Table 1 for high risk estimates of certain combinations of occupational noise and other occupational contaminants. It shows the established combinations of high risk exposure and related potential effects.

Combination	Location of exposure	Effects
Noise and outdoor air pollutants (PM)	Industrial areas	Cardiovascular
Noise and asphyxiants (CO)	Workplace	Cardiovascular
Noise and solvents	Chemical plants	Hearing loss
Noise and mercury	Industrial, nutritional	Hearing loss
Noise and pesticides	Agricultural areas	Cardiovascular

The remarks made for environmental exposure and methodological approaches apply principally also for occupational exposures, except that nutritional exposure to mercury and to pesticides may be additional controlling or confounding variables.

3.   Priority issues in future research and policy making

For time constraints, Group B could not discuss priority issues. Tables 2 and 3 give some indication of which chemical pollutant exposures could be first considered in their interaction with noise exposure. In order to define the "way forward" in noise-chemical interaction a small workshop (of perhaps five members of this Workshop) may be envisaged to identify high priority issues in future research and policy making based on the literature survey presented in this workshop. The results of the deliberation could then be circulated among all members of this workshop.

Abstract

Introduction
The issue of combined exposure to noise, air pollution and chemicals has raised recently the interest of several bodies of the European Commission such as DG Environment, DG SANCO and DG Research in the context of the EC 7th Framework Programme. There are open questions whether prevailing environmental concentrations of air pollutants and chemicals can lead to ototoxic health impacts. Therefore this issue needs to be thoroughly explored and investigated to help the EC to revise the existing standards and guidelines concerning combined exposure to noise, air pollutants and chemicals.

Objectives of the Workshop

The aim of the workshop was to review and discuss the existing scientific evidence whether prevailing environmental exposures to single and concomitant agents together with noise could lead to ototoxic or other health impacts. The final aim was to identify the research needs and to give recommendations for research and policy making in the EU level.

Results and conclusions

It was agreed that research in the future should be focused on really established combinations (high correlations) and interactions (known effect) with main perspective on the traffic bundle of exposure. It was also discussed and agreed upon that the best knowledge exists on the health effects due to combined exposure to noise and solvents or heavy metals in occupational environments, especially on most of the auditory and non-auditory effects. Possible factors that may have confounding or aggravating effects on the results of noise studies were identified. Such factors are: age, gender, smoking, obesity, alcohol, socio-economic status, occupation, education, family status, active military, experience, hereditary disease, medication, medical status, race and ethnicity, physical activity, noisy leisure activities, stress reducing activities, diet & nutrition, housing condition (crowding), and residential status.

Research priorities and recommendations for the future

The highest priority was given to issues related to research on noise and outdoor air pollutants. This is due to the fact that it may concern the largest population compared to the other stressors in this analysis and there is some evidence of serious health outcomes such as cardiovascular effects. The next priority was given to the research on the effects of noise and solvents in occupational settings and to research on noise and organophosphates.

In the future research, priority should be given to:

1. evaluation of existing data collections whether re-analyses are possible with respect to combined exposure from traffic sources (road, rail and air),
2. analyses of existing data concerning noise and other stressors interactions in both occupational and environmental settings,
3. detailed assessment of combined exposures to noise, vibrations and PM, CO, NO_x, and VOCs with specific studies in urban areas and, especially, cardiovascular health endpoints should be studied as priority health endpoints,
4. identification of causal mechanisms through careful review of toxicological experimental studies.

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