Workshop on Chemical Pollution, Respiratory Allergy and Asthma 16-17 June 2005, Leuven

Workshop Report No. 6

Brussels, December 2005

ECETOC WORKSHOP REPORT No. 6

European Centre for Ecotoxicology and Toxicology of Chemicals
4 Avenue E. Van Nieuwenhuyse (Bte 6), B-1160 Brussels, Belgium.

The workshop was sponsored by the

Cefic Long-range Research Initiative (LRI)

Chemical Pollution, Respiratory Allergy and Asthma

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1. EXECUTIVE SUMMARY

Atopic allergy and asthma remain important health issues. It is therefore of significance that in more modernised societies there has, during the last four decades, been a substantial increase in the prevalence of these diseases. The observed changes have been too rapid to be accounted for by modifications to the gene pool and there is a general acknowledgement that alterations in lifestyle, combined with changing environmental factors, are responsible for the increases in prevalence.

Against this background there has been speculation that exposure to some specific chemicals in particular, and chemical pollution in general, may play an important pathogenetic role. Several mechanisms through which this might occur have been proposed. However, there are in addition, a number of other factors that have been implicated as playing potentially important roles, and among these are diet (both quantity and quality), reduced exposure neonatally and during infancy to infectious micro-organisms, and changes in indoor air quality.

The purpose of this Workshop was to determine whether and to what extent chemicals have played a role in the increased burden of allergy and asthma in 'westernised' societies. It is clear that further research is required to define the factors that have impacted on the prevalence of asthma and atopic allergy. However, a major conclusion drawn was that although contributions by some types of chemical exposure have been suggested, in comparison with other acquired and environmental factors the contribution of chemicals is likely to have been modest.

2. WORKSHOP OVERVIEW

In industrialised countries there has been an increase in the prevalence of asthma and of atopic disease. The increase has been too rapid to be caused by a change in the gene pool. Among the factors that have been implicated are the indoor environment, diet, vaccination programmes and the 'hygiene hypothesis' (which suggests that a decreased infectious challenge during infancy predisposes atopic allergy). There is some evidence that the highest prevalence of allergy is associated with conditions where levels of pollution are comparatively low. Nevertheless, there is a prevailing view among some that chemicals in the environment contribute to the increased prevalence of asthma and atopic allergy.

The Workshop brought together some 40 scientific and clinical experts from industry, academia and government agencies, to consider and debate specific questions regarding the apparent relationship between chemical pollution, asthma and allergic disease. There were wide-ranging and informed discussions about the nature of factors that contribute to the development of asthma and allergy and from these emerged consensus views on the likely contribution of chemicals to changes in the prevalence of these diseases, and agreement on the key research issues that now need to be addressed.

The Workshop began with detailed presentations, followed by specific topics for consideration by breakout groups, and a final plenary discussion.

This report summarises the introductory lectures given by invited speakers and outlines the plenary discussions and the outcome of the breakout groups.

3. PLENARY LECTURES AND BREAKOUT GROUPS

3.1 Plenary Lectures

As an introduction, Professor Kimber outlined the objective and context of the workshop within the framework of the Long Range Research Initiative (LRI) programme. On the first day, six invited experts gave plenary lectures, the topics of which had been selected to stimulate the discussions in the subsequent breakout groups (Appendices 1 and 2).

Professor Helms outlined key clinical aspects of asthma and respiratory allergy and their burden on society. He reminded attendees that asthma is a clinical diagnosis that has been defined as variable airflow obstruction associated with narrowing and inflammation of the airways, which varies spontaneously or with treatment. Disease prevalence also varies with age, gender and geographical region.

He showed that wheezing can occur at any period of life, being more common in the young and the elderly. Although the underlying causes remain elusive it is clear that viral infections have a large role in precipitating episodes in childhood, that atopy (allergy) features prominently in adolescence and early adult life and that irreversible and progressive chronic obstructive pulmonary disease (COPD) becomes more prominent in middle age and elderly adults. Disease progression and prevalence are modified by gender in that both asthma and allergic rhinitis (hay fever) are initially more prevalent in boys but become more frequent in young women after puberty. The relationship between asthma and geographical region has been well defined with the highest levels worldwide in English speaking countries; especially the UK and within Europe there is a Northwest-Southeast gradient. This wide variation has triggered investigations into the interaction between genetic variants and environmental exposures.

The current cost of asthma in Europe has been estimated as €17.7 billion per annum (European Lung White Book, 2003), costs that are likely to increase due to the increased numbers of affected children/adolescents making the transition to adults, and the increasing use of long term prophylactic therapy associated with patient needs and the concept that the airways of young asthmatics may remodel, possibly leading to irreversible and progressive airway obstruction into adult life.

Dr. Cullinan spoke on determinants of the increasing prevalence of allergy and asthma. He expressed the opinion that the rate of asthma increase over the past 50 years has been so rapid that environmental factors must have been responsible. Geographical differences in asthma prevalence can be seen between countries across Europe and, on a smaller scale, between rural and urban areas or between farming and non-farming families. These are all real differences,

which appear to have an environmental origin; they may, for example, be explained by a 'hygiene hypothesis', by differences in chemical exposures, etc.

Two examples of the impact of chemicals on asthma were given:

- In a cross sectional study of 1,900 Brussels school children aged 7-14, an association was found between regular attendance at chlorinated swimming pools and an increase in lung epithelium permeability and asthma.
- The second example related to a longitudinal study of 7,000 children, which found a correlation between childhood wheeze and maternal exposure to domestic chemicals during pregnancy (usage of cleaners, disinfectants, etc. assessed by questionnaire).

The overall conclusion was that in an increasingly susceptible population, chemical exposures may be one of the reasons for the increasing presence of asthmatic illnesses.

Dr. Zock gave a presentation on possible associations between indoor/outdoor pollution and respiratory disease. He noted that outdoor and indoor air pollutants can be both gaseous and particulate and may originate from natural or synthetic sources.

The most important outdoor pollutants are ozone, the gaseous oxides of carbon, nitrogen, sulphur and particulate matter. There is a greater range of indoor pollutants varying from secondary tobacco smoke to air fresheners, combustion by-products, building materials and household cleaners.

The link between pollutants and respiratory effects ranging from sensitisation to asthma, bronchitis and death has usually been made at times of abnormally high exposure such as in occupational settings or during dense fogs like the one in London during December 1952. During and after such events there is an increase in respiratory symptoms and mortality. Currently there is much research attention concerning long-term health effects of chronic exposure to moderate levels of air pollution, in particular of ultra-fine particles.

The link between indoor exposure and respiratory effects has been less studied even though people spend much more time indoors (80-90%) than outside. However Dr. Zock cited one recent cross sectional study (Medina-Ramón *et al*, 2003) of more than 4,500 Spanish women which showed that there was a higher prevalence of asthma in those who had at some time been employed in domestic cleaning work than those who had not. A case control study (Medina-Ramón *et al*, 2005) indicated that the cleaning products most likely to cause asthma were ammonia, degreasing sprays and bleach. In addition, a recent study suggested that infant wheeze was associated with the use of cleaning agents by the mother during pregnancy (Rumchev *et al*, 2004).
He concluded that more work was needed on indoor exposures to chemicals.

Professor Seaton made a presentation on the impact of diet on respiratory allergy and asthma (Devereux and Seaton, 2005; Martindale *et al*, 2005). His hypothesis is that the increase in asthma is not due to a more toxic environment but rather to dietary changes (decreases in intake of antioxidants, selenium and vitamin E) making the population more susceptible. He supported this position by reference to the fact that over the past 60 years our intake of green vegetables and potatoes has fallen by 55% and 65% respectively and that serum selenium levels are falling at similar rates.

He described three recent case-control studies investigating the relationship between diet and asthma:

- The first, in rural Scotland, found that the lowest intakes of vitamins C, E and manganese were associated with a more than fivefold increase in the risk of bronchial reactivity.
- The second study using food frequency questionnaires, confirmed that a low intake of vitamin E is associated with adult onset of wheeze.
- The third, on children in Saudi Arabia, concluded that the risk factors for wheezy illness were family history, atopy, fast food and the lowest intakes of milk, vegetables, fibre, various minerals and vitamin E.

Finally he described an ongoing study aimed at determining if diet could influence immune development *in utero*. The conclusions that can be drawn from this study at present are that maternal vitamin E intake and selenium status during pregnancy are inversely associated with wheeze at age 2 years.

The overall conclusion is that a poor diet, low in selenium and vitamin E, is probably a major contributor to the rise in asthma.

Professor Diaz-Sanchez discussed the link between air pollution (diesel exhaust particles [DEP] and environmental tobacco smoke [ETS]) and airway disease, the mechanisms involved, factors conferring individual susceptibility and possible ways to respond.

DEPs (a carbon core surrounded by poly-aromatic hydrocarbons, metals, etc.) are the major source of particulates, especially in Europe and Japan, to which we are exposed. It has been found (Diaz-Sanchez *et al*, 2000) that they significantly reduce allergen threshold and that, in their presence, only 20% of the normal amount of allergen is needed to produce allergic symptoms.

In addition keyhole limpet haemocyanin, a substance to which humans are not normally exposed, produced no allergic reaction but, when administered together with DEP, six out of ten atopic

subjects were sensitised. It is clear (Diaz-Sanchez *et al*, 1999) that DEPs can act as mucosal adjuvants to a *de novo* IgE response and may increase allergic sensitisation. Also DEPs increase airway responsiveness in asthmatic subjects (Nordenhäll *et al*, 2000).

ETS produces similar effects to those of DEP. It causes IgE and allergen-induced Th2 responses and enhances allergen-induced histamine release. In a variety of individuals the levels of IgE in response to exposure to ETS were similar to those for DEP.

There is evidence that reactive oxygen species are involved in the response induced by DEP (Boland *et al*, 2000) and that the thiol antioxidants, bucillamine and N-acetylcysteine, are capable of preventing these adjuvant effects. It follows that antioxidant treatment strategies may serve to alleviate allergic inflammation and may provide a rational basis for treating the contribution of particulate matter to asthmatic disease.

With regard to the inter-individual differences in sensitivity to ETS and DEP, reference was made to the investigations, which have been carried out on glutathione-S-transferase (GST) which has 3 different functional polymorphisms: GSTM1, GSTP1 and GSTT1. These studies (Fryer *et al*, 2000; Gilliland *et al*, 2004) have shown that there is a clear genetic predisposition for allergy/asthma in combination with DEP/ETS exposure.

The following actions were proposed as possible ways to reduce the risk of allergy/asthma:

- Decrease exposure to DEP.
- Consider medication like corticosteroids or non-steroid anti-inflammatory agents.
- Increase intake of vitamin C and E (eat more vegetables/fruit).
- Consider an antioxidant supplement.
- Increase intake of an enzyme (sulphorane), found in broccoli sprouts, which has been shown to abolish the specific allergic IgE response in an OVA/DEP allergy mouse model.

Dr. Lambrecht gave a very detailed presentation on possible mechanisms underlying the sensitisation to inhaled antigens and the adjuvant action of some substances. He paid particular attention to the role played by the various subtypes of dendritic cells found in humans and mice.

The way in which allergens presented at the surface of the lung can produce an immunologic reaction, despite the barrier function of the respiratory epithelium, has been explained by Vermaelen *et al* (2001). They found that the fluorescein isothiocyanate labelled ovalbumin (OVA) which they administered to mice was located within the dendritic cells (DC) so it is assumed that these cells provide the link between the antigen present at the surface of the lung and the proliferation, maturation and activation of T cells in the mediastinal lymph nodes.

It has further been shown that both myeloid (mDC) and plasmacytoid (pDC) dendritic cells can take up antigen in the airways but the former initiates T cell division in antigen specific T cells and the latter mediates tolerance to the inhaled antigen. It is hypothesised therefore that the balance between the mDCs and pDCs presenting antigen might influence the decision between immunity and tolerance.

An excess of mDC would be expected to lead to immunity (increased lymphocytes, neutrophils and eosinophils) whereas the presence of more pDCs would lead to tolerance (decrease of lymphocytes, neutrophils and eosinophils). This has been demonstrated in practice (de Heer *et al*, 2004):

- Intravenous pDC administration inhibits airway inflammation in the OVA/alum model.
- Depletion of pDCs during priming leads to asthmatic features upon rechallenge.

It is concluded that:

- When a harmless antigen presents to the mDCs then the pDCs suppress the mDCs and prevent naïve T cell proliferation. The balance is in favour of pDCs (tolerance).
- If an adjuvant is added, the balance can shift to mDCs and now the mDCs get a positive signal from the pDC which causes naïve T cells to turn into effecter cells.
- Adjuvants work by changing the mDC/pDC balance.

More detailed information on this model can be found in a recent overview article by this group (de Heer *et al*, 2005).

3.2 Breakout Groups

The following topics were discussed in the three breakout groups on the second day:

What is the contribution of chemicals to the increasing prevalence of allergy and asthma? (all breakout groups)

What are the gaps in scientific knowledge and research needs in the following areas?

- *Clinical medicine*
- *Epidemiology*
- *Mechanisms.*

Report from all breakout groups: What is the contribution of chemicals to the increasing prevalence of allergy and asthma?

The central question that the breakout groups were asked to address from their different perspectives was:

Are chemicals responsible for the increased prevalence of asthma and atopic allergic disease that has been witnessed in 'westernised' societies during the last four decades? If they are responsible, how important is their role?

Although there were some differences of opinion between breakout groups on specific issues, such as the likely importance of certain environmental factors, and the merits of proposed research topics, there were important areas where a consensus was achieved. These can be summarised as follows:

- There is no doubt that environmental and lifestyle factors impact on the development of asthma and the acquisition of allergic disease.

- The nature and relative importance of factors that may be responsible for the increased prevalence of asthma and allergic disease in 'westernised' countries and cultures are not clear.

- Although hypotheses focused on aspects of lifestyle, and in particular the 'hygiene hypothesis' have attracted support, those important elements which have impacted upon the prevalence of asthma and allergy are yet to be clearly defined.

- In this context there are probably other factors, such as the roles played by changes in the quantity and quality of diet and by infectious diseases, the importance of which have not previously been appreciated fully.

- Some chemicals and other environmental factors are known to impact on the elicitation and/or exacerbation of asthmatic reactions. However, the relevance of chemical exposure for the development of asthma and the acquisition of allergic sensitisation is uncertain.

- Although some chemicals may impact on the development of asthma and allergy, it is likely that other factors have played and continue to play more important roles.

Report from breakout group #1: What are the gaps in scientific knowledge and research needs in clinical medicine?

Chairman: Professor Nemery, *Rapporteur*: Dr. Flückiger.

The group concluded that although a number of factors are known to exacerbate asthma or provoke attacks in individuals with pre-existing bronchial hyper-reactivity, much less is understood about influences on the initiation of asthma. Genetic predisposition has been shown to have an impact, but this does not explain the rise in asthma prevalence in the past decades or the apparent levelling off of this increase in the most recent years. Environmental factors that may have had an impact on these changes in asthma prevalence are poorly characterised, in particular changes in the quality of indoor air, the environment where most Europeans spend the majority of their time.

Most of the existing studies leave the following clinical questions unanswered:

- Was the observed asthma an exacerbation of existing latent asthma or was it newly appearing asthma?

- What is the influence of key environmental factors? If environmental factors are implicated as potential causative agents or contributors, they are often poorly characterised, both qualitatively and quantitatively. This is particularly true for the indoor environment.

- Can clinical asthma be caused by smells and other factors leading to olfactory, vagal or trigeminal stimulation? In other words, can clinical asthma be caused via a mechanism that is neither immunological nor irritant to the mucous membranes of the respiratory tract?

- What are the patho-physiological characteristics of asthma in very young children? There is evidence that antenatal factors and the environment in infancy may play a role, but so far,

studies covering the very young have generally been based only on questionnaires completed by parents.

- What exactly characterises the phenomenon generally described as 'growing out of asthma', which is often observed in young adults? Does this asthma disappear or does it simply become sub-clinical, only to reappear later in life?

Key issues that need elucidation by further studies were identified as follows:

- *Studies in the very young* where asthma prevalence is the highest. Investigations are needed that make use of modern clinical tools (oscillometry, incentive spirometry) and that do not rely solely on questionnaires. In this age group, intervention studies with changes in nutrition or changes in the indoor environment would be of particular interest. If such interventions have an impact, it would be of interest to know at what time they would have to take place to be most effective.

- *Studies in older children and young adults*, an age group where asthma prevalence decreases. It would be of interest to understand to what extent clinical and test parameters become normal concurrent with the improvement of symptoms. Furthermore, studies are needed to determine whether environmental factors can be identified that may help to explain why asthma resolves clinically in some individuals, but not in others.

- *Long-term studies in adults*. These studies should follow pulmonary function in subjects across several decades and by means of modern clinical and test tools. They should take into account environmental, nutritional and other lifestyle factors.

- *Studies in population groups whose lifestyle and living environment is likely to change* rapidly over the coming years and decades: populations of Eastern Europe and of certain East Asian regions, such as for instance certain parts of China.

Report from breakout group #2: For epidemiological studies, what are the gaps in scientific knowledge and what are the research needs?

Chairman: Dr. Evans, *Rapporteur*: Professor Jaakkola.

The following areas were identified as representing gaps in scientific knowledge:

- The lack of information on the impact of low dose and chronic exposures to chemicals in the general environment. This is less well understood than occupational exposures to chemical inducers of asthma.

- What are the likely attributable risks when large populations are exposed continuously to low concentrations of chemicals? It might be anticipated that low dose exposure to chemicals causes asthma infrequently because the weight of evidence suggests a dose relationship with the greatest risk for induction of sensitisation resulting from high levels of exposure.

- More work is needed to understand the influence of cumulative vs. peak inhalation exposures to chemicals.

- There is a lack of information about the impact of indoor pollutants (with the exception of ETS) compared with outdoor pollutants. For example, the use of household chemicals has during recent years changed substantially with respect to their diversity, quantities used, and the means for their delivery (e.g. use of aerosolised delivery).

- The factors that contribute to exposure profiles in the indoor environment (e.g. air ventilation rates and air flow patterns) are poorly understood. Indoor environments have changed in 'westernised' societies in the last few decades with the introduction of new building materials and building design resulting in reduced ventilation rates and higher airborne concentrations of pollutants.

- Chemical mixtures pose a particular challenge to understand, as there is evidence that the health effects of exposure to mixtures of chemicals are not necessarily additive.

The group then discussed the evidence that exposure to chemicals before birth may be associated with a higher risk of asthma in children after birth (Li *et al*, 2005) and that exposure in childhood may also be correlated to adverse responses to chemicals later in life. The following gaps in the epidemiological knowledge were identified:

- Knowledge is limited about the factors that influence the development of asthma (or susceptibility to asthma) before birth and during childhood.

- The effects of air pollution on lung function in infants are not well understood, largely because of methodological limitations in studying airway function in this age group.

To address these knowledge gaps an *a priori* hypothesis is required and it was proposed that the influence of chemicals before birth (and during critical periods of foetal lung development) may be important. This hypothesis could be addressed in a large prospective birth cohort study in which the development of sensitisation, and the occurrence of allergy and asthma, would be followed prospectively (Martindale *et al*, 2005) amongst a population considered likely to

undergo an increased prevalence of such conditions (e.g. developing countries). Collection and analysis of umbilical cord blood (Devereux *et al*, 2001) would provide insight into the development before birth of immunological responses associated with maternal exposure to chemicals. The design of such a study would have to take into account the influence of a wide range of factors including: maternal diet; subsequent influence of the infant/child's diet; maternal occupation and socio-economic status, and the influence of confounding factors in the home environment (e.g. cigarette smoking).

Others proposals for research included:

- An investigation of triggers for new onset asthma amongst children, although this study may be constrained by issues of consent and the difficulty of discerning asthma-like symptoms in the very young.

- An investigation of new onset asthma in adults in an occupational setting where exposures can be measured and where health effects resulting from such exposures can be monitored clinically using suitable biomarkers as indicators of genetic susceptibility. This study should consider the major chemical exposures whether sensitising and/or irritant in nature. The cleaning work sector was considered an appropriate example, in which many people are employed. However, the high turnover of temporary staff in this sector may limit the feasibility of a longitudinal study.

Report from breakout group #3: What are the gaps in scientific knowledge and research needs on mechanisms?

Chairman: Professor Kimber, *Rapporteur*: Mrs. Colson.

The influences of environmental and other acquired factors on the pathogenesis and prevalence of asthma and atopic allergic disease are clearly very complex. The task this group addressed was a definition of the important gaps in our knowledge and identification of research needs to inform our understanding of relevant biological mechanisms.

The group recognised that effective research into relevant mechanisms should be informed by advances in clinical medicine and by the results of epidemiological surveys. One issue that the group felt might be of potential benefit in guiding future research directions was the fact that, in some areas at least, the increasing prevalence of asthma and atopic allergy might have reached a plateau. If such is the case then identification of the important factors driving increased susceptibility to asthma and allergy might be facilitated which, in turn, could inform the focus of future mechanistic investigations.

The key issues identified were as follows:

- *Prospective immunological studies.* There is no doubt that changes in 'westernised' countries in the prevalence of asthma and atopic allergy have been too rapid to be accounted for by a change or changes in the gene pool; the implication being that environmental factors and/or alterations in lifestyle are responsible (von Mutius *et al*, 1992; Strachan, 1996; Kimber 1998; Peden, 2000). The relative importance of such factors has been difficult to characterise and it is possible that prospective epidemiological studies of either cultures or countries undergoing rapid socio-economic change and/or of migrant populations that are moving between cultures or countries of differing socio-economic status and/or degree of 'westernisation' may be valuable in this context.

- *Immunological versus non-immunological effects.* Changes have been observed in the prevalence of both asthma and atopic allergic disease. Although it is commonly assumed that similar or identical factors are implicated in both instances, this is not necessarily the case and one area that warrants further attention is the determination of whether and to what extent there are different factors that impact on immunological and non-immunological processes.

- *Adjuvant properties of chemicals.* If exposure to certain chemicals and/or chemical pollution plays a role in the acquisition of allergic sensitisation then the implication is that some chemicals may behave as adjuvants (antigen non-specific moderators or enhancers of immune function). Although there is evidence from experimental systems that some chemicals (such as formaldehyde) and particulates (such as DEP) can act as adjuvants in some circumstances, the extent to which this activity translates into a risk for human health, and an increased ability to acquire allergic disease, has not yet been established (Diaz-Sanchez *et al*, 2003*;* Diaz-Sanchez and Riedl, 2005). This also is an area worthy of further investment, as is research designed to provide a more detailed understanding of the cellular and molecular mechanisms through which adjuvants are able to influence the quantity and/or quality of immune response.

- *Relevant conditions of exposure.* If chemicals are believed to impact in some way on the development of asthma or the acquisition of allergic sensitisation then it is necessary to explore the important exposure metrics (Peden, 2000). For instance, clarity is required with respect to: (a) the relevant route(s) of exposure, (b) the extent and/or duration of exposure: is low-level exposure over long periods of time more important than concentrated levels of high exposure? (c) is it necessary that exposure to a chemical is concurrent with exposure to an allergen? and (d) are there life stages at which exposure to chemicals (for instance *in utero* or during infancy) will have a greater impact on the development of allergy and/or asthma? In the absence of a clear understanding of whether chemicals *per se,* and specific

chemicals in particular, have the potential to affect allergy and asthma, these are difficult issues to address, but nevertheless remain important questions.

- *Mixtures.* It must also be acknowledged that the potential impact of chemicals, and/or other environmental factors, on the development of allergy and asthma may be extremely complex, not least because the relevant biological responses may result from the synergistic effects of several factors experienced simultaneously.

In conclusion, the view of this group was that the issues summarised above represent the most important knowledge gaps in this area and that an investment in appropriate research would yield important dividends in clarifying the ways in which environmental factors are able to influence the development and manifestation of asthma and allergic disease.

Plenary Discussion

Following a review of the conclusions reached by the individual breakout groups, and of the knowledge gaps and research needs identified, there was a final plenary session to the workshop. The purpose was to consider which identified research needs were the key ones and whether any additional ones were relevant. The participants discussed in greater detail the following two areas worthy of research investment:

- *Better information about exposure to chemicals in the home environment.* Since there has been a clear increase in the incidence of asthma, information on increases or decreases in the exposure to chemicals used in households would be of great value in evaluating whether a correlation exists. Exposure can be affected by air exchange/ventilation rates in homes, and it would be of interest to determine whether these have changed over the last decades, for instance, due to the increasing introduction of energy saving measures. Such information would also be of value to ongoing birth cohort studies, and could be linked to them.

- *Well-designed prospective birth cohort studies (prenatal, postnatal).* There should be multi-centre studies, conducted in several countries, thus covering a variety of lifestyles. It would be important to take into account more of the confounding factors compared with those that are part of current studies. A few specific elements for a potential study protocol were mentioned, such as analysis of umbilical cord blood, followed by exposure measurements in children, observing behavioural aspects between parents and children, and measuring relevant biomarkers.

4. CONCLUSIONS

The workshop reached the following conclusions:

In industrial countries the prevalence of atopy and asthma has increased, mainly in children, over the past four decades or so. In areas of high prevalence, a plateau may now have been reached, but in many developing countries urbanisation seems to be associated with a rapid increase in atopy and asthma. The exact reasons for these trends are still largely unknown despite considerable epidemiological and experimental research. It appears likely that the 'causes' of asthma have their impact at a very young age, probably even before birth. These causes are likely to be complex, or the mystery would have been solved easily (unless the causal factor is a ubiquitous agent, such that there are no suitable 'unexposed' controls with whom the asthmatics can be compared).

Among the many hypotheses proposed to explain the increased prevalence of asthma and atopy, the most popular has been the so-called 'hygiene hypothesis', in which the relative absence of infections in early childhood orientates the immune system towards an 'allergic' (selective type 2) phenotype. Although this hypothesis is not without merit, most experts now agree that it does not accommodate all the facts and probably does not represent the whole story. Changes in diet that have accompanied 'westernisation' may be implicated, but convincing data about the role of dietary factors in the pathogenesis of asthma are not yet available.

As asthma is a respiratory disease, a reason that naturally comes to mind – among scientists and lay people alike – is that something might have changed in the air we breathe. The question is: could agents that pollute the indoor or outdoor air be responsible for the higher occurrence of asthma? The short answer to this question is that there is no evidence that air pollution or environmental chemicals are responsible alone for the recent asthma epidemic. Nevertheless, the possible contribution of chemicals to the pathogenesis of asthma merits attention from the scientific community.

There is little doubt that exposure to indoor or outdoor air pollutants, particularly cigarette smoke, is a significant trigger for the clinical manifestations of asthma although how exactly these pollutants exacerbate asthma is still not clear. However, whether such exposures impact on the initial causation of asthma is much less certain.

Several chemicals are capable of causing asthma through allergic sensitisation. This mechanism is well established for a number of occupational agents (such as diisocyanates), but it is unlikely that sensitisation to specific chemicals plays any substantial role in the initiation of asthma outside the workplace.

Environmental agents do not need to act as sensitisers themselves. They may influence the process of sensitisation to common environmental allergens, such as those from house dust mites, pets or pollen. There are experimental data indicating that complex mixtures of pollutants, such as diesel exhaust particles or cigarette smoke, may act as adjuvants promoting immune responses and the acquisition of allergic sensitisation. Some epidemiological data also suggest that exposure to (loosely defined) irritants in the home environment may also constitute a risk factor for asthma in children or in adults (particularly amongst those employed as cleaners). It is conceivable that damage caused by irritants to the respiratory epithelium allows inhaled allergens to reach antigen-presenting cells more effectively, or that the inflammatory changes caused in the mucosa favour allergic sensitisation.

Considerable research is still required to discover the environmental factors – taken in a very broad sense to include also diet – that have resulted in the increased prevalence of asthma and atopic allergy in modern ('westernised') societies. A significant challenge for epidemiological studies is to obtain relevant and accurate exposure data, either by environmental measurements or by suitable biomonitoring. Another important issue, not only in clinical-epidemiological studies, but also in experimental studies, is the need for accurate definitions of the asthma phenotype. In this respect, it is important to acknowledge that a high proportion of asthma does not appear to be caused by allergy.

This workshop has shown that a substantial amount of clinical, epidemiological and experimental research has been conducted to unravel the environmental determinants that might be responsible for the changes in the epidemiology of asthma and allergy in the past forty years. Yet, we still do not have a satisfactory overall explanation for these changes. One possible explanation is that the cause is so diffusely, and increasingly, present in our environment that everybody is, or has been, exposed to it. This makes asthma look like a 'genetic' disease because it is virtually impossible to compare exposed to non-exposed people. Another, equally possible explanation is that the environmental causes of asthma are multiple and complex, acting together or in succession, thus making it difficult to discover the various culprits. These two mechanisms are not mutually exclusive, and further research – preferably translational – should continue to test these hypotheses.

ABBREVIATIONS

DC	Dendritic cells
DEP	Diesel exhaust particles
ETS	Environmental tobacco smoke
GST	Glutathione-S-transferase
Ig	Immunoglobulin
OVA	Ovalbumin
ROS	Reactive oxygen species
Th cell	T helper cell

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APPENDIX 1: WORKSHOP PROGRAMME

Thursday 16 June 2005

12.30-13.30	Registration, Snacks and Coffee	
13.30-13.45	**Welcome**	Dr. Mike Gribble Secretary General ECETOC
	Introduction	Prof. Ian Kimber Syngenta
		Session Chair: Prof. Ben Nemery Catholic University of Leuven
13.45-14.15	**Asthma and Respiratory Allergy: Clinical Aspects and Societal Burden**	Prof. Peter Helms University of Aberdeen
14.15-14.45	**Determinants of the Increasing Prevalence of Allergy and Asthma (Epidemiological Evidence)**	Dr. Paul Cullinan Imperial College London
14.45-15.15	**Possible Associations between Indoor/Outdoor Pollution and Respiratory Disease**	Dr. Jan-Paul Zock University of Barcelona
15.15-15.45	Coffee Break	
		Session Chair: Dr. Gareth Evans Health & Safety Laboratory, Buxton
15.45-16.15	**Dietary Impacts on Respiratory Allergy and Asthma**	Prof. Anthony Seaton University of Aberdeen
16.15-16.45	**Possible Mechanisms of Adjuvancy**	Prof. David Diaz-Sanchez University of California, Los Angeles
16.45-17.15	**Perspectives on Mechanisms**	Dr. Bart Lambrecht Erasmus University Medical Centre, Rotterdam
17.15-17.45	**General Discussion**	Chair: Prof. Ian Kimber
17.45-18.30	**[Meeting of the Organising Committee only]**	
19.30-22.00	Dinner	

Friday 17 June 2005

08.30-08.45	**Introduction to the Breakout Groups**	Prof. Ian Kimber
08.45-10.45	Breakout groups to address defined questions displayed during the meeting **I** **II** **III**	
10.45-11.00	Coffee Break	
11.00-12.30	**Report from the Breakout Groups**	Rapporteurs
12.03-13.30	Lunch	
13.30-14.30	**Plenary Discussion**	(Moderator: Dr. Christa Hennes ECETOC)
14.30-15.00	Coffee Break	
15.00-15.30	**General Conclusions**	Prof. Ian Kimber

Close of Workshop

APPENDIX 2: PRESENTATION ABSTRACTS

Asthma and Respiratory Allergy: Clinical Aspects and Societal Burden

Peter J. Helms
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Asthma is a clinical diagnosis and all consensus statements defining its features refer to variable airflow obstruction, which resolves either spontaneously or with treatment. A recent additional feature that is now included in the definition is the presence of chronic inflammation of the airways. The disease is often, but not invariably, associated with allergic sensitisation and most cases first present in childhood. A male predominance in early childhood is exchanged for a female predominance after puberty. Whereas trigger factors of existing disease, such as allergens, cigarette smoke, air pollution and viral infections, are well described, the identification of causative factors, other than a genetic predisposition, remains elusive and is the focus of much research interest. Increases in population prevalence the past four to five decades point to important environmental factors interacting with genetic susceptibility. The close association of asthma with allergic rhinitis (hay fever) has led to the 'united airway' concept that may be relevant in explaining exacerbations and in therapeutic responses. Therapeutic interventions are largely focussed on short-term bronchodilator relief and long-term anti-inflammatory treatment. Being the most common disorder in childhood and in the top five of chronic diseases in adult populations in developed economies, the economic costs of treatment and loss of function are significant. Direct and indirect costs have been estimated at €17.7 billion per annum in Europe [1]. Wide variations in prevalence across Europe indicate either significant differences in environmental exposures and/or different genetic contributions in association with population diversity. Current attention is being directed to genetic determinants of response to treatment and the interaction between genetic variants and environmental exposures. The airway re-modelling concept implies that individuals with severe persistent disease and with chronic inflammation of the airways may develop fixed long-term airway obstruction into adult life that may overlap with or merge with disabling chronic obstructive lung disease. With the current high level of recruitment to the asthma phenotype in childhood and the possibility of long-term adverse respiratory outcomes the identification of contributory and potentially reversible environmental determinants has become an urgent priority.

Determinants of the Increasing Prevalence of Allergy and Asthma

Paul Cullinan
Department of Occupational and Environmental Medicine
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London, UK

Childhood wheezing is often – but not always – associated with allergy to airborne biological material. Such allergy is termed 'atopy'. When there is a pattern of repeated episodic wheeze it is generally termed 'asthma'. There is little doubt – at least in the economically developed world – that the frequencies of asthma, atopy and indeed of most types of childhood wheeze have increased at some point over the past 50 years. The speed of this change indicates that environmental factors have been responsible; a vast array has been implicated. For most there is little robust supporting evidence.

A small number, however, appear more plausible: dietary changes and the effects of atmospheric 'pollutants' are covered by other speakers. This presentation will focus on the broader influences of temporal shifts – and geographic variations – in early childhood 'hygiene'; and the intriguing role of family size/birth order. Particular emphasis will be laid on information from European populations. It will be argued that explanations such as these are probably responsible for the larger part of any increases in disease incidence. At the same time, any factors – chemical or other – that provoke significant symptoms in a large enough susceptible population will lead to an increase in apparent disease prevalence.

Possible Associations between Indoor/Outdoor Pollution and Respiratory Disease

Jan-Paul Zock
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Indoor and outdoor air pollution consists of a heterogeneous mixture of chemical and biological agents, both gases and particles, originating from multiple sources. Total respiratory exposure to air pollution of an individual is determined by the time spent in different microenvironments, the airborne concentrations in these microenvironments, and respiratory rates related to each activity. Particularly for the outdoor environment, evidence and awareness of adverse respiratory health effects were initiated by large outbreaks of respiratory disorders (hospital admissions and increased respiratory mortality) related to periods of extreme air pollution such as the London smog in 1952.

During the last decade, epidemiological studies have focused on large population studies evaluating effects of low to moderate levels of indoor and outdoor chemical pollution, with special reference to sensitive groups such as children, elderly, and individuals with chronic respiratory diseases. The outcomes studied are typically respiratory symptoms, lung function and bronchial responsiveness, which are mostly not specific for one particular disease. Observed effects indicate the aggravation of a pre-existing respiratory disease as well as the new-onset of respiratory disease. As not uncommon in observational epidemiology, although statistical associations may be weak and average effects appear small and as such not clinically relevant, the public health impact may be large. Effect mechanisms include local inflammation, oxidative stress, mucous membrane irritation, and specific sensitisation. This presentation highlights respiratory effects of outdoor exposure to fine particles, indoor exposure to nitrogen dioxide, and the use of air fresheners and other cleaning sprays.

Dietary Impacts on Respiratory Allergy and Asthma

Anthony Seaton
Department of Environmental and Occupational Medicine
University of Aberdeen and Institute of Occupational Medicine
Edinburgh, UK

The causes of the remarkable rise in asthma and allergies in developed countries since the 1960s have been much debated. In 1994 I published the reasons why I believed such a rise could not reasonably be attributed to increasing exposure to allergens or pollution but was more likely to be a consequence of decreased population intake of antioxidants reflected in the diet of pregnant women. The basis of this hypothesis was that such changes in diet across a population increased the susceptibility of the young to allergens and other precipitants of allergy and asthma. This hypothesis attracted less attention worldwide than the so-called 'hygiene hypothesis' and it initially proved difficult to attract research funding to test it.

In this talk I shall outline the evidence my colleagues and I have gathered associating diet with airway hyper-reactivity, adult-onset asthma, childhood asthma in Saudi Arabia (a non-'westernised' country), neonatal T-cell responses to allergens, and asthma in young children born to mothers with poor antioxidant intake. In all these studies, one micronutrient has consistently shown negative associations with risk of asthma and in the most recent studies linking maternal diet with outcome in the offspring, another micronutrient has also shown a similar association. We estimate that, if these associations are causative, the effects of dietary change in intake of these two micronutrients in the UK population are sufficient to explain a large part of the observed rise in asthma in the young population. The importance of this in public health terms is obvious and intervention studies are urgently required.

Consideration of these results leads us to question whether the observed associations, though with antioxidant micronutrients, are truly due to an antioxidant effect. In addition to epidemiological intervention testing, *in vitro* examination of the associations is being pursued. The audience is invited to consider the possibility that dietary change may have played a role in countries other than the UK that have shared in the rise in asthma.

Possible Mechanisms of Adjuvancy

David Diaz-Sanchez
Associate Professor
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Los Angeles, U.S.A.

The observation that urbanisation is a major risk factor for allergy and asthma has been recognised since the middle of the 19th century. Although many factors are probably involved it seems clear that air pollution can affect human respiratory health. Research in this area has concentrated mainly on 3 primary areas: identification of the health effects (e.g. asthma), identification of responsible pollutants (e.g. ozone, diesel particles), and the likely mechanisms involved. Studies in this last area have led us to conclude that air pollutants may act through a common pathway, that of initiation of oxidative stress on multiple cell types leading to an inflammatory cascade that causes further generation of reactive oxygen species (ROS) and thus further inflammation. This concept has led to two new areas of study: what confers susceptibility to pollution and what intervention strategies can we devise to reduce the adverse effects of pollutants. One way to break the vicious circle of ROS generation and inflammation is to make a vigorous cytoprotective or antioxidant response to the pollutants. Our studies show that individuals who have fully functional forms of phase II detoxifying antioxidant enzymes are less sensitive to the pro-inflammatory and pro-allergenic effects of diesel exhaust particles (DEP) than those with non-functional forms. Thus, while DEP can augment allergen-specific IgE and histamine levels in nearly all allergic subjects, the levels in individuals with variants of gene polymorphisms that result in the absence of glutathione-S-transferase M1 (GSTM1) are up to 100 fold greater than in individuals with 'normal' variants. Given the importance of these antioxidant responses, we propose that an important future therapeutic strategy will be one that can augment the body's natural cytoprotective defenses.

Perspectives on Mechanisms - Dendritic Cell Subsets and Sensitisation to Inhaled Antigen

Bart N. Lambrecht
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Allergic asthma is one of the most common chronic diseases in Western society, characterised by variable airway obstruction, mucus hypersecretion and infiltration of the airway wall with Th2 cells, eosinophils, and mast cells. If we are to understand how this disease is initiated and devise new causal therapies for this disease, it is important to elucidate how Th2 cells are activated and respond to intrinsically harmless allergens. Dendritic cells (DCs) are the most important antigen presenting cells in the lung and are mainly recognised for their exceptional potential to generate a primary immune response and sensitisation to aeroallergens. Myeloid (m) DCs take up antigen in the airways and migrate to the mediastinal lymph nodes where T cell division is initiated in antigen specific T cells. At the same time plasmacytoid (p)DCs take up the antigen and mediate tolerance to the inhaled antigen. When pDCs are depleted from the lungs of mice, inhalation of harmless antigen leads to exclusive antigen presentation by mDCs and to stable Th2 priming and inflammatory lesions upon rechallenge with specific antigen. Therefore, adjuvant factors (diesel exhaust, viral infections, alum) might promote allergy by either enhancing the Th2 priming capacity of mDCs or by suppressing the tolerogenic capacities of pDCs.

Much less attention has been paid to the role of DCs in established inflammation. Based on functional studies in a murine model for asthma, we propose that DCs are equally essential for generating allergen specific effector Th2 responses in ongoing inflammation in sensitised mice. When CD11c+ DCs were depleted from the airways of mice during ongoing inflammation, Th2 cells no longer produced effector cytokines and asthma no longer developed. Therefore, some environmental agents known to exacerbate asthma might also work by enhancing the effector functions of DCs in already sensitised individuals, leading to a worsening of asthma symptoms.

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ECETOC WORKSHOP REPORTS

No.	Title
No. 1	Workshop on Availability, Interpretation and Use of Environmental Monitoring Data. 20-21 March 2003, Brussels
No. 2	Strategy Report on Challenges, Opportunities and Research Needs Arising from the Definition, Assessment and Management of Ecological Quality Status as Required by the EU Water Framework Directive Based on the Workshop EQS and WFD versus PNEC and REACH - Are They Doing the Job ? 27-28 November 2003, Budapest
No. 3	Workshop on Use of Human Data in Risk Assessment. 23-24 February 2004, Cardiff
No. 4	Influence of Maternal Toxicity in Studies on Developmental Toxicity. 2 March 2004, Berlin
No. 5	Workshop on Alternative Testing Approaches in Environmental Risk Assessment. 7-9 July 2004, Crécy-la-Chapelle