

## ANNEX 3

### RESULTS OF LITERATURE REVIEW: EFFECTS OF AIR POLLUTION ON CHILDREN'S HEALTH AND DEVELOPMENT

1. A literature search for publications relating to studies of the possible effects of exposure to air pollutants on children's health and development, appearing between January 2004 and January 2008 has been undertaken. The purpose of this exercise was to discover whether sufficient evidence has accumulated to call for changes in the opinions expressed in the WHO Report *"Effects of Air Pollution on Children's Health and Development: a Review of the Evidence"* published in 2005.

2. A detailed search for publications relating to

- Effects of air pollution on adverse pregnancy outcomes, subdivided by studies of effects on:
  - Intra-uterine growth retardation/reduction
  - Low birth weight
  - Prematurity/pre-term delivery
  - Infant mortality
  - Birth defects
- Effects of air pollution on the child's respiratory system
  - Asthma, allergies and respiratory symptoms/diseases
  - Lung function

has been undertaken.

The search strategy used is as follows:

#### SEARCH STRATEGY

This search was based on the WHO book *"Effects of Air Pollution on Children's Health and Development: a Review of the Evidence"*.

The search was limited to dates from January 2004- January 2008. (The WHO book was published in 2005).

Search terms:

air pollut\* AND children  
air pollut\* AND childhood

air pollut\* AND (intrauterine growth retardation OR IURG OR intrauterine growth reduction)  
air pollut\* AND (birthweight OR birth weight)

air pollut\* AND (prematurity OR preterm birth)

air pollut\* AND infant mortality

air pollut\* AND (lung function OR asthma OR allergies OR respiratory infection\*)

air pollut\* AND children AND cancer

air pollut\* AND childhood AND cancer

air pollut\* and neurodev\* AND children

air pollut\* AND neurobeh\* AND children

air pollut\* AND cognit\* AND children

### **Databases searched PUBMED AND TOXLINE only**

The entire search – including abstracts of all the papers identified is available on the COMEAP website.

3. A short summary of impressions gained by scanning the abstracts is provided here.

### **Intrauterine growth, low birth weight and prematurity/pre-term delivery**

4. Forty two abstracts relating to studies of effects on intrauterine growth, low birth weight and prematurity/pre-term delivery were identified. Studies have been undertaken in both developed and developing countries. In general, careful allowance for potential confounding factors has been made, especially as regards maternal smoking. Ambient levels of a number of pollutants have been found to be related to indices of retarded fetal development (e.g., low birth weight) and also to premature delivery. PM<sub>2.5</sub> figures strongly amongst pollutants found to have an effect. Not all studies demonstrated an effect, for example a careful study by Hansen *et al* (2007) found no strong evidence to suggest an association between air pollution during pregnancy and optimal fetal growth in Brisbane (Australia). But the majority of studies did find such an effect. Some studies sought to identify differential effects of various pollutants during the trimesters of pregnancy. Some progress has been made (Bell *et al*, 2007) but it seems too early to come to a clear view on this. Some workers have sought to look at the effect of genetic polymorphisms on sensitivity to air pollutants as reflected in pregnancy outcomes: both the GSTm1 and CYP/A1\*2C genes and the Msp1TC/CC and Ncol Ile/Val/Val/Val genotypes have been implicated (Sram *et al*, Suh *et al*). Exploring mechanisms of effect is difficult in studies such as reported here though effects on the vasculature have been reported. Pre-term delivery may be associated with an increase in production of prostaglandins, perhaps as a result of an inflammatory process. Our conclusion is that despite the fact that the evidence base remains not completely consistent and though the pollutants playing the largest part remain difficult or impossible to identify, the position has changed (we think) since the WHO report. Though causality

remains questionable the evidence relating to effects on fetal development now appears suggestive of causality.

### **Infant mortality**

5. Twenty one studies bearing on the possible effect of air pollutants on mortality rates amongst very young babies were found. The great majority of these studies support the assertion that exposure to air pollution is associated with an increased risk of death in this age group. A number of studies have focused upon indoor air pollution produced by burning biomass fuel for cooking and heating in developing countries.

6. One study (Hajat *et al*, 2007) has focused on effects in the UK and comprises a time-series analysis of air pollutants and infant mortality in 10 English cities over the period 1990-2000. The only pollutant found to be associated with infant mortality was sulphur dioxide [10  $\mu\text{g}/\text{m}^3$  increase in concentration, 24 hour average, associated with a RR of death of 1.02 (CI: 1.01-1.04)]. We conclude that evidence linking air pollution with infant mortality continues to accumulate. The pollutants playing the largest part are not yet clearly known: sulphur dioxide was stressed by Hajat *et al* (2007) but Woodruff *et al* (2008) in a recent paper from the United States (air pollution averaged over the first 2 months of life of all children born in US counties with > 250,000 residents: 2.5 million births and 6,639 post neonatal infant deaths) showed an association with  $\text{PM}_{10}$  (RR = 1.16 (CI = 1.06-1.27) per 10  $\mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{10}$ ). Interestingly, ozone was reported as being associated with deaths from sudden infant death syndrome (SIDS) (RR = 1.20 (CI = 1.09-1.32) for a 10 ppb (20  $\mu\text{g}/\text{m}^3$ ) increase in ozone concentration). We see no reason to dissent from the WHO view that exposure to air pollution may be associated with an increased risk of death in very young children.

### **Birth defects**

7. We found only 5 studies bearing on the possible effect of air pollution on birth defects. Only 1 (Gilboa *et al*, 2005) shows a clear effect: comparisons of highest and lowest quartiles of exposure (during weeks 3-8 of pregnancy) and occurrence of congenital heart defects revealed that  $\text{PM}_{10}$  and  $\text{SO}_2$  were associated with such defects. For ozone and carbon monoxide, inverse associations with septal defects were found. We conclude that this is a developing area in need of further work before a clear conclusion can be reached. In this, we agree with the findings of the WHO report: the evidence is insufficient to allow conclusions to be drawn.

## **Asthma, allergies and respiratory disease**

8. Two hundred and forty abstracts of publications appearing between January 2004 and January 2008 have been found. Not all relate to original studies: some reviews and methodological papers appear. However, this is a large body of evidence and before considering the findings we reprint, here, the conclusions of the WHO group:

*The evidence for a link between increased prevalence and incidence of cough and bronchitis and air pollution, particularly from particulates, was “sufficient to infer causality”. There is also sufficient evidence for a causal link between deficits in lung function and exposure to air pollution.*

*There was little evidence for a causal association between the prevalence/incidence of asthma and air pollution in general, though the evidence is suggestive for a causal association between the prevalence/incidence of asthma symptoms and living in close proximity to traffic. The evidence for an association between the prevalence/incidence of hay fever and exposure to traffic was “suggestive of causality”.*

*The evidence for an association between air pollution exposure and the frequency of hospital admissions or emergency department visits for asthma was “sufficient to infer causality”. These effects were seen for different traffic-related pollutants, including particulate matter and nitrogen dioxide.*

As before, our approach has been to discover whether recent work provides grounds for dissenting from these conclusions.

9. Two hundred and forty papers dealing with possible effects of air pollutants on children’s respiratory diseases were identified as having been published between January 2004 and January 2008. These varied widely in terms of the pollutants considered and the indices of childhood respiratory disease examined. A large number comprised questionnaire-based studies, others focused on admissions to hospital. A few studies looked at sensitivity to allergens in relation to ambient concentrations of air pollutants. A few, again, looked at air pollution and expired air NO concentration as an index of pulmonary inflammation. A small number of studies examined the conferral of increased sensitivity or susceptibility to effects of air pollutants by genotype variations.

10. The overwhelming impression gained is that the majority of studies have shown associations between ambient levels of air pollutants or exposure to pollutants (sometimes measured directly, in other cases estimated by proximity to roads or as counts of local traffic density) and indices of respiratory illness in children. Only a small number of studies lead to this association being questioned. One such study (Kuehni *et al*, 2006) considered the effects of possible over-reporting by parents of symptoms in children from families living near roads. The authors point out that only a small extent of over-reporting (10%) could explain associations of the magnitude commonly reported.

11. In examining these abstracts we have focused on those most likely to shed light on the effects of common ambient air pollutants. We have not focused on the effects of indoor burning of biomass in developing countries (though we think the indoor pollutants generated in this way may well have an effect on child health) or on the effects of chlorination by-products encountered at swimming pools: a statement on the possible effects of such pollutants has recently been placed on our website: "*Asthma and Exposure to Chlorine and Associated Reaction Products at Swimming Pools*" available at: <http://www.advisorybodies.doh.gov.uk/comeap/statementsreports/swimasthma2007.pdf>. We have also not considered in detail pollutants produced by volcanoes, by ice-surfacing machines at ice rinks or the high concentrations of sulphur dioxide sometimes associated with pulp mills. It is noted that a number of studies focus on indoor exposure to nitrogen dioxide produced by unflued heating devices and other gas appliances. We note that indoor concentrations of nitrogen dioxide can often exceed those found outdoors.

12. Some 97 of the 240 abstracts identified report associations between ambient levels of air pollution and indices of respiratory disease. These studies come from both developed and developing countries. There is an emphasis on the effects of traffic-generated air pollutants and, in some, carbon monoxide concentrations as used as an index of traffic-generated pollutants. It is not possible to separate out the effects of the various components of the traffic-generated mixture: a number of studies focus on particles (PM<sub>10</sub>, PM<sub>2.5</sub>) and the authors seem to regard these as the major causative agent. As in the past, the role of nitrogen dioxide is unclear: some authors see it as a toxicologically active air pollutant (and refer to indoor studies which stress possible effects of nitrogen dioxide) whilst others continue to see it as an index of or surrogate for the traffic-generated pollution mixture. Causality is difficult to establish but the study by Bayer-Oglesby *et al* (2005) which showed that a reduction in air pollution exposures was associated with an improvement in respiratory health in children seems especially suggestive of an effect of air pollutants on respiratory symptoms. Interestingly, a decline in PM<sub>10</sub> was associated with a decline in the presence of chronic cough (OR for decline in PM<sub>10</sub> of 10 µg/m<sup>3</sup>: 0.65 (95% CI: 0.54-0.79)). This suggests that particulate air pollution plays a part in maintaining a state of airway irritation.

13. Intervention studies can provide powerful support for the causality of observed associations between air pollutants and ill-health. The study from Romania (Cara *et al*, 2007) reported the effects of closing an “iron, steel and coke factory”. A significant reduction in wheeze in early life was reported. The authors do not equate wheeze with asthma but the conclusion that air pollution was playing a part in maintaining airway irritation and thus bronchoconstriction is difficult to avoid. A study by El-Zein *et al* (2007) reported the effects on health of a ban on diesel-powered vehicles. A significant fall in respiratory admissions amongst the < 17 age group occurred in the first year of the ban. The effects of the ban became insignificant in the second year. No data on air pollution levels before or after the ban were available.

14. A number of studies have looked at the effects of genotype variation (polymorphisms) or susceptibility to air pollutants (e.g., Li *et al*, 2006; Islam *et al*, 2007; Salam *et al*, 2007; Ramirez-Aguilar *et al*, 2006). Attention has been focused on genotypes where anti-oxidant responses are impaired. An increased sensitivity to ozone has been observed in such cases. Interestingly the reference by Islam *et al* (2007) suggests that anti-oxidant gene activity provides defence against only rather low concentrations of ozone.

15. References by Yu *et al* (2005), Carbajal-Arroya *et al* (2007), Annesi-Maesano *et al* (2007) and Bener *et al* (2007) (but not Endre *et al*, 2007) suggest that exposure to air pollutants increases the likelihood of development of allergic disease. A study by Oftedal *et al* (2007) did not find this effect.

16. In conclusion, we find no reason to dissent from the conclusions of the WHO report as listed above. Air pollution probably plays a causal role (albeit not a large one – generally) in respiratory admissions to hospital, for disease including asthma, amongst children. That exposure to air pollutants actually causes asthma remains uncertain though the evidence regarding its effects on likelihood of primary sensitisation to allergens is suggestive.

### **Effects of air pollutants on lung function in children**

17. We have identified 40 publications referring to effects of air pollutants on indices of lung function in children appearing between January 2004 and January 2008. Some focus on effects of living near sources of pollutants, commonly roads; others involve cross-sectional designs and in a limited number of cases cohorts have been studied. The overwhelming conclusion of these studies is that exposure to ambient concentrations of air pollutants leads to a reduction in indices of lung function. In many instances the concentrations of the air pollutants studied are similar to those found in the UK today.

18. Workers have tended to focus on pollutants of most concern in the localities studied. Studies focusing on roads emphasise particles and oxides of

nitrogen. In a few cases carbon monoxide is mentioned but only in the context of it being an index of traffic-generated air pollutants. Studies from California (Gauderman *et al*, 2004; Gauderman *et al* 2007 and Islam *et al*, 2007) have focused on pollutants found on the North American west coast: ozone, nitrogen oxides and acid are stressed. PM<sub>2.5</sub> is also included in these studies. These studies (Californian Children's Health Study: several publications) are important as they follow a cohort of children growing up from 10 to 18 years of age. Living in relatively polluted areas was found to depress growth of lung function.

19. The Californian Children's Health Study also included a study of the development of new cases of asthma in a cohort of children not suffering from asthma at age 10. The authors reported that a reduction in development of lung function was associated with an increased risk of developing asthma (Islam *et al*, 2007). This led them to argue that a protective effect of good airway development was diminished by exposure to air pollutants.

20. A particularly important study by Oftedal *et al* (2008) has been published. The authors focused on modelling individual exposure to outdoor air pollutants and found significant effects of both long-term and short-term exposure to nitrogen dioxide. No short-term effect of PM was reported but, interestingly, the short-term effects of nitrogen dioxide become stronger with increasing time lags. The effects were seen on peak forced expiratory flow (PEF) but no effect on forced volumes (FEV<sub>1</sub>) were reported.

21. In conclusion, we see no reason to dissent from the WHO view that exposure to air pollutants can impair development of lung function in children.

## **References (Numbers refer to the number of the reference as listed in the literature search)**

### **Intrauterine growth retardation, low birth weight, prematurity/pre-term birth**

(14)

Bell ML, Ebisu K, Belanger K. Ambient air pollution and low birth weight in Connecticut and Massachusetts. *Environ Health Perspect.* 2007 Jul;115(7):1118-24.

(12)

Hansen C, Neller A, Williams G, Simpson R. Low levels of ambient air pollution during pregnancy and fetal growth among term neonates among term neonates in Brisbane, Australia. *Environ Res.* 2007 Mar;103(3):383-9. Epub 2006 Aug 4.

(20)

Sram RJ, Binkova B, Dejmek J, Chvatalova I, Solansky I, Topinka J. Association of DNA adducts and genotypes with birth weight. *Mutat Res.* 2006 Sep 28;608(2):121-8. Epub Jul 11.

(22)

Suh YJ, Kim BM, Park BH, Park H, Kim YJ, Kim H, Hong YC, Ha EH. Cytochrome P450IA1 polymorphisms along with PM(10) exposure contribute to the risk of birth weight reduction. *Reprod Toxicol.* 2007 Nov-Dec; 24(3-4):281-8. Epub 2007 Jul 7.

### **Infant mortality**

(1)

Hajat S, Armstrong B, Wilkinson P, Busby A, Dolk H. Outdoor air pollution and infant mortality: analysis of daily time-series data in 10 English cities. *J Epidemiol Community Health.* 2007 Aug;61(8):719-22.

(2)

Woodruff TJ, Darrow LA, Parker JD. Air pollution and postneonatal infant mortality in the United States, 1999-2002. *Environ Health Perspect.* 2008 Jan;116(1):110-5.

### **Birth defects**

(1)

Gilboa SM, Mendola P, Olshan AF, Harness C, Loomis D, Langlois PH, Savitz DA, Herring AH. Comparison of residential geocoding methods in population-based study of air quality and birth defects. *Environ Res.* 2006 Jun;101(2):256-62. Epub 2006 Feb 17.

### **Asthma, allergies and respiratory symptoms/diseases**

(77)

Annesi-Maesano I, Moreau D, Caillaud D, Lavaud F, Le Moullec Y, Taytard A, Pauli G, Charpin D. Residential proximity fine particles related to allergic sensitisation and asthma in primary school children. *Respir Med.* 2007 Aug;101(8):1721-9. Epub 2007 Apr 17.

(177)

Bayer-Oglesby L, Grize L, Gassner M, Takken-Sahli K, Sennhauser FH, Neu U, Schindler C, Braun-Fahrlander C. Decline of ambient air pollution levels and improved respiratory health in Swiss children. *Environ Health Perspect.* 2005 Nov;113(11):1632-7.

(78)

Bener A, Ehlayel M, Sabbah A. The pattern and genetics of pediatric extrinsic asthma risk factors in polluted environment. *Allerg Immunol (Paris)*. 2007 Feb;39(2):58-63.

(48)

Câra AC, Buntinx F, Van den Akker M, Dinant GJ, Manolovici C. Industrial air pollution and children's respiratory health: a natural experiment in Călărași. *Eur J Gen Pract*. 2007;13(3):135-43.

(76)

Carbajal-Arroyo L, Barraza-Villarreal A, Durand-Pardo R, Moreno-Macías H, Espinoza-Laín R, Chiarella-Ortigosa P, Romieu I. Impact of traffic flow on the asthma prevalence among school children in Lima, Peru. *Asthma*. 2007 Apr;44(3):197-202.

(63)

El-Zein A, Nuwayhid I, El-Fadel M, Mroueh S. Did a ban on diesel-fuel reduce emergency respiratory admissions for children? *Sci Total Environ*. 2007 Oct 1;384(1-3):134-40. Epub 2007 Jul 30.

(91)

Endre L, Láng S, Vámos A, Bobvos J, Páldy A, Farkas I, Collinsné Horváth Z, Varró MJ. [Increase in prevalence of childhood asthma in Budapest between 1995 and 2003: correlation with air pollution data and total pollen count] [Article in Hungarian] *Orv Hetil*. 2007 Feb 4;148(5):211-6.

(36)

Islam T, McConnell R, Gauderman WJ, Avol E, Peters JM, Gilliland FD. Ozone, Oxidant Defense Genes and Risk of Asthma During Adolescence. *Am J Respir Crit Care Med*. 2007 Nov 29 [Epub ahead of print]

(128)

Kuehni CE, Strippoli MP, Zwahlen M, Silverman M. Association between reported exposure to road traffic and respiratory symptoms in children: evidence of bias. *Int J Epidemiol*. 2006 Jun;35(3):779-86. Epub 2006 Mar 2.

(22)

Li YF, Gauderman WJ, Avol E, Dubeau L, Gilliland FD. Associations of tumor necrosis factor G-308A with childhood asthma and wheezing. *Am J Respir Crit Care Med*. 2006 May 1;173(9):970-6. Epub 2006 Feb 2.

(46)

Oftedal B, Brunekreef B, Nystad W, Nafstad P. Residential outdoor air pollution and allergen sensitization in schoolchildren in Oslo, Norway. *Clin Exp Allergy*. 2007 Nov;37(11):1632-40. Epub 2007 Sep 17.

(96)

Ramirez-Aguilar M, Sienna-Monge JJ, Moreno-Macías H, del Rio-Navarro BE, David G, Marzec J, Hernández-Avila M, London S. GSTM1 and GSTP1 and respiratory health in asthmatic children exposed to ozone. *Eur Respir J*. 2006 Nov;28(5):953-9. Epub 2006 Jul 26.

(57)

Salam MT, Gauderman WJ, McConnell R, Lin PC, Gilliland FD. Transforming growth factor- 1 C-509T polymorphism, oxidant stress, and early-onset childhood asthma. *Am J Respir Crit Care Med*. 2007 Dec 15;176(12):1192-9. Epub 2007 Aug 2.

(10)

Yu JH, Lue KH, Sun HL, Lin YH, Chou MC. The relationship of air pollution to the prevalence of allergic diseases in Taichung and Chu-Shan in 2002. *J Microbiol Immunol Infect*. 2005 Apr;38(2):123-6.

### **Lung function**

(8)

Gauderman WJ, Avol E, Gilliland F, Vora H, Thomas D, Berhane K, McConnell R, Kuenzli N, Lurmann F, Rappaport E, Margolis H, Bates D, Peters J. The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med*. 2004 Sep 9;351(11):1057-67. Erratum in: *Engl J Med*. 2005 Mar 24;352(12):1276. Comment in: *N Engl J Med*. 2004 Dec 16;351(25):2652-3; author reply 2652-3. *N Engl J Med*. 2004 Dec 16;351(25):2652-3; author reply 2652-3. *N Engl J Med*. 2004 Dec 16;351(25):2652-3; author reply 2652-3. *N Engl J Med*. 2004 Sep 9;351(11):1132-4.

(18)

Gauderman WJ, Vora H, McConnell R, Berhane K, Gilliland F, Thomas D, Lurmann F, Avol E, Kunzli N, Jerrett M, Peters J. Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. *Lancet*. 2007 Feb 17;369(9561):571-7. Comment in: *Lancet*. 2007 Feb 17;369(9561):535-7.

(31)

Islam T, Gauderman WJ, Berhane K, McConnell R, Avol E, Peters JM, Gilliland FD. Relationship between air pollution, lung function and asthma in adolescents. *Thorax*. 2007 Nov;62(11):957-63. Epub 2007 May 21.