

## ANNEX 5

### WHO conclusions for neurobehavioural impacts of air pollutants

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The original conclusions published by the World Health Organization in 2005 (WHO report “Effects of Air Pollution on Children’s Health and Development: a Review of the Evidence”) are included in bold, followed by a summary of the recent literature and a conclusion/recommendation. At the end of the document a list of future considerations has been included.

**Lead. Primarily based on the large number of well-controlled prospective studies covering prenatal and postnatal exposure, there is considered to be *sufficient* evidence that neurobehavioural deficit in terms of cognitive impairment is caused by developmental exposure at low environmental levels.**

An increasing number of studies published since the WHO report (2005) support the conclusion that neurodevelopmental effects of lead exposure occur at concentrations well below the presumed critical level of 100 µg/l blood. Lanphear et al. (2005) suggest that “the current effects of lead exposure on human brain development could be even greater than previously thought.”

Adverse neurodevelopmental effects of low level lead (<100 µg/l in blood) arise from both prenatal (Hu et al., 2006; Ronchetti et al., 2006; Schnaas et al., 2006) and postnatal (Chiodo et al., 2004; Despres et al., 2005; Min et al., 2007) exposures. Chiodo et al. (2004) reported associations between neurobehavioural impairment and blood lead levels as low as 30 µg/l and concluded that there was no apparent lower threshold for postnatal lead exposure. Similarly, there was no evidence of a threshold dose in the study by Schnaas et al. (2006) which examined the effects of prenatal lead exposure on the IQ of children tested at 6-10 years of age; the greatest impairment on IQ occurred within the first few micrograms of blood lead measured.

The first trimester of pregnancy appears to be the most critical in terms of lead exposure and impairment to mental development, when conducting direct comparisons of all trimesters (Hu et al., 2006), although positive associations of lead and IQ deficits are still evident when only measuring exposures beyond 12 weeks of pregnancy (Schnaas et al., 2006).

These latest findings suggest the establishment of lower action limits for lead exposure during pregnancy and infancy. Hu et al. (2006) proposed the consideration of pre-pregnancy interventions to prevent neurotoxic effects of lead in the fetus. Certainly, follow-up data from a trial of chelation therapy in children aged 7 years with previous blood lead levels >100 µg/l showed no benefit in neurodevelopment (Dietrich et al., 2004), supporting the conclusions

of Schnaas and colleagues (2006), that lead exposure may result in “lasting and possibly permanent effects”.

- CONCLUSION – RECENT LITERATURE SUPPORTS ORIGINAL WHO CONCLUSION FOR LEAD

**Organic mercury. The evidence that developmental exposure is causally linked with neurobehavioural deficit is considered to be *suggestive*. This is due to the fact that two large prospective studies in children from fish-eating populations arrived at conflicting findings.**

The two large prospective studies referred to in the WHO report are the Seychelles Child Development Study (Davidson *et al.*, 1998; Myers *et al.*, 2003) and the Faeroe Islands study (Grandjean *et al.*, 1997). Both studies have been reviewed on several occasions [e.g. reports by the Agency for Toxic Substances and Disease Registry (ATSDR, 1999) and the National Institute of Environmental Health Sciences (NIEHS, 1998)], and have been found to be of sound scientific merit. The Seychelles study examined an initial cohort of 779 children five times after birth at 6, 19, 29, 66 and 107 months, while the Faeroe Islands study examined children at 7 and 14 years (n=435). For the Seychelles study, although 46 different primary endpoints were measured across five ages, only 1 neurological endpoint proved to demonstrate a positive adverse association with prenatal methylmercury exposure (Myers *et al.*, 2003). In contrast, the Faeroe Island study demonstrated adverse associations between prenatal methylmercury and tests of memory, attention, language and visual spatial perception at 7 years of age (Grandjean *et al.*, 1997).

Davidson *et al.* (2004) have analysed differences between these studies, finding that the Seychelles children received their methylmercury exposure predominantly from daily fish consumption, while in the Faeroe Islands exposure resulted from episodes of pilot whale meat consumption; they suggest that ‘it is possible that the delivery of a high intermittent dose of MeHg may effect CNS development differently than daily low-dose exposure, although this hypothesis has yet to be tested’ (Davidson *et al.*, 2004). Near daily fish consumption was comparable to that consumed by the general population in the USA, and as such the authors speculated that the results of the Seychelles study may be of more relevance to public health (Myers *et al.*, 2003). However, Grandjean has revealed that frozen and dried portions of whale meat were consumed by the Faeroe Island study participants over extended periods of time (Stern *et al.*, 2004), thus questioning the occurrence of “high intermittent doses” of methylmercury. Furthermore, the influence of such high doses appears to be comparable between the Seychelles and Faeroe Island studies when examining mercury concentrations in pregnancy-period maternal hair (Stern *et al.*, 2004). Thus, daily low-dose versus intermittent high-dose of methylmercury does not appear to account for the differences between the two studies.

The two studies also differ in that the Seychelles study used only maternal hair, while the Faeroe Islands study used both maternal hair and cord blood, to assess *in utero* exposure. However, using hair samples alone, adverse associations of methylmercury and neurodevelopment could still be demonstrated in the Faeroe Islands study, though they were weaker (Grandjean *et al.*, 1997). Pilot whale meat and blubber also contains polychlorinated biphenyls (PCBs), exposure to which was not detected in the Seychelles. The authors of the Faeroe Island study subsequently published a paper suggesting that PCBs may interact with and therefore potentiate methylmercury-induced toxicity, although methylmercury toxicity remains significant even after correcting for PCBs (Grandjean *et al.*, 2001). Grandjean and colleagues (2001) suggest that detection of PCB in cord tissue requires validation to establish whether this exposure assessment is indicative of PCBs in the child.

In 2000, the National Research Council (NRC) concluded that sufficient evidence was available to concur with the US Environmental Protection Agency's recommendation to lower the reference dose for methylmercury from 0.5 to 0.1 µg/kg/day (NRC, 2000). However, researchers of the Seychelles study indicated that this conclusion preceded the report by the Faeroe Island authors that PCBs might confound the assessed effects of methylmercury from whale meat, and furthermore, they suggested that the findings of the Seychelles study supersede those of the NRC committee (Myers *et al.*, 2003; Davidson *et al.*, 2004). In a response by the NRC (Stern *et al.*, 2004) it states "failure to detect adverse effects in the Seychelles study could well be due to the substantial sample-to-sample variation expected when trying to identify relatively subtle effects on development in an inherently "noisy" system of complex, multi-determined neurobehavioural end points."

An update of the Seychelles study was published by van Wijngaarden *et al.*, 2006. The results of this 9-year follow-up study suggested that as the children matured in the Seychelles, the neurodevelopmental associations with prenatal MeHg exposure were detectable at lower exposures (~4.5 ppm lower than previous reports suggested). In addition, neurobehavioral endpoints appeared to become more sensitive and specific as the children matured, thus enhancing the ability of the authors to detect the effects of the prenatal MeHg exposure. The extended data set suggested that while there was little evidence for an adverse effect of methyl mercury on neurobehavioural parameters across most of the range of maternal hair mercury levels measured, at the highest exposure concentrations mercury exposure appeared to impact neurobehavioral development. This study is scheduled to continue and aims to follow-up the cohort to assess the impact of prenatal exposure on the potential late appearing health effects in adolescence and young adulthood.

Both the Seychelles and Faeroe Islands studies assessed neurodevelopmental status using the Bender Visual Motor Gestalt Test, however the method of test administration and scoring was different between each study. Therefore, Davidson *et al.* (2008) repeated the test on children from the Seychelles study using the same test and scoring protocol as used in

the Faeroe Islands. In this study, no association was detected for all children between prenatal methylmercury exposure and the ability to copy geometric figures (Copying Task), which differed to the results of the Faeroe Island study. Note, however, that the effect was significant for females; no explanation for this result is provided. Davidson *et al.* (2008) did find a significant association between methylmercury and Reproductive Task scores, which test spatial memory, however, this association was lost on removal of an outlier. The Faeroe Island study demonstrated an adverse association with the Reproductive Tasks at lower methylmercury concentrations than those encountered in the Seychelles study (Grandjean *et al.*, 1997). Therefore, in general the results of the Seychelles follow-up study remain similar to previous reports regardless of the task protocol and scoring employed, and the authors conclude a lack of association between methylmercury exposure and neurobehavioural development Davidson *et al.* (2008).

A cross-sectional cohort study of 82 children (mean age 7.2 years) published by Ip *et al.*, 2004 provides evidence that environmental mercury exposure, as measured in hair and blood, is not associated with an increased incidence of autism. Kwok-Kueng *et al.* (2007) includes a meta-analysis of the correlation of hair mercury with reference markers (urine, cord blood and blood) in epidemiological studies. The measurements of hair mercury were found to be correlated with blood and cord blood, but the epidemiological evidence indicated no link between mercury poisoning and autism.

Further evidence in support of adverse neurodevelopmental effects associated with methylmercury exposure was published by Trasande *et al.* in 2006. This study used data from two previously published dose-response models to aggregate the loss in cognition with methyl mercury pollution attributable to coal-fired power plant pollution. They concluded prenatal exposure to MeHg results in significant reductions in children's IQ.

Gao and co-workers' recent study (2007) examined the impact of prenatal MeHg exposure on neurobehavioral development in the Chinese population, and conducted neonatal behavioural neurological assessments in 384 3-day-old babies. Mercury levels in maternal hair and umbilical cord blood were much lower (4- to 5-fold less) than reported in either the Seychelles or Faeroe Island studies. Increased prenatal mercury exposure was associated with impaired neurobehavioral function in males, but not in females. The authors conclude that the gender-specific results may be due to chance, and recommend long-term follow-up studies.

All researchers in this area agree the need to continue investigation into the most appropriate derivation of safe exposure levels to methylmercury.

- PROPOSED CONCLUSION: EVIDENCE FOR A LINK BETWEEN METHYL MERCURY AND NEURODEVELOPMENTAL EFFECTS IN CHILDREN REMAINS SUGGESTIVE, BUT EVIDENCE APPEARS TO BE MOUNTING TO STRENGTHEN THIS CONCLUSION.

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**Manganese. The evidence for a link between developmental exposure of children at environmental levels and neurobehavioural adversity is considered *insufficient*, owing to the limited data available to date.**

Ericson et al. (2007) examined the potential for prenatal manganese to cause neurobehavioural deficits in 27 children randomly selected from a prospective longitudinal study of development that began in the USA in 1991. Children with higher prenatal manganese levels, assessed by tooth enamel deposits dating to the 20<sup>th</sup> gestational week (n=27), showed significant increases in behavioural disinhibition, including hyperactive, impulsive, and inattentive traits, at ages ranging from 3-9 years. The authors attribute these adverse effects of manganese to dopaminergic perturbation, since manganese preferentially affects dopaminergic networks; reduced numbers and/or dysfunction of dopaminergic neurons can give rise to behavioural disinhibition, a symptom of attention deficit-hyperactivity disorder (ADHD). No effects on cognitive function were observed in the children studied.

In a review article by Soldin and Aschner (2007), evidence is presented for manganese-induced toxicity during brain development, although the authors acknowledge data are currently sparse. They hypothesise that, in addition to dopaminergic networks, disruption of thyroid hormones contributes to the neurodevelopmental effects of prenatal manganese, and call for further experimental exploration.

- CONCLUSION: RECENT LITERATURE SUPPORTS ORIGINAL WHO CONCLUSION FOR MANGANESE.

IT IS NOTED THAT INGESTION IS LIKELY TO BE THE MAJOR ROUTE OF INTAKE OF MANGANESE. INTAKE BY INHALATION IS LIKELY TO BE SMALL BUT WE HAVE NOT ATTEMPTED TO QUANTIFY THIS.

**Environmental PCBs.** The evidence from prospective cohort studies linking early developmental exposure to neurobehavioural deficit in terms of cognitive, neurological or psychomotor development is considered *suggestive*. This evaluation considers the fact that, (a) not all of the published studies have documented a coherent spectrum of neurobehavioural deficit; (b) neurodevelopmental adversity has been documented relative to PCB levels in different matrices (e.g. milk, cord serum and maternal serum); and (c) owing to inevitable co-exposure to other members of the PHAH family, such as the dibenzo-*p*-dioxins, it is difficult to clearly identify the PCBs as the only causative agent.

Chevrier et al. (2007) investigated the relationship between maternal blood PCBs and thyroid-stimulating hormone (TSH) levels in children shortly after birth. Thyroid hormones are known to be essential for neurological development, and it has been suggested that PCBs may impact on neurodevelopment via disruption of thyroid hormone. The authors looked at the combined effects of all 34 PCBs measured, as well as grouping the PCBs according to their ability to induce specific biotransformation enzymes. Total PCB levels were not associated with changes in blood TSH. In contrast there was a positive association between exposure to those PCBs thought to induce uridinediphosphate glucuronosyltransferase (UDP-GT) and neonatal blood TSH. This study provides a feasible mechanistic explanation as to how PCBs may impact on neurological development of children, but requires further work to link this mechanistic endpoint to an actual neurological endpoint. Importantly, the findings argue against summing all PCBs when examining exposures, and supports grouping PCBs based on their potential mechanism of action.

A study by Nakajima et al. (2006) investigated the effect of prenatal exposure to background levels of PCBs and dioxins on infant neurodevelopment in Japan/Sapporo (n=134 infant-mother pairs). A number of polychlorinated dibenzo-*p*-dioxin (PCDD) isomers, total PCDD isomers and total PCDD/polychlorinated dibenzofurans (PCDFs) were negatively associated with a mental development index. Some specific isomers of PCDD and PCDFs were also found to be negatively associated with psychomotor development indices. The authors suggest their results indicate that, for several isomers of dioxins, exposure during the prenatal period is more likely to affect motor than mental development.

- **CONCLUSION – RECENT LITERATURE SUPPORTS ORIGINAL WHO CONCLUSION FOR PCBs**

## **Black Carbon**

The WHO report does not review any literature pertaining to the effects of carbon particles on neurobehavioural development. A recent paper by Suglia et al. (2008) indicates that black carbon is associated with decreases in cognitive function for both verbal and nonverbal intelligence and memory tests. This study used Boston children from a prospective birth cohort study

(1986-2001) (n=202; average age 9.7 years). Local black carbon concentrations were estimated using a spatiotemporal land-use regression model that predicted traffic exposure using data from 80 locations in the Greater Boston area. The authors suggest that black carbon may be acting as a surrogate marker for other traffic particles; thus, toxicity may not be due to black carbon *per se*. However, numerous *in vitro* and *in vivo* animal studies have shown that black carbon can increase oxidative stress and induce inflammatory processes (e.g. Stone et al., 2007), which would have deleterious effects on cells of the central nervous system. Furthermore, ultrafine particles can be translocated from the lung to other organs, including the brain, as well as direct olfactory nerve translocation from the nose to the brain (Elder et al., 2006). This route of access to the brain has, as yet, only been demonstrated in animal models. It is, however, possible that translocation along nerve fibres could also occur in man.

### **PAH**

A study by Perera et al. (2006) investigated prenatal exposure to the pollutants polycyclic aromatic hydrocarbons (PAHs), environmental tobacco smoke (ETS) and pesticides, and subsequent impact upon neurobehavioural development of New York children. High prenatal exposure to PAHs was not associated with psychomotor development, but it was associated with lower mental development, which increased with age. The authors argued that further work is required to confirm these findings.

Perera et al. (2007) also measured the impact of PAH exposure to New York children born 1 month after the 9/11 event and who resided within a 1 mile radius of the World Trade Centre. Elevated PAH exposure, in conjunction with environmental tobacco smoke exposure, appeared to be associated with a modest reduction in cognitive development (neither induced a significant effect alone), suggesting that the effects of ambient air pollution PAHs may interact with other pollutant types/sources. However, maternal stress during pregnancy is known to decrease infant mental development and could be a confounding factor in this study. Exposure to other substances released by the collapse of the buildings could also have played a part.

### **Mixtures**

A study by Windham et al. (2006) examined incidence of autism spectrum disorders (ASD) and exposure to hazardous air pollutants in children born to mothers resident at delivery in San Francisco Bay counties. Importantly, this study looked at mixtures of compounds – a total of 25 in all – which is likely to be of greater relevance to humans than focussing on only those compounds with probable neurotoxic effects in isolation. The data are suggestive of a link between autism and ambient air concentrations of metals, and possibility chlorinated solvents. A moderate association was found with higher diesel particulate matter levels, which the authors suggest may be partly due to correlation with metals. A limitation of this study is that air pollutants were in fact measured in 1996, and were assumed to be similar in 1994, the year births occurred. Also, the authors have no data on mothers' location during

the first trimester of pregnancy, which may be the most critical for autism (Arndt et al., 2005).

### Future Considerations

- Long-term follow-up studies are warranted to determine whether prenatal exposure to air pollutants permanently reduces or merely slows neurodevelopment.
- Further *in vitro* models and *in vivo* animal studies are required to assess routes of exposures to air pollutants: whether these cross the placenta for *in utero* exposure; oral and inhalational route translocation to the brain, including olfactory nerve transport, in the postnatal developing nervous system.
- Mechanisms of neural toxicity should be elucidated in *in vitro* models and *in vivo* animal studies, and determination of whether individual susceptibility to toxicity is attributed to genetic polymorphisms in those genes involved.

The authors of various studies included in this report have identified the need to examine whether the early-life neurobehavioural deficits are maintained in adulthood, and we await these follow-up data with interest. The exposure and mechanistic studies should be conducted in relation to mixtures of compounds, and not be confined to previously established neurotoxicants. In addition to synergistic and/or additive interactions between chemicals, animal studies suggest that a general inflammatory response to air pollution occurs in the brain (Tin-Tin-Win-Shwe et al., 2006), which may impact on neurodevelopment. If this translates to children, then the collective pollutant load will better predict response as opposed to levels of single chemicals.

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