Environmental pollution

Protecting our unborn children: how to measure exposure to thousands of chemicals?

J Tuomisto

First perspective on the paper by Ortega García *et al*
(see page 642)

For 30 years cancers have been the most feared diseases linked to environmental chemicals. Recently developmental effects, especially those of the central nervous system, appear to have taken their place at least in part. Both the chemicals involved and the ways of exposure are manifold. Methyl mercury, polychlorinated biphenyls (PCBs), and dioxins derive from fish. Lead comes from multiple sources, historically from leaded gasoline and paints, in some countries also from plumbing. Polybrominated diphenyl-ethers are added to synthetic materials as flame retardants. We are exposed to pesticide residues in our food as well as in our home environment.

Most of these potential new dangers are plagued with controversy. In many cases it is a question of dose. There is no doubt about the developmental neurotoxicity of lead or methyl mercury, but are the present environmental exposures high enough to cause risk? In some cases there are disputes on plausible mechanisms. Such is the case with effects based on endocrine disruption. Is sufficient disturbance of oestrogen or the thyroid hormone system likely, if we are exposed to environmental chemicals which are orders of magnitude weaker than natural hormones, or to chemicals having weak effects on hormone synthesis or metabolism? One of the tricky questions is: When? An otherwise innocuous exposure might be important at a certain developmental stage, within a time window perhaps only lasting a few days during embryonic or fetal development. All of these questions wait for reliable and plausible scientific answers.

There are great uncertainties on the best measures of exposure to environmental contaminants as recently spelled out by Spurgeon with regard to methyl mercury.¹ A dozen good quality epidemiological studies using cord blood, maternal hair, or child hair as a proxy of mercury exposure were reviewed. Yet it was not possible to determine whether there is an association between prenatal

exposure to methyl mercury from seafood and adverse neurodevelopmental effects in children. This is 50 years after the Minamata disaster showed clear adverse outcomes at high exposure levels.²

There are some 50 000–100 000 commercial chemicals in use in different countries. The most important determinant of risk from these chemicals is the likelihood and level of human exposure. Without exposure there can be no risk. Therefore more important than a mere number of chemicals, is relevant information on people being exposed to them. This is all the more important when we try to assess the risks during fetal life.

It is often stated that fetuses or newborns are more sensitive than adults. This is sometimes true, sometimes not. It is obvious that chemicals interfering with critical stages of development may be more toxic, or even only toxic, during these sensitive periods. An example is again methyl mercury, which disturbs migration of neurones in the developing central nervous system.³ Also, disturbances of thyroid hormone metabolism have much more striking effects on the developing than the adult central nervous system;⁴ in fact, they affect development in general. This is most dramatically seen in developing frogs as profound disturbances of metamorphosis. An essential feature of frog metamorphosis is a synchronised hormone–receptor–tissue interaction,⁵ and desynchronisation of developmental steps may lead to severe morphological and functional abnormalities.

On the other hand, the fetus is protected by several mechanisms. The placental barrier protects against many polar compounds whose concentrations are therefore lower in the fetus than in the mother. Due to misunderstood pharmacokinetics, the fetus is in some cases thought of being excessively sensitive. Dioxins cause developmental effects in animals at doses not toxic to the dam, and yet the concentrations are much lower in the fetus. However, dioxins as lipophilic compounds are

stored in fat, and because fetal fat content is much lower than adult fat content, it is natural that total dioxin concentration is low.⁶ The problem is that we have very little information on the active free concentrations of dioxins and other toxic compounds in the fetus.

Different contaminants are pharmacokinetically very different. Many pesticides and several potential endocrine disruptors such as phthalates and polyphe-nols have a short half life. This means that the timing of the sample used as a proxy for fetal concentration is very critical. Cord blood, for instance, may not reflect the concentration in fetus during the critical time window. The half-life of mercury is longer, but it is doubtful if total mercury concentrations of hair or blood samples reflect accurately the exposure to methyl mercury which seems to be more crucial than total mercury.¹ Some pesticides such as DDT and its metabolite p,p'-DDE, as well as dioxins and PCBs, have long half-lives, sometimes of many years. Therefore timing is not so crucial. These fat soluble non-polar compounds also like fat, and the concentrations in different tissues are very similar, if expressed per gram fat. This has enabled us to use breast milk, serum, adipose tissue, or placental concentrations of dioxins to some extent interchangeably for expressing maternal levels.⁷

Exposure assessment is not easy with most environmental neurotoxins. Therefore novel methods are urgently needed to help us to solve the controversies. Meconium, the first greenish faeces of a newborn, has been used to some extent in analysing cocaine to reveal maternal abuse,⁸ cotinine to indicate maternal smoking,⁹ and pesticides to show exposure during fetal life.^{10–12} Xenobiotics are assumed to enter the meconium in bile and swallowed amniotic fluid. Meconium is reported to accumulate, starting between 12th and 16th week of pregnancy, and as a sticky substance its contents remain fairly stable over the months, reflecting exposures from the second trimester of pregnancy through delivery.^{13, 14} The advantages of meconium are ease and the non-invasive nature of collection. Furthermore, the analytical sensitivity for many compounds is better than when using urine or cord blood samples.

In an interesting pilot study, Ortega García *et al* have divided meconium into three parts: 0–10 hours, 10–24 hours, and 24–48 hours after birth.¹⁵ Concentrations of some environmental contaminants such as some congeners of PCBs, hexachlorobenzene, and β -hexachlorocyclohexane increase from the first meconium stool to the third, perhaps enabling the timing of the

highest exposure of the fetus to be determined. However, as PCB concentrations in the mother do not vary to a marked extent within a time frame of some months, this cannot be the reason for the increase. One should then assume either an increased penetration to the fetus during late pregnancy, or disappearance of the chemicals from meconium over time.

It is a pity that the authors¹⁵ did not measure fat content of the meconium samples in order to be able to express the lipid soluble chemicals on a lipid basis. This would help the reader to compare the concentrations with previous studies on maternal concentrations of the same chemicals. In a very limited study, cord blood concentrations of dioxins were in the same range as those in meconium when both were expressed per lipid.⁷ Current information on fetal or neonatal concentrations of persistent environmental chemicals is very patchy, because for ethical and technical reasons samples are not easy to obtain. Therefore all efforts to find novel tools for this research are valuable. After careful validation studies, meconium might be another tool to help environmental health researchers solve

these overwhelmingly difficult issues on children's health and wellbeing.

Arch Dis Child 2006;**91**:627–628.
doi: 10.1136/adc.2006.095059

Correspondence to: Prof. J Tuomisto, Department of Environmental Health, KTL (National Public Health Institute), PO Box 95, FIN-70701, Kuopio, Finland; jouko.tuomisto@ktl.fi

Competing interests: none

REFERENCES

- 1 Spurgeon A. Prenatal methylmercury exposure and developmental outcomes: review of the evidence and discussion of future directions. *Environ Health Perspect* 2006;**114**:307–12.
- 2 Harada M. Minamata disease: methylmercury poisoning in Japan caused by environmental pollution. *Crit Rev Toxicol* 1995;**25**:1–24.
- 3 Rice D, Barone S. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. *Environ Health Perspect* 2000;**108**(suppl 3):511–33.
- 4 Zoeller RT, Dowling ALS, Herzig CTA, et al. Thyroid hormone, brain development, and the environment. *Environ Health Perspect* 2002;**110**:355–61.
- 5 Buchholz DR, Paul BD, Fu L, et al. Molecular and developmental analyses of thyroid hormone receptor function in *Xenopus laevis*, the African clawed frog. *Gen Comp Endocrinol* 2006;**145**:1–19.
- 6 Miettinen HM, Pulkkinen P, Jämsä T, et al. Effects of in utero and lactational TCDD exposure on

bone development in differentially sensitive rat lines. *Toxicol Sci* 2005;**85**:1003–12.

- 7 Abraham K, Pöpke O, Gross A, et al. Time course of PCDD/PCDF/PCB concentrations in breastfeeding mothers and their infants. *Chemosphere* 1998;**37**:1731–41.
- 8 Callahan CM, Grant TM, Phipps P, et al. Measurement of gestational cocaine exposure—sensitivity of infants hair, meconium, and urine. *J Pediatr* 1992;**120**:763–8.
- 9 Pereg D, Laqueux J, Dewailly E, et al. Cigarette smoking during pregnancy: comparison of biomarkers for inclusion in epidemiological studies. *Biomarkers* 2001;**6**:161–73.
- 10 Whyatt RM, Barr DB. Measurement of organophosphate metabolites in postpartum meconium as a potential biomarker of prenatal exposure: a validation study. *Environ Health Perspect* 2001;**109**:417–20.
- 11 Ostrea EM, Morales V, Ngaumgna E, et al. Prevalence of fetal exposure to environmental toxins as determined by meconium analysis. *Neurotoxicology* 2002;**23**:329–39.
- 12 Wessels D, Barr DB, Mendola P. Use of biomarkers to indicate exposure of children to organophosphate pesticides: implications for a longitudinal study of children's environmental health. *Environ Health Perspect* 2003;**111**:1939–46.
- 13 Moriya F, Chan KM, Noguchi TT, et al. Testing for drugs of abuse in meconium of newborn infants. *J Anal Toxicol* 1994;**18**:41–5.
- 14 Ostrea EM Jr. Testing for exposure to illicit drugs and other agents in the neonate: a review of laboratory methods and the role of meconium analysis. *Curr Probl Pediatr* 1999;**29**:37–56.
- 15 Ortega García JA, Carrizo Gallardo D, Ferris i Tortajada J, et al. Meconium and neurotoxicants: searching for a prenatal exposure timing. *Arch Dis Child* 2006;**91**:642–6.

Environmental pollution

Meconium analysis to detect fetal exposure to neurotoxicants

E M Ostrea Jr, D M Bielawski, N C Posecion Jr

Second perspective on the paper by Ortega García *et al* (see page 642)

An accurate detection of fetal exposure to drugs and other compounds (xenobiotics) is essential for studying the true prevalence of antenatal exposure to these compounds and their possible adverse effects on the fetus and infant. The ideal matrix to analyse is one that can be obtained non-invasively and is representative of a wide period of exposure of the fetus throughout gestation. Meconium is formed by the fetus as early as the 12th week of gestation, accumulates throughout pregnancy, and is normally excreted after birth by the infant. Throughout gestation, xenobiotics and their metabolites are principally deposited in meconium either directly from bile secretion or from fetal swallowing of amniotic fluid which contains these compounds which are excreted via the fetal urine. Meconium

is therefore a repository of many of the xenobiotics that the fetus is exposed to throughout pregnancy and its analysis has consequently been used for the detection of fetal exposure to illicit drugs. In addition, meconium has also been successfully analysed to detect fetal exposure to various licit drugs and over the counter medications as well as to cotinine and fatty acid ethyl esters which are indices of fetal exposure to tobacco and alcohol, respectively.¹

Recently, meconium has also been analysed to detect fetal exposure to toxicants in the environment, specifically pesticides and heavy metals.² In the first published study, a cohort of newborn infants from Manila, Philippines showed the following pesticides in meconium: chlordane, chlorpyrifos, diazinon, DDT (dichlorodiphenyl trichloroethane),

lindane, malathion, parathion, and pentachlorophenol. Of the heavy metals, lead, mercury, and cadmium were also detected in meconium. Other studies have subsequently reported on the presence of DDT and its metabolite, DDE (dichlorodiphenyl dichloroethylene) in meconium³ as well as the metabolites of organophosphate.⁴ Multiple classes of pesticides have also been analysed in meconium which will help in determining the interaction of these compounds in various clinical outcome studies.⁵ In an article published in this issue,⁶ organochlorine compounds were detected in meconium, specifically pentachlorobenzene, hexachlorobenzene, polychlorinated biphenyls, DDT, DDE, and hexachlorocyclohexane isomers. Concentrations of some of these compounds were also significantly and positively correlated with their concentrations in the infants' cord blood.

Compared to other matrices, meconium is a more sensitive matrix to analyse for neurotoxicants in the environment because of its wide window of exposure to these compounds. In an ongoing study we are conducting which compares the analysis of various matrices (maternal blood, maternal hair, infant hair, cord blood, and meconium) to detect exposure to various pesticides, preliminary results among 750 mother/infant dyads has shown a significantly higher percentage of exposure by meconium analysis.⁷