

**Levels of persistent toxic substances (PTS) in blood from delivering women
from selected areas of South Africa.**

A pilot study

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1. Summary.

A number of persistent toxic substances (PTS) are recognised as being responsible for adverse development and health effect in children. The growing foetus and new born child are especially sensitive to the toxic effects of many persistent heavy metals and organic pollutants found in the environment, that may exert its toxicity for decades because of resistance to degradation. Several of these substances move from mother to foetus via the umbilical cord and to the child via mother's breast milk. The levels of these contaminants in maternal blood during pregnancy give an indication of the potential risk to the developing foetus. Of particular concern are long-term, subtle effects that might influence reproductive health, pregnancy outcomes, reduce defence against diseases, affect children's mental development, or increase the risk of cancer.

Several of multidisciplinary international projects are in progress that study levels of PTS in people of different geographical regions to establish the relationship between levels of these chemicals and health. One example is the Arctic Monitoring and Assessment Programme (AMAP) that started in 1991 and includes eight arctic countries (Canada, Denmark, Finland, Iceland, Norway, Russia and Sweden and [The USA](#)).

South Africa having dimensions of both developed and developing countries has the potential to contribute to global research in the science of environmental pollutants and human health outcomes. Although a number of South African studies addressed some of the concerns related to persistent toxic substances and health, there is a lack of comprehensive research in this field, particularly dealing with maternal and child health.

Under the umbrella of the MRC's programme of work entitled, Chemical Exposures and the Human Environment, a protocol for a project entitled "Preliminary Study Of Risk Of Pre-Natal Exposure To Neurotoxic Metals In Four South African Settings" has been developed. During a visit to South Africa by Prof. Jon Øyvind Odland from the Institute of Community Medicine, University of Tromsø, Norway (31 March to 2 April), which included site visits and meetings to discuss synergies between the work of the MRC and AMAP, it was decided to extend the SA project towards compatibility with the AMAP and other global research (studies in Central Vietnam and Southern Chile were recently initiated by AMAP Human Health Group). The project will measure not only toxic metals as proposed originally, but also essential trace elements and persistent organic pollutants (POP's).

The collaborative project would include scientists from the South African Medical Research Council (Environmental Health section of the Health and Development Research Group), the South African Council of Geoscience, the University of Tromsø, Norway, the Norwegian Institute of Air Research, the Norwegian National Institute of Occupational Health, and Centre du Toxicologie de Quebec, Canada.

The main objectives of the pilot study are to facilitate investigation of possible health risks related to exposure to persistent toxic substances (PTS) in selected areas of South Africa, including food security that can be affected by environmental contamination. This will include assessment of levels of environmental toxins in maternal blood from 12 randomly selected delivering women in each of 6 locations, based on calculations for significant

statistical power in a pilot study. If the results from this pilot study give rise to medical concern, a more comprehensive longitudinal study of sources and reproductive outcomes will be planned.

2. Objectives and outline

Main objectives

- To facilitate risk assessment of human reproductive health related to exposure to persistent toxic substances, including food security.

Additional supporting objectives

- To assess levels of PTS in maternal blood, cord blood and urine of selected populations in South Africa.
- To assess levels of PTS in soil, water and air in selected sites in the South Africa.
- To elucidate food as a source of exposure of contaminants.
- To create data for future dietary advises and pollution control protocols.
- To cooperate in basic training of scientists and health workers in research, field work, sampling technique and questionnaire handling, as well as to facilitate the exchange of scientists, laboratory personnel and students for educational purposes and scientific cooperation.

Outline and relevance for South African reproductive health

As a country with dimensions of both developing and industrialized nations, South Africa is in a unique position globally.

As is the case in many developing countries exposure to toxic substances in the general population and in some occupational settings has been neglected for many decades. There are now concrete plans in SA to reduce the incidence of preventable non communicable diseases related to both acute and chronic exposure to toxic substances. To facilitate this work an assessment of levels of toxic substances in human materials is mandatory. (Stewart 2002).

To date South African research linking environmental exposure to persistent toxic substances and human health has been scarce. Although some information on the concentrations of toxicants in soil, water and animals exists, very little published information can be found. In addition, the gender specific research, including research on reproductive health, is needed to determine the extent of exposure to toxic substances.

Persistent toxic substances can be grouped into two main categories, namely toxic metals and persistent organic pollutants (POP), both groups being produced and used in South Africa. South Africa being rich in mineral deposits is mining for a number of economically important metals (lead, manganese, platinum, chromium, gold). The country is also a major producer of

metals from imported enriched deposits (aluminium, zinc or copper). Potential exists for emission of toxic metals during secondary smelting activities in stainless steel production (nickel, manganese, vanadium, and chromium) or automobile emission of lead and manganese used as petrol additives. Another area of concern is the rise in informal mining and industrial activities, including gold mining, which may be associated with mercury pollution of the environment. Rapid uncontrolled urbanization and a wide range of anthropogenic activities also contribute to the environmental degradation and pollution.

Although industries are constantly upgrading technologies to meet international standards of production and environmental compliance, previous outdated technologies and control mechanisms used in the past may have contributed to toxic metal contamination around certain industrial, including mining and smelting sites. Most of these metals if present in the living environment, may exert its toxicity on humans over a long time, affecting the development of the foetus and young children. Studies on levels of lead in blood of young children have shown that both urban and rural environments are polluted with lead (Mathee et al. 2003; von Schirnding et al. 2001). A number of South African studies used animals as bioindicators for environmental contamination by toxic metals. such as vanadium (McCrindle et al. 2001), manganese (Elsenbroek and Neser, 2002) and other heavy metals (Schuwerak et al. 2001).

There are concerns also in respect to pollution associated with fertilizers and pesticides in [South Africa](#). Pesticide exposure in women needs special attention, because the female population exposure is often aggravated by economic policy changes associated with structural adjustment programs and globalisation (London et al. 2002). Case studies of long-term organophosphate exposures among South African farm workers have documented associations with serious neurological symptoms, vibration sense and tremor, (London et al. 1998a, 1998b). Recent studies have demonstrated high levels of agrochemicals, such as endosulfan and chlorpyrifos in rural surface and groundwater in the Western Cape (Dalvie et al. 2003).

3. Background on the different substances and elements

3.1. Persistent organic pollutants

The effects of organic environmental pollutants on health are most often subtle since they usually occur in concentrations which are not expected to result in acute toxic symptoms. What should be expected is long-term, possibly transgenerational, effects on the neurologic and reproductive systems. These effects are confounded by many other factors and can be difficult to measure even in longterm epidemiological studies in large populations. The most vulnerable periods for toxic impact on human development are the embryonic and fetal periods, making studies on pregnancy exposure and pregnancy outcome especially important.

3.1.1 Clinical outcomes of concern:

There is a worldwide growing concern that exposure to persistent toxic substances (PTS) is responsible for serious detrimental effects on the development of the sensitive central nervous

system during the foetal stage, resulting in adverse effects, like decreased IQ, behavioural problems, respiratory problems and increased cancer risk.

Low birth weight and growth retardation has been found associated with high levels of PCBs and dioxins in studies with laboratory animals (Allen et al. 1980; Overmann et al. 1987; Brezner et al. 1984), in children born of mothers exposed to accidental high levels of organic contaminants (Harada 1976; Rogan et al. 1988), and in children born of mothers who consumed PCB-contaminated fish (Fein et al. 1984). Patandin et al. (1998) have demonstrated that human *in utero* exposure to PCBs is negatively associated with birth weight and postnatal growth until 3 months of age. In a case-control study performed in 10 Californian counties Bell et al. (2001) have shown increased risk for fetal deaths due to congenital anomalies, especially with pesticide exposure in the weeks 3-8 of pregnancy.

Negative effects on IQ and behaviour are documented in European as well as American children (Gladen et al. 1988; Jacobson et al. 1990; Stewart et al. 2000; Huisman et al. 1995; Ptandin et al. 1999; Jacobson and Jacobson 1996; Walkowiak et al. 2001). Interference with maternal thyroid hormone metabolism, as well as the unborn and newborn child can be responsible for these effects on brain development. Maternal thyroxine is totally responsible for the early gestation thyroid metabolism. Low levels in the mother might lead to insufficient development. Lower levels have been found associated with PCB levels before delivery (Koopman-Esseboom et al. 1994). Transient effects on thyroid metabolism are found in a period shortly after birth in relation to dioxin exposure (Koopman-Esseboom et al. 1994; Pluim et al. 1992). These effects disappear up to two years of age (Ilsen et al. 1996). It is plausible that the dependency of maternal T4 in early pregnancy and the high need of T4 shortly after birth makes both periods vulnerable for environmental influences (Pop et al. 1999). Also lower levels of testosterone and estrogens might be caused by abnormal enzyme induction in the liver, leading to breakdown of these steroids in the unborn baby, disrupting brain development in the vulnerable period around the 30th week of pregnancy. In this period myelinisation develops rapidly and language, visuo-spatial abilities and sex-specific brain characteristics are formed.

Psychological follow-up studies in humans up to the age of 11 (Jacobson and Jacobson 1996) show a retardation of 2 years in IQ. Recent follow-up studies in the Netherlands at the age of 8-12 years demonstrate a functional basis for this finding with help of neurophysiological Magnetic Encephalo Graphic (MEG/EEG) measurements. A delay in myelinisation is found from 1-3 years in relation to the level of dioxins in the perinatal period (Ten Tusscher Gavin, Dr. Thesis, University of Amsterdam 2002). These findings are in accordance with the follow-up findings in Taiwan after the Yucheng-disaster in 1979 (Chen et al. 1994). Damaging effects on the liver found shortly after birth are transient, but underlines that damage occurs in that period (Pluim et al. 1994).

Effects on the hematopoietic system are detected immediately after birth on the white blood cells and the thrombocytes (Pluim et al. 1994; Weisglas-Kuperus et al. 2000). An increase of infections in the middle ear is described in the Rotterdam study in relation with current levels of PCBs at the age of 4 years. At the age of 8 years still lower thrombocyte counts are found based on a toxic influence at the megakaryocyte level or earlier on the stem cell (Ten Tusscher et al. submitted).

At the age of 8-12 years negative effects on lung function in the sense of more obstruction is detected in relation to perinatal exposure to dioxins in a study from the Netherlands (Ten Tusscher et al. 2001).

3.1.2. Relevant contaminants

Most research and monitoring work on persistent toxic substances (PTS) has mainly been focused on pesticides (e.g. DDT-group, Lindane and cyclodiene analogues), industrial compounds and by-products (e.g. dioxins and PCB), as well as heavy metals (e.g. mercury, lead, cadmium and nickel). However, during the last few years there has been an increased interest for “new” xenobiotics, metabolites and the presence of until now not described contaminants. The “new” environmental toxins include a number of organic compounds and compound classes. Some of the more persistent polar pesticides currently in use belong to this group. In the following relevant halogenated contaminants are described.

DDT-group

The DDT-group consists of 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (*p,p'*-DDT) and its metabolic products 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (*p,p'*-DDE) and 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane (*p,p'*-DDD), as well as the corresponding *o,p'*-isomer. DDT was commonly used as a pesticide on a variety of agricultural crops, and is still in use for the control of mosquitoes that spread malaria. DDT and its metabolites are stored in fatty tissue and are excreted very slowly and primarily via urine and faeces.

Acute lethal oral doses (LD50) in test animals range between approximately 115-800 mg/kg body weight. Levels of expected effects for chronic exposure to DDT, DDE and DDD for most mammalian test species range between 10-100 mg/kg body weight/day for respiratory, cardiovascular, gastrointestinal, haematological, hepatic and renal outcomes. However, the more serious effects (neurological, developmental, reproductive and carcinogenic) have “lowest observed adverse effect level”-values in the 8-50 mg/kg body weight/day range when exposure is chronic. DDT and DDE are both considered to have weak estrogenic responses with potencies relative to estradiol of between approximately 0.01-0.0001 (Soto et al. 1992). This estrogenic effect is probably responsible for DDTs impacts on reproduction in animals. DDE has recently been shown to be a potent androgen receptor antagonist (Kelce et al. 1995).

In humans, acute lethal exposures are probably greater than 250 mg/kg body weight. Very little data on the effect of chronic exposure is available. The WHO has proposed on accepted daily intake (ADI) of 20 micro g/kg body weight/day for DDT, DDE and for total DDT (sum DDT, DDE and DDD). Because DDT and its metabolites are found in breast milk, excretion also occurs during breast feeding. DDT can readily cross the placenta.

Epidemiologic studies have not established an association between DDT exposure and cancer, even though cancer is an outcome of long term animal feeding studies. Studies of breast cancer risk among women living in the north of Vietnam suggest that recent and past exposure to *p,p'*-DDT does not play an important role in the etiology of breast cancer among

women living in a country with tropical climate where insecticide use for mosquito control is common (Schechter et al. 1996, Schechter et al. 1997). IARC has classified DDT and DDE as “possibly” carcinogens to humans based on animal evidence. Suppression of reflexes in neonates appears to be associated with levels of DDE in breast milk exceeding 4 micro g/g lipid, however, it has not been substantiated if DDE is the causative factor (Rogan et al. 1986). Elevated levels of DDE in human breast milk (3 micro g/g lipid) have been correlated with a shortening of breast-feeding duration and inhibition of lactation was hypothesised as the cause (Rogan et al. 1987).

The use of DDT as an important insecticide has been declining in the temperate regions of the Northern Hemisphere since the 1960’s and especially since the mid-70’s when it was banned by many western nations. As for RSA we have no updated information in the literature.

Hexachlorocyclohexanes

Hexachlorocyclohexanes (HCHs) are a group of organochlorine pesticides including the isomers alpha, beta, gamma (more commonly known as Lindane), delta and epsilon HCH. Many countries in the world use large amounts of Lindane.

Gamma-HCH (Lindane) is the most toxic of the HCH isomers. Excessive exposures can affect the liver, the nervous system, the kidney, the reproductive system, and perhaps the immune system. IARC (1987) classifies it as possibly carcinogenic to humans. No effects have been reported in populations exposed to low level environmental concentrations. The TDI for all HCHs is 0.3 microg/kg body weight/day (WHO 1991).

HCHs, especially beta-HCH, accumulate readily in fatty tissues and are excreted slowly via faeces, breast milk and urine (WHO 1991). Levels of alpha-, beta- and gamma-HCH in breast milk in the general population in Europe, Canada and the US range between 10-40 ng/g lipid, 10-500 ng/g lipid and <1-10 ng/g lipid, respectively. The most recently measured “background levels” of HCHs in blood, serum, plasma, milk and adipose tissues are relatively low compared to values reported during the 1960’s and 1970’s and much lower than levels reported from countries with extensive current usage. Because of its persistence, beta-HCH is found at the highest level of the four isomers reported.

The exposure of babies resulting from present beta-HCH concentrations found in breast milk has been identified as a matter of concern by the WHO, but not as a reason to stop promoting breast-feeding. The high beta-HCH levels that have been found in some breast milk samples in countries using HCH exceed the TDI of 0.3 microg/kg body weight/day, temporarily and locally. The beta-HCH concentrations in the blood of babies lie within the same range as those in the mothers. As for RSA we have no updated literature.

Toxaphene

Toxaphene is an insecticide consisting of several hundred bornanes, bornenes, bornadiens and camphenes. Toxaphene is one of the most heavily used pesticide, but is now banned in most countries. It is commonly found in human tissue, however, its historical quantification has been compromised by difficulties in analysis and in the estimation of amounts of the various

chemicals that make up toxaphene. As a result, comparisons of published data on toxaphene are difficult.

The lethal oral dose (LD50) in rats is between 80 and 90 mg/kg body weight (Gaines 1969), however a range of other effects including death can follow chronic exposure at exposure levels of 20 to 30 micro g/kg body weight/day (ATSDR 1994). Large doses of toxaphene are likely to affect the nervous system (seizures, tremors, convulsions, paralysis and both behavioural and biochemical effects), the liver (enzyme induction) and the kidney (enzyme release, fatty degenerative changes and focal necrosis). Intermediate exposure duration may affect the adrenals, the immune system and fetal development. This research base is limited to short term and intermediate term (less than a lifetime) animal studies conducted with technical grade toxaphene. There are no suitable studies to confirm the effects of technical or environmentally available toxaphene on human populations. Because so little is known about the effects of long-term exposure to both technical and environmental toxaphene in animals and humans, there is considerable uncertainty over the applicability of a tolerable daily intake (TDI). Canada uses 0.2 micro g/kg body weight/day. In the USA, the ATSDR (1994) has proposed an “intermediate-duration oral exposure minimal risk level” of 1 microg/kg body weight/day. The WHO has not proposed a TDI.

Animal studies suggest that toxaphene is an animal carcinogen. It has been classified by IARC (1987) as possibly carcinogenic to humans. Although toxaphene does not appear to be a very active estrogenic mimic (Soto et al.1992), it has been shown (Arnold et al. 1996) that the estrogenic effect of toxaphene was three fold increased by interaction with other chlorinated contaminants, such as dieldrin and endosulfan. Recent data indicate that toxaphene is a potent estrogen receptor antagonist (Jørgensen, pers com).

Toxaphene is readily absorbed. Intakes are entirely dependant on the type and amount of food consumed. The highest levels in food occur in seal blubber, beluga blubber and fatty tissues of fish. Absorbed toxaphene is readily metabolised and excreted (90 % in 24-36 hours) however some constituents remain in fatty tissues for prolonged periods (ATSDR 1994). Stern and coworkers (1992) report that the two most common identifications are an octachlorocamphene named T2 (Parlar no 26) and a nonachlorocamphene named T12 (Parlar no 50). The toxicological information available for the congeners is highly limited.

Toxaphene use or exposure in RSA have not been explored.

Dioxins

Polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) are two structurally similar families of compounds that include 75 and 135 congeners, respectively. Seventeen members of these two families of chemicals are highly toxic and contribute most of the toxicity to complex mixtures of dioxins and furans. The seventeen more toxic congeners in both families have chlorine substitutions in the 2,3,7 and 8 positions. These more toxic congeners cause a variable and wide range of deleterious effects in laboratory animals (Environment Canada and Health Canada 1990).

The general population is exposed to small amounts of complex mixtures of PCDDs and PCDFs and other organochlorines. In a few incidents, workers and others who have been exposed to very large amounts of a limited number of these compounds in the USA, Italy and Japan have developed chloracne, a skin disorder. There is also evidence that high level exposure to dioxins and furans can cause variations in serum lipid levels, other dermatological effects related to chloracne, microsomal enzyme induction and gastrointestinal alterations (Schultz et al. 1990). Other studies of high level occupational exposures have found associations with some types of cancer (Zober et al. 1990). Pluim and coworkers (1993) concluded that *in utero* lactational exposures to PCDDs/PCDFs are capable of affecting the hypothalamic/pituitary/thyroid regulatory system in human infants.

The best documented poisonings by PCDFs in humans are the Yusho and Yu-cheng incidents when rice oil was accidentally contaminated with polychlorinated biphenyls (PCBs) from electrical transformer fluid. The PCBs were heavily contaminated with PCDFs. Investigators have reported low birth weight, early tooth eruption, sensory losses, skin discoloration, swollen eyelids (Kuratsure et al. 1972) and retarded development (Rogan et al. 1988) in infants exposed transplacentally. The mean total consumption of PCDFs by the Yusho and Yu-cheng patients has been estimated to be 0.9 microg/kg body weight/day (Hayabuchi et al. 1979). The smallest amount of total PCDFs causing chloracne has been estimated to be 0.16 microg/kg body weight/day.

Average daily intake of PCDDs and PCDFs over a lifetime is similar in most industrialised regions, between 2 and 10 pg 2,3,7,8-TCDD TEQ/kg body weight/day (Birmingham et al. 1989). Back calculations from human tissue levels in Canada confirmed this estimated intake (Environment Canada and Health Canada 1990). The mean PCDD and PCDF concentrations in the breast milk of Arctic and non-Arctic populations are also similar: 10-20 pg 2,3,7,8-TCDD TEQs/g lipid (Ryan et al. 1993, Nygren et al. 1986). Breast milk levels in the Netherlands can be slightly higher, 30 pg 2,3,7,8-TCDD TEQs/g lipid (Koopman-Esseboom et al. 1994).

Schecter et al have discussed TCDD levels of Vietnamese populations in several publications (Schecter et al. 1992, Schecter et al. 1993, Schecter et al. 1994, Schecter et al. 1995, Schecter et al. 1996, Schecter et al. 1997). Vietnamese adults over the age of 40 were assessed in different areas. In general, considerable variation in TCDD levels were observed, with elevated levels from certain areas in the south and also in the soldiers from the north of Vietnam who had served in the south. Data from Michigan Vietnam veterans of chlorinated dioxin, dibenzofuran, coplanar, mono-ortho, and di-ortho substituted PCB congener could not be explained by exposure in Vietnam, rather indicating the total dioxin-like toxicity for the general American population. Levels in human milk, adipose tissue and blood are generally higher in Vietnamese populations, thus health consequences are more likely to be found in Vietnamese people living in Vietnam.

Serum dioxin has been correlated to male hormones, like testosterone and gonadotropines, without consistent or meaningful associations (Henriksen et al. 1996). The same conclusion was reached for serum dioxin and immune system alteration (Michalek et al. 1999). On contrary, a compensatory metabolic relationship between dioxin and insulin regulations has been shown (Michalek et al. 1999).

Pregnancy outcome among US women Vietnam veterans was studied with self-reported pregnancy outcome reports from more than 4000 Vietnam veterans, compared to an equally sized control group (Kang et al. 2000). There were no associations between Vietnam service and miscarriage or stillbirth, low birth weight, pre-term delivery or infant death. However, the risk of having “moderate to severe” birth defects was significantly elevated among Vietnam veterans. A comparable study of male veterans provided little or no support for the theory that paternal exposure should be associated with adverse reproductive outcome (Wolfe et al. 1995). Lindbohm, in an editorial comment, will not conclude definitely based on this study (Lindbohm 1995). Later, Michalek and coworkers came to the same conclusion (Michalek et al. 1998).

We have no information about dioxins sources or human levels in the RSA.

PCB

Polychlorinated biphenyls (PCBs) are a group of 209 congeners which were commercially produced as mixtures. Their manufacture and new usage is banned in most western countries, but they are still present in older electrical transformers and at a number of contaminated industrial sites and waste sites.

Levels of total PCBs have declined since the 1980's in breast milk of women in many industrialised countries (Newsome et al. 1995). Historical values are, however, difficult to compare because of changing analytical techniques and quantitation methods (reported PCB concentrations based on an Aroclor 1260 standard are double those based on a sum of PCB congeners).

The toxicity of PCBs as mixtures is complicated by the large and varying amounts of the 209 congeners in the mixture and the micro-contaminants present (e.g. PCDFs). Individual congeners and mixtures can affect liver function, reproduction, infant birth weights, neuro-behavioural development and the immune system and may cause cancer in laboratory animals (ATSDR 1995). The TDI for PCBs is 1 microg/kg body weight/day.

Assessing the human health effects of PCBs is very difficult because PCB mixtures frequently used in animal studies or identified in accidental poisonings frequently contain micro-contaminants such as PCDFs. Many of the effects of exposure to PCBs observed in humans reflect exposure to high levels of both PCBs and PCDFs. PCDFs are believed responsible for many of the observed human health effects. For Yusho and Yu-cheng, the earliest toxicological signs included chloracne. In Yu-cheng, increased upper respiratory tract infection rates were associated with decreased serum IgA and IgM plus increased IgG levels (WHO 1988).

A small group of PCB congeners have dioxin like activity and have been assigned dioxin toxic equivalency factors (Ahlborg et al. 1994). In a number of human tissue samples such as breast milk or adipose tissue it was found that the dioxin-like PCBs contributed a large proportion of the total 2,3,7,8 TCDD TEQs (Dewailly et al. 1992). Because PCB congeners

co-exist with dioxins and furans in the environment, ascribing an effect to one or the other contaminant is almost impossible.

Data obtained from epidemiological studies on cohorts of US infants from Michigan (Jacobson et al. 1990) and North Carolina (Gladden et al. 1991, Rogan et al. 1987) suggest adverse neuro-behavioural effects from *in utero* exposure to PCBs. High cord blood concentrations were associated with small height at birth (Dewailly et al. 1993), low birth weight and small head circumference (Jacobson et al. 1990). Birth size among male infants Inuits was inversely related to PCB concentration in breast milk of the mother (Dewailly et al. 1993). Perinatal exposures to PCBs/dioxins/furans may impair immune responses to infection as suggested by a 20 fold higher incidence of infectious diseases (e.g. meningitis, measles) and ear infections (otitis media among one year old Inuits with high PCB exposures) than among lesser exposed controls. The infectious disease data may be confounded by a lower seroconversion rate (successful immunisation) among Inuits compared to controls (Dewailly et al. 1993). PCBs in human materials have not been explored so far.

3.2 Toxic metals as persistent toxic substances

Metal sources in the environment may be natural or anthropogenic. While some metals are needed to sustain life most can be toxic if present in high concentrations. Metals occur in different forms: as ions, vapours, or salts. They may enter the human body through inhalation, ingestion or dermal absorption. Some forms of metals are more toxic than others, and speciation of these forms is important when studying toxic effects.

Anthropogenic sources of metals may have severe impacts on the local environment, but signs of environmental change across a larger region and on a broader scale are subtle and difficult to interpret. Based on current understanding of the behaviour of metals in the environment and their toxicology, we can predict the impact of some metals on human health.

Toxic metals, when released into the environment, may exert toxicity to all living organisms over a very long time. It is pertinent that short and long-term environmental and health risk factors of toxic metals are well understood and evaluated. It is thought that toxicity of metals released even in trace concentrations into the environment exceeds that of all other radioactive and organic pollutants combined (Nriagu and Pacyna, 1988). Major risk factors for exposure to metals are: age, health status, nutritional and essential metal status, housing and socio-economic status. Age is one of the most important risk factors for infants and young children because of their body size, and relatively higher rates of uptake of toxins from the lungs and gastro-intestinal tract, and the immaturity of the blood-brain barrier. The following relevant toxic metals are described.

Lead (Pb)

Human exposures to lead compounds in environmental and occupational settings are of concern due to their non-biodegradable nature and long biological half-lives. Of particular concern in relation to health are effects following long-term low-level exposure to lead. Over the past 20 years understanding of lead toxicity has increased. In relation to a wide range of biochemical and

functional effects, it is now considered that there may be no safe level of exposure to lead, particularly in relation to the developing central nervous system (Goyer 1993). The principal sources of lead exposure in the living environment are industrial activities and mining, paint, petrol, dust and soil.

Health impacts:

Central nervous system (CNS)

Most attention has been devoted to the association between elevated blood lead levels and effects on cognitive and behavioural development of the central nervous system (CNS) of infants and young children. In this regard, past attention was focused mainly on encephalopathy amongst children with blood lead levels equalling or in excess of 80 µg/dl. This was characterized clinically by ataxia, coma, and convulsions and was often fatal. Survivors suffered a number of neurological complications such as mental retardation, deafness, blindness, and convulsions (Goyer and Rhyne 1973). The progressive loss of intellectual ability in siblings of affected children, but who had lower lead exposure, contributed to the concept of sub clinical or symptomatic CNS effects. In a 1974 NIEHS symposium, three studies were presented that were concerned with neuropsychological outcomes in children with blood levels below 40 µg/dl. De la Burde and Choate (1972) reported impairment of fine motor function, concept formation, and altered behavioural profiles in 70 preschool children with blood lead levels higher than 30 µg/dl. In a follow-up study in 1975 on the same group of children who had reached the age of 7 to 8 years, continued CNS impairment was determined (De la Burde and Choate 1975). The results of these and similar studies were summarized by the United States Environmental Protection Agency (US EPA), which concluded that CNS effects in infants and young children occur with PbB levels in the 10-15 µg/dl ranges (EPA 1989; Grant and Davis 1989). The World Health Organization Regional Office for Europe (WHO/Euro), in collaboration with the European Community, conducted a similar study involving children in eight European countries. A total of 1879 school-aged children with blood lead levels ranging from below 5 µg/dl to about 60 µg/dl were assessed using multiple psychometric intelligence tests. Analyses demonstrated a significant linear relationship between blood lead, visual-motor integration, serial choice reaction performance and psychometric intelligence. The study failed to identify a biological exposure limit below which adverse health effects might not be expected (Winneke et al. 1990). The reversibility of CNS effects was also studied and it was concluded that blood lead levels higher than 30 µg/dL are associated with CNS deficits that persist into young adulthood (Needleman et al. 1990).

Cardiovascular system

A significant linear association between blood lead concentration and high blood pressure in adults has been demonstrated (Harlan et al. 1985; Sharp et al. 1989). Although the mechanism whereby lead affects blood pressure is not known, the calcium – mediated control of vascular smooth muscle contraction and renal effect mediated through rennin – angiotensin system has been suggested (Schwartz 1991; Chai and Webb 1988).

Bone metabolism

Bone is a major target tissue for lead storage, and may affect bone metabolism. Of particular concern is the mobilization of lead stored in bone during physiological and pathological conditions and events such as pregnancy, lactation, osteoporosis, and renal disease (Rabinovitz 1991; Pounds et al. 1991).

Human reproduction

It has been recognised that severe lead intoxication is associated with sterility, abortion, stillbirths and neonatal morbidity and mortality from exposure in *utero* (Goyer and Rhyne 1973). The potential for effects of low-level lead exposure on reproduction in humans is also receiving attention (Telisman et al. 1990).

Aggression, delinquency in children and child abuse

In recent years attention to the relationship between childhood lead exposure, and the emergence of aggressive behaviour and early delinquency has increased. Fifty years ago Byers noticed that children treated for acute plumbism also demonstrated violent and aggressive behaviour (Byers and Lord 1943). A number of studies in recent years have found an association between lead and impaired reaction time, distractibility, disorganisation, impulsivity and restlessness (Bellinger et al. 1994). A correlation between lead and hyperactivity, combined with antisocial behaviour in Scottish children was reported (Thomson et al. 1989). A raised level of lead in dentine is thought to relate to higher inattention and restlessness scores in New Zealand children (Fergusson et al. 1993). Elevated lead levels in males have been associated with delinquent juvenile behaviour and subsequent adult criminality in later life (Denno 1990). Needleman *et al* studied the association between bone lead levels and delinquent behaviour in children aged 7 and 11 years (Needleman et al. 1996). No association between bone lead and inferior school performance was found but there was a higher aggression score among this group. These data suggest that altered social behaviour may be among the earliest expressions of lead toxicity.

In the USA, the mean blood lead levels in children have decreased from 13.7 µg/dL to 3.2 µg/dL in recent years. However, many thousands of children continue to have toxic lead burdens including neurotoxic effects (Prikle et al. 1994, ATSDR 1988). There are a number of reports suggesting that there is a prevalence of lead poisoning in abused and neglected children (Flaherty 1995; Bithoney et al. 1993).

Lead exposure in South Africa

The main sources of environmental lead exposure in South Africa are petrol, paint, industrial use, mining and informal sector. In occupational settings regular surveillance of employees aimed at early detection of excessive lead absorption is performed (Van Heerden and Metz 1991; Röllin et al 1988). A study by Robins et al. (1997) investigated associations between occupational lead exposure and semen quality among male workers but produced conflicting results. Although unleaded petrol was introduced in South Africa in 1996 only 20-30% of vehicles are using unleaded petrol at present. The current maximum permissible lead content is 0.4g/litre and 0.013g/l in leaded and unleaded petrol respectively. This is in contrast with developed countries where most or all petrol used is of the unleaded variety. During the past decade, the MRC has been at the forefront of research regarding environmental lead exposure and blood lead levels amongst school children from various South African settings (von Schirnding et al. 1991, 1996, 2001; Mathee et al. 2003a; 2003b). This and other research (Nriagu et al. 1996; Liggins and Nriagu 1998) indicated that large numbers of South African children in inner-city and informal settlement areas have unacceptably high blood lead levels. There is also an evidence of raised

blood lead levels amongst children living in certain peri-urban and rural areas, indicating pervasive lead contamination in the country.

It is expected that a planned phase out of leaded petrol in South Africa by 2006 will further reduce blood lead concentrations in children. However, existing environmental contamination, poverty, poor housing and the use of lead in informal industries will continue to pose a risk to the population.

Manganese (Mn)

Environmental sources of manganese (CAS-7439-96-5) may be both natural and anthropogenic. Naturally, manganese is the twelfth most abundant element in the earth's crust, comprising about 0.1%, and the fifth most abundant metal (ATSDR 1992). It is widely distributed in rocks, soil, food, water and living organisms. Its modern industrial use is widespread (Johns, 1996) and since the beginning of the century, manganese ore production has increased 30-fold, exceeding 20 million tons per year (Alessio and Lucchini, 1996). Scientific concern has arisen due to its widespread use in ceramics, manufacture of matches, glass, soldering, metal alloys, batteries, aluminium cans, and electronic components. Fungicides and fertilizers containing manganese are still used extensively in developing countries, as are fossil fuels, another significant source of manganese. Another modern compound containing manganese is the gasoline additive methylcyclopentadienyl manganese tricarbonyl (MMT) that was introduced to automobile fuel formulas as an octane boosting and anti-knock agent, thus either replacing or reducing the lead content in petrol in some countries.

Biologically, manganese is considered to be an essential metal important to mitochondrial oxidative processes (ATSDR 2000) for all living mammals, but at the same time highly toxic at higher concentrations. Mn does not occur as a free metal but exists in 11 oxidation states, with only the Mn (II) and Mn (III) oxidative states being of biological significance.

Health impacts:

Both, deficiency and excess of Mn may have detrimental health effects. Importantly, excessive intake of manganese either through inhalation or ingestion may result in pathology, particularly to the central nervous system (CNS) (Keen et al, 1990). The rate of absorption by inhalation is strongly dependent on the form and size of the manganese containing particulate matter. Excessive exposure via inhalation has been shown to cause effects on the lungs and accumulate in the brain, causing irreversible brain disease, to some extent similar to Parkinson's disease. These effects are well documented in excessive occupational exposures (Politis 1980, Mergler 1994), and, importantly, correlation between low doses of exposure in occupational settings, blood manganese levels and neurological health outcomes have been reported (Lucchini et al., 1995). There is very limited information on particulate deposition in children.

Absorption of ingested manganese is regulated by homeostatic mechanisms that may be increased by iron deficiency. Individuals with anaemia absorb about twice as much manganese as healthy individuals with the same exposure). Infants have a greatly increased absorption and retention capacity for ingested manganese compared to adults. In addition, the

blood brain barrier being underdeveloped in infants, may allow for relatively free ingress of manganese into the brain (Mena 1969, 1987). In children, contaminated house dust and soil, combined with hand to mouth behaviour, could be major contributors to body burdens of manganese, both by ingestion and respiration. The elderly may also be at risk from excessive exposure to manganese, due to increased susceptibility of aging brain cells to injury.

It has been reported that the neonate may be particularly vulnerable to high levels of manganese. In addition, studies on mice injected with manganese chloride tetrahydrate during gestation have shown fetotoxicity (Sanchez-Domingo 1993). In occupational settings it has been shown that exposure to manganese can have a neurotoxic effect. There are two types of effects: *acute exposure* that manifests in psychiatric symptoms known as “manganese madness” with hallucinations, emotional, compulsive and aberrant behaviour; and *chronic exposure* producing neurological symptoms with muscular weakness, impaired speech, clumsiness, tremor, mild rigidity, and appearance of hypokinetic facial expression (Politis et al. 1980). These symptoms mimic Parkinson disease.

Animal experiments showed that clearance from the brain, the critical target organ, appears to be slow (Mena 1974). This slow clearance mechanism opens the possibility of accumulation of manganese in tissues under conditions of chronic exposure.

Little information exists on environmental exposures to low levels of organometallic manganese originating from the octane enhancer fuel additives MMT (methylcyclopentadienyl manganese tricarbonyl) and public health. Its use was approved in Canada in 1976 at a concentration of 18mg/L of petrol in both leaded and unleaded forms. Consideration must be given to the fact that, unlike point-source industrial emissions, emissions from vehicles are widely transported and distributed in the environment, and have the potential to contribute to manganese exposure of the general population to a much greater extent than that calculated from actual emission data.

In 1991, the United States Environmental Protection Agency (EPA) stated that the potential of widespread inhalation exposure to particulate emissions that resulted from the combustion of petrol containing MMT was of concern, and the possibility of increased environmental manganese loading from these activities created a new public health issue. In 1999 the American Medical Association Council on Scientific Affairs passed a resolution to reduce health risks from the use of MMT in gasoline and called for more research determining possible health effects of long-term, low-dose exposures to MMT and its combustion products (Lyznicki et al., 1999, Davis, 1998).

Manganese exposure in South Africa

Sources of environmental exposures to manganese in South Africa are mining and related metal industries, other modern industries, agriculture (fertilizers and fungicides) and petrol (Hermanus 2000). Currently in South Africa, oil companies are developing alternative petrol formulations as part of ongoing automobile technology development, as well as in preparation for phase-out of leaded petrol by 2006. In late 2000, MMT was introduced to petrol in one area of the country.

In light of the paucity of epidemiological studies on community exposure to manganese, the South African Medical Research Council undertook a study to establish environmental and biological baselines for manganese in different parts of the country. Preliminary results from the study which is still underway, indicate different environmental and biological loading in two urban settings (Röllin et al. in preparation 2003).

Most of the studies of impacts of MMT have been performed in North America and cannot be extrapolated directly to South African situation. There are a numbers of factors, which differ considerably between the two settings. The majority of vehicles are not equipped with catalytic converters, are relatively old and poorly maintained leading to higher emissions. Local climatic conditions may influence manganese emission. Poor health and nutritional status in a large portion of the population, including a high prevalence of infectious diseases (lung diseases, TB, HIV/AIDS) makes the population more susceptible to environmental toxins.

Mercury (Hg)

Mercury occurs naturally as elemental mercury and as organic and inorganic compounds. Much of the mercury in the environment is strongly bound to sediments and organic matter, and thus unavailable to organisms. The most important anthropogenic sources of mercury are combustion of fossil fuels, particularly coal, waste incineration, the chlorine-alkali industry, non-ferrous metal production and paper manufacture. Mercury is used in thermometers, barometers, dental fillings, batteries, and fluorescent lamps. It is also used in informal gold mining presently on increase in developing countries, including South Africa. Although mercury use is illegal in most countries, amalgamation is the preferred method employed by artisanal gold miners. It is estimated that for every 1 gram of gold produced, 3-5 grams of mercury are released into the environment. Environmental and health impacts resulting from the misuse of mercury and the effects on international waterbodies are a source of global concern (AMAP 1998; GMP Newsletter 2003). Microorganisms can convert inorganic mercury into methyl mercury, which is a fat-soluble molecule that easily passes through cell membranes, accumulates in animals, and biomagnifies in the food chain.

Health impacts

Mercury is a nerve toxin and the main health concern is its effect on the brain, particularly in the growing foetus and young children. The phrase 'mad as a hatter' and the term 'hatter's shake' stem from mercury poisoning of hat makers using the metal for curing felt. Mercuric mercury not only produces toxicity in human but it is also fetotoxic to animals and effects on embryonic development causing fetal malformations in pregnant rodents has been shown (Chang et al. 1980). Danielson et al. (1984) and Holt and Webb (1986) have showed that mercuric mercury accumulates in placenta of the mouse and inhibits the foetal uptake of essential metabolites. Mercury can damage reproduction in mammals by interfering with the formation of sperm. Neurological and reproductive effects have also been seen in birds. In fish, its effects also include a decreased sense of smell, damage to the gills, blindness, and changes in the ability to absorb nutrients in the intestines. Plants can be sensitive to mercury, where high concentrations lead to stunted growth. Methyl mercury has been recognized as a cause of neurological disturbances and death in human adults and teratogenic anomalies in newborn infants (Koos and Longo 1976; Matsumoto et al. 1965).

Mercury exposure in South Africa

The main sources of mercury exposure in South Africa are mining and other industrial uses including mercury recovery plants. Although legislation exists that all workplaces using mercury need to register and conduct biological and environmental monitoring, studies show that only a limited number of workplaces actually conduct these tests on a regular basis (Weiner and Ross 1996). The chronic neurobehavioral effects of elevated occupational exposure to mercury has been reported (Powell 2000). An evidence of environmental mercury pollution, fish contamination and health problems in the community residing in the vicinity of a mercury processing plant were found (Oosthuizen and Ehrlich 2001). Growth of informal industrial activities including mining that use mercury ([e.g., informal gold digging in old mines](#)) is also of concern, especially activities that employ women, elderly and children.

Cadmium (Cd)

Cadmium is toxic to most forms of life. It can be taken up directly from water, and to some extent from air and via food, and it has a tendency to accumulate in both plants and animals. Mushrooms in particular can be very rich in cadmium. Cadmium is a by-product in the production of zinc and lead, and the pyrometallurgical production of zinc is the most important anthropogenic source to the environment. Other major sources are fossil fuel combustion and waste incineration. Cadmium is used in a wide spectrum of applications, including alloys, pigments, metal coatings, batteries, and in the electronics industry. It is also a contaminant in chemical fertilizer, manure, compost, and sewage sludge.

Cadmium is moderately toxic to aquatic invertebrates, reducing their growth and decreasing the survival of larvae. In fish, cadmium poisoning can lead to an ion imbalance and interfere with calcium metabolism. In higher animals, cadmium accumulates in kidneys and liver, where most of it binds to a metalloprotein (metallothionein MT) that makes the metal harmless to the animal. If the uptake is greater than this natural defence mechanism, cadmium can damage the kidneys and upset metabolism of vitamin D and calcium. Kidney damage and a decalcification of the skeleton are the serious chronic effects of high cadmium exposure. Kidney damage in seabirds has been seen at cadmium levels in the tissue of 60 to 480 micrograms per gram. Based on human toxicology, cadmium concentrations of 100 to 200 micrograms per gram (wet weight) in the kidneys probably represent a risk for mammals. With a half-life of decades, cadmium leaves the body extremely slowly.

Cadmium exposure in South Africa

It is thought that cadmium is emitted to the environment as a by-products of industrial and mining operation. Studies on the accumulation of cadmium in the terrestrial isopod (*Porcellio laevis*) were published (Odendaal and Reinecke 1999). The potential use of the South African river crab as a bioindicator species for cadmium pollution were also investigated (Schuwerack et al. 2001).

Aluminium (Al)

Aluminium is considered to be a detrimental element to living systems, with the potential to cause toxicity to the skeletal, haematopoietic and central nervous systems (Alfrey et al. 1976). The contributory role of aluminium in the dialysis encephalopathy syndrome has been shown and the role of aluminium in Alzheimer Disease etiology is still highly controversial. Numerous reports on cognitive impairment or other neurological effects associated with occupational exposure to aluminium dust or fumes have been published (McLaughlin et al. 1962; Sjörgen et al. 1990; Sjörgen et al. 1996). It is now accepted that long-term exposure to aluminium, particularly by inhalation, may cause aluminium accumulation in human tissues, which may lead to neurotoxicity (Rifat et al. 1990; White et al. 1992; Bast-Pattersen et al. 1994). A number of studies showed a small positive correlation between levels of Al in drinking water and dementias (Yokel, 2000 review). Due to continued concern about the neurotoxicity of aluminium, the U.S. Environmental Protection Agency (EPA) has put aluminium on its candidate list of contaminants. U.S. FDA recently implemented labelling requirements and Canada established operational guidance limits for drinking water as a precautionary principle. Biological indices of aluminium uptake, retention and excretion as well as the mechanism of aluminium uptake to brain and its retention and efflux are not clearly understood. The low molecular mass complex is thought to play an important role in the intracellular accumulation of aluminium (Röllin and Nogueira, 1997; Yokel 2002).

Aluminium exposure in South Africa

South Africa is a major global producer of primary and secondary aluminium and exposure to Al in occupational settings have been extensively researched. (Röllin et al. 1991, 1996, 2002). However exposure to aluminium in populations residing in the vicinity of smelters and aluminium foundries have not been investigated.

Arsenic (As)

Arsenic may be present in the environment both in inorganic and organic forms. Sources of arsenic are mainly herbicides, insecticides, rodenticides, paint pigments and wood preservatives (Baxley et al. 1981) and mining activities (Baxley et al. 1981). Arsenic can also occur naturally in certain areas and contaminate water sources (Bagla and Kaiser 1996).

Health impacts

Acute arsenic poisoning usually results after accidental or deliberate ingestion with gastrointestinal disturbances occurring immediately, followed by death from circulatory failure. At least one case of human neonatal death has been ascribed to maternal ingestion of arsenic (Lugo et al 1969). Chronic exposure to arsenic from water sources may result in skin keratoses and hyperpigmentation (Bagla 1996). Arsenic induced skin lesions may be associated with increased risk of skin, bladder and lung cancers (Cuzick et al 1992). Arsenate tetragenicity has been demonstrated in golden hamsters (Ferm and Carpenter 1969) and rats (Beaudoin 1974). With regard to arsenite it was found that arsenite treatment in mice resulted in high rates of foetal deaths and decrease of foetal weights (Hood 1972).

Arsenic exposure in South Africa

A number of studies reported elevated arsenic concentration in lakes (Greichus et al . 1977) and arsenic resistance in species of multi-host ticks (Matthewson and Baker 1975) as well as

fungating Bowen's disease thought to be associated with arsenic intoxication (Liebowitz et al 1982).

Chromium (Cr)

Chromium is a naturally occurring element found in rocks, animals, plants, soil, and in volcanic dust and gases. Chromium is present in the environment in several different forms. Chromium(III) occurs naturally in the environment and is an essential nutrient that helps body to use sugar, protein, and fat. Chromium(VI) and chromates are widely used in industries, such as leather, textiles, chrome-plating, steel mills and dye-producing (Langard 1983, Langard&Norseth 1979). Other sources of chromium emissions include oil and coal combustion, cement plants, industrial paint and coating manufacture, and cooling towers, which use chromium(VI) as a rust inhibitor.

Occupational exposures to chromium(VI) compounds can be acute and cause lung cancer. Owing to the deposition of industrial waste, including chromates, in the soil, contamination of drinking water resources and an increase in their concentration in ambient air might be expected (Becker et al 1991, Langard&Norseth 1979).

Hexavalent chromium(VI) is an established mutagen as well as human carcinogen (IARC, 1990, Langardt, 1990). The carcinogenic action of some chromium compounds has been demonstrated in laboratory animals (Cohen, 1993, Leonard, 1980). Soluble CrVI compounds have a corrosive action to skin and mucous membranes, especially to the nasal septum (Cohen, 1993). Inhaled aerosols of CrVI are readily absorbed from the respiratory tract. In addition, some of the chromium compounds are found to be neurotoxic, as well as allergenic (IPCS, 1988, 1991). It is considered that genotoxic and carcinogenic activity of chromium VI is connected with its metabolism in the cell. Unlike trivalent chromium(III), hexavalent chromium(VI) penetrates easily the cell membrane, and is rapidly taken up by the cell. Intracellularly hexavalent chromium undergoes a complicated cascade of reductive metabolic processes, until it is converted to trivalent chromium(III) which is stable (Cohen et al. 1993; De Flora et al 1990; Helleday et al 2000). Although there is no scientific evidence that exposure to chromium will result in birth effects or other developmental effects in people, these effects have been observed in animals exposed to hexavalent chromium.

Vanadium (V)

Vanadium is a trace element which is found at very low concentrations in most living organisms. Convincing evidence indicates that it may be essential for animals (French 1993), although conclusive demonstration of its essentiality in human being is still lacking (Harland 1994). Vanadium is extensively used in modern industry, expanding from mining and its classic use in steel production to electronics. It is also released into the environment through the combustion of fossil fuels (Hope 1994, Nriagu 1988).

Generally, the toxicity of vanadium compounds is low, with pentavalent compounds being the most toxic. Exposure to vanadium dusts may cause irritation of the skin and the respiratory track (Carlson 1987,) and may lead to a greenish-black discoloration to the tongue (Thomas 1956).

Several important actions of vanadium have been described, including insulin-like properties making vanadium a potential substitute for insulin in diabetes management (Tolman et al. 1979; Schechter and Karlish 1980)

Depending on circularly levels, vanadium may also cause a number of adverse effects in mammals, such as hemopoietic changes and renal toxicities as well as inhibition of enzymes (Cantley 1977).

Chromium and vanadium sources in South Africa

Chromium and vanadium are mined in South Africa and also used in primary and secondary industrial activities. Geochemical maps of Mpumalanga, South Africa show the existence of anomalous metal accumulations in soils which can be attributed to both natural and industrial causes. A systematic regional geochemical survey, based on samples collected at a density of one per square kilometre, shows the presence of large (4 to 12 km) chrome and vanadium anomalies located around steel mills of the area (including other metals such as manganese, titanium and scandium). The anomalies are thought to result from dust or smoke fallout of the steel mills. Discussions with health authorities in the area have revealed that some steel mill workers/community show physical signs of exposure to vanadium (Cloete personal communication).

3.3 Interaction of essential metals with toxic metals

Interaction of a toxic metal with essential trace elements in a living organism after environmental or occupational exposure plays an integral role in its toxicity (Gulumian et al. 1995). Toxicity of toxic metals can be increased or lessened by the metabolic status of the essential trace elements, which can be affected either through inborn genetic defects, exposure to toxic substances and diet. For example it has been shown that chronic low-level exposure to lead during pregnancy and early child development can result in behavioural alternations in the absence of overt toxicity (Miller et al. 1990). This perturbation of the functioning of the central nervous system may be a the result of deficiencies in essential metals resulting from lead-induced impairment of mineral availability and/or an increased sensitivity to lead in the absence of adequate levels of essential minerals such as zinc. Number of studies show the interaction of cadmium and aluminium with essential metals (Petering et al. 1979; Wenk and Stemmer 1981; Röllin et al. 1991,1993). Also possible impacts of cadmium, lead and mercury on pregnancy outcome are thoroughly assessed in the literature (reviews in: AMAP 1998; Odland et. al. 1999a; 1999b; 2000). For example low selenium status (selenium is an essential nutrient in small amounts but toxic in higher concentrations, damaging hair and nails) may be associated with an increased risk of cancer (Salonen et al, 1984, Schroeder et al 1970) and an increased risk of ischemic heart disease (Huttunen 1986).. Furthermore this competitive interaction between toxic ions and essential metal ions will also interfere with functions of many ligands and result in metabolic changes.

Thus concurrent determination of toxic and essential trace metals in the proposed study will contribute to in depth evaluation and understanding of these interactions.

The most important essential elements in maternal blood are planned to be analysed due to the concern of nutritional status of both the mothers and their newborns, as well as the interaction with toxic elements:

Co, Cu, F (in relation to Aluminium exposure), Mo, Se, Zn, and I (in relation to the thyroid status of mother and child). Some of those elements are best explained by maternal blood concentrations (e.g., Cu, Se), others by urine excretion, using spot sample concentrations (e.g., Co, F, I). Iron status is best expressed as ferritin and transferrin receptor concentrations in blood: The traditional and well accepted marker of iron status in human blood is ferritin. Ellingsen et al. (2003 in press) have demonstrated that manganese-exposed workers have higher intracellular iron concentrations in the erythrocyte precursors than controls, resulting in a down-regulation of transferrin receptors on the cell surface. Since manganese exposure might be an important part of this study due to known exposures through mining processes, it is of high importance to include transferrin receptors as well.

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4. Suggested reproductive and developmental endpoints for a comprehensive study.

4.1 Before term delivery

- Spontaneous abortions 1. trimester
- Spontaneous abortions 2. trimester
- Preterm abortion

4.2 Term and preterm delivery

- Birth weight
- Child's body mass index at birth
- Gestational age
- Gender
- Caput circumference
- Congenital malformations observed immediately after delivery
- Thyroid status at birth
- Haematopoietic status at birth
- Blood PTS-levels at birth
- Blood toxic metals at birth
- Blood essential elements at birth

4.3 Later development of child

- Growth pattern weight 6, 12, 18 months
- Growth pattern height 6, 12, 18 months
- Growth pattern caput circumference, 6, 12, 18 months
- Discovered malformations 6, 12, 18 months
- Cognitive development 24 months
- Thyroid status 6, 12, 18 months
- Liver function 6, 12, 18 months

- Neurophysiologic status (MEG/EEG) 8-12 years
- Haematopoietic status at 6, 12, 18 months
- Infectious status at 6, 12, 18 months – otitis media frequency
- Lung function 8-12 years measured by spirometry

For a comprehensive study it is crucial to initiate the creation of a regional birth registry in close cooperation with the local and central health authorities. Some basic principles and standards for this work are described by Odland et al. (1999c).

5. Design of the pilot study

5.1 Locations

- Johannesburg - urban population
- Richards Bay - industrial population
- Witbank - industrial and mining population
- Western Cape - fishing population
- East Rand, Johannesburg – informal mining
- North-West SA – rural, traditional population

5.2. Sample size

The pilot study will include 12 delivering women from each location. The women will be included based on a written, informed consent.

5.3. End point factors

The following information is preferable for the pilot study:

- Maternal age
- Maternal weight and height
- Parity
- Spontaneous abortions
- Occupation
- [Paternal occupation](#)
- Economic situation
- [Living conditions](#)
- [Heating indoor](#)
- Major illnesses and medication (if daily)

- Major food sources in daily life (fish, meat, vegetables etc..) before pregnancy and during pregnancy
- Smoking habits
- Birth weight of baby
- Birth length of baby
- Caput circumference of baby
- Gestational age of baby
- Gender of baby
- Congenital malformations
- Levels of selected persistent toxic substances in maternal plasma
- Levels of selected essential elements in maternal plasma
- Levels of selected toxic metals in maternal blood
- Hormonal status and lipid profile in maternal plasma

5.4. Questionnaire

To be developed for the main study. As for the pilot study the information in 5.3 is satisfactory.

5.5. Sampling procedure

Equipment and sampling protocol is provided by the CTQ Laboratory, Quebec, Canada.

[The preferred time of maternal blood sampling and urine sampling \(morning urine, spot sampling\) is at the last medical consultation before delivery, 36-39 weeks of gestation, before the delivery process starts \(Aaset et al. 2001\). If possible, cord blood will be included after delivery.](#)

5.6. Chemical analysis

During the pilot study the contaminants will be analysed partly by the Norwegian Institute for Air Research (Tromsø, Norway), the National Institute of Occupational Health (Oslo, Norway), the Centre de Toxicologie du Quebec, (Quebec, Canada) and Council for Geoscience, Pretoria, South Africa.

Analytes in maternal plasma or blood for the pilot study:

- The DDT-group
- The HCH-group
- Toxaphenes (selected congeners)

- HCB
- PCB (selected congeners)
- Dioxins (pooled samples will be considered)
- Toxic metals Cd, Pb, Al, Hg, Cr, As, V, Mn
- Essential elements Cu, [iron expressed by ferritin and transferrin receptors](#), Se, Zn
- Hormonal status of mother post partum: FSH, LH, ACTH, Prolactin, TSH, FT4, [FT3](#), Estradiol, progesterone
- Lipid profile; Cholesterol, Triglycerides
 - [Analytes in maternal urine for the pilot study: Co, F, I, Mn, Mo](#)

5.7. Data storing and assessment

Data storing and assessment will be carried out by the main partners in close cooperation.

5.8. Exclusion factors

The ideal design of the pilot study is to perform sampling from consecutive mothers and children from each location. The almost endemic prevalence of HIV and tuberculosis in certain locations of South Africa raises the question of excluding HIV positive patients or patients with active tuberculosis. This question is regarded as very important by the research group, and we suggest to exclude those patients in the pilot study.

6. Costs and timetable of pilot study

<u>General costs, including strategy meeting in SA</u>	<u>NOK</u>
Sampling and sampling equipment and per diem cost	<u>21 000</u>
Chemical analysis	<u>245 000</u>
Capacity building	<u>70 000</u>
Travelling expenses	<u>70 000</u>
Data management, treatment and publication	<u>56 000</u>
Miscellaneous	<u>50 000</u>
Total pilot study costs, general	<u>512 000</u>

<u>SA costs</u>		<u>NOK</u>
Travel to sites	Airfares – 10 flights to study sites by project staff	<u>38 000</u>
Subsistence		<u>7 000</u>
Car hire at sites, insurance, fuel	Car hire for 78 days	<u>40 000</u>
Accommodation	108 nights at Rand 600 per night	<u>57 000</u>
Salaries	2 Field scientists 1 project manager (MRC) 2 research scientists(MRC) 1 research scientist (CGS)	<u>60 000</u> nil (covered by MRC) nil (covered by CGS)
Soil, air and water analysis in SA		28 800
Courier service to Norway and Canada	Once each:CanadaR 3500; Norway R 3800	7300
Office costs (printing, data input, telephones etc)	Estimated R 10 000	Nil (costs to MRC)
Reports	Printing in colour	<u>15 000</u>
Incidental		5 000
	Subtotal	<u>258 100</u>
Administration of funds	15 % (to MRC)	<u>36 715</u>
	Total	<u>396 815</u>
<u>Total budget pilot study</u>		<u>908 815</u>

7. Main study

The pilot study will decide the need for a more comprehensive study. A regional, fully developed birth registry to be the basic tool from the beginning of such a study. If levels of dioxins and PCBs are found high in the pilot study, dietary interventions might be considered in a case- control study; e.g., dioxin- and PCB- free diets high in green vegetables to increase excretion and prevent the enterohepatic circle of fat soluble compounds; or introducing omega-3-fatty acids in a controlled trial.

8. Publication

All data belong to the project team as a whole. Results will be presented at international conferences and published in international scientific journals based on mutual agreement between the partners. Comprehensive report on the study funding will be compiled for South African governmental departments and research institutions.

9. Project team

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