



Identificatie van indicatoren voor impact van endocrien verstorende stoffen
/hormonale stoffen (in het Engels)

Identification of indicators for the impact of endocrine/hormone disrupting substances

Studie uitgevoerd door Universiteit Gent en Katholieke Universiteit Leuven

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The authors

Summary

Based on the evidence we gathered on the possible health impacts of endocrine disruption, we generated a list of pathologies possibly related to endocrine disruptors. The availability of medical data on the relevant pathologies in Flanders was then explored through contacts with many organizations and experts. A suggested strategy was developed for the retrieval of these data and linking them to data on environmental pollution. The relevant pathologies were then ranked according to the evidence available and the relevance to the Flemish situation in a descending order of priority (see below).

Rank	Pathology
1	Breast cancer (female)
2	Female infertility
3	Male infertility
4	Non-Hodgkin lymphomas
5	Prostate cancer
6	Delayed puberty
7	Sex ratio
8	Congenital anomalies (in general)
9	Intrauterine growth retardation
10	Prematurity
11	Testicular cancer
12	Disturbances in mental and psychomotor development
13	Cryptorchidism
14	Hypospadias
15	Precocious puberty
16	Thyroid gland diseases
17	Immune system diseases (immunosuppression)
18	Endometriosis
19	Time to pregnancy

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1 Abbreviations

Anti-TPO: antithyroid peroxidase antibody
APD: anatomopathological reports (AntatomoPathologisch Discussie)
BFRs: brominated flame retardants
CEG: committee for the evaluation of medication practice (Comitee voor de Evaluatie van Geneesmiddelenpraktijk)
CI: confidence interval
CLBs: centers for guiding pupils (Centra voor Leerling Begelijding)
COS: centers for developmental disturbances (Centra voor OntwikkelingSstoornissen)
CT: computerized tomography
DDE: dichlorodiphenyl dichloroethylene
DDT: dichlorodiphenyltrichloroethane
DEHP: di(2-ethylhexyl)phthalate
DES: diethylstilbesterol
DG: directorate general
ER: estrogen receptor
ERSPC: European randomized screening for prostate cancer
EUROHAZCON: a multicentre case-control study of the risk of **congenital anomalies** associated with residence near **hazardous-waste** landfill sites in **Europe**
EUROCAT: European concerted action on congenital anomalies and twins
FOD Mineco: FOD economy, small and medium sized companies, independents and energy (FOD economie, KMO, middenstand en energie)
FOD: Federal government department (**Federale OverheidsDienst**)
FSH: follicle stimulating hormone
GAD: glutamic acid decarboxylase
GMD: global medical file (Gloobaal Medisch Dossier)
GnRH: gonadotropin relasing hormone
HCB: hexachlorobenzene
HCE: heptachloroepoxide
HCG: human chorionic gonadotropin
HMG: human menopausal gonadotropin
ICD: International Classification of Diseases
ID number: identification number
IMA: intermutuality agency (InterMutualistisch Agentschap)
IUGR: intrauterine growth retardation
IVF/ICSI: *in vitro* fertilization/intracytoplasmic sperm injection
KB: Royal decree (koninklijk besluit)
LH: lutrinizing hormone
MCSS: multiple chemical sensitivy syndrome
MKG: minimal clinical findings (Minimale Klinische Gegevens)
MOC: multi-disciplinary oncological consultation (multidisciplinair oncologisch consult)
MRI: magnetic resonance imaging
NICO: a project for electronization of CLB data (netoverstijgend ICT-project voor CLB gegevens in samenwerking met departement onderwijs)
NIS: national institute of statistics
OR: odds ratio
PAH: poly-aromatic hydrocarbon
PBBs: polybrominated biphenyls
PCAH: polychlorinated aromatic hydrocarbons
PCBs: polychlorinated biphenyls
PFOA: perfluorooctanic acid

PFOS: perfluorooctyl sulfonic acid
PPM: parts per million
PSA: prostate specific antigen
RIZIV: national institute for sickness and invalidity insurance (Rijks Instituut voor Ziekte- en Invaliditeits Verzekeringen)
RR: relative risk
SMR: standardized mortality ratio
SPE: study center for perinatal epidemiology (studiecentrum voor perinatale epidemiologie)
T4: tetraiodothyronine
TEQ: toxic equivalence
TESE: testicular sperm extraction
TSH: thyroid-stimulating hormone
TTP: time to pregnancy
VLK: the Flemish League against cancer (Vlaamse liga tegen kanker)
VMM: the Flemish environmental agency (Vlaams milieu maatschappij)
VUB: Free University Brussels (Vrije Universiteit Brussel)
WWF: world-wide fund

2 Simplified definitions of some medical terms

(For more details see page 28)

Adipose tissue: bodily fat

Cryptorchidism: a congenital abnormality of the male genitalia characterized by failure of the testis to descend along its normal path into the scrotum from the posterior abdominal wall. The testis maybe high scrotal, inguinal or impalpable

Endometrium: the inner lining of the uterus (a mucous membrane)

Endometriosis: the abnormal presence of endometrium outside the uterus.

Estradiol: the most powerful "female hormone" that occurs naturally. Estradiol has physiological functions in the male also

Fibroid: benign uterine tumor made up of fibrous and muscular tissue

Gestation: pregnancy

Hypospadias: a congenital abnormality of the male genitalia characterized by incomplete development of the urethra so that the external urethral opening (meatus) is on the ventral surface of the penis or on the scrotum, rather than at the tip of the penis

Hypothyroidism: decreased function of the thyroid gland

Intrauterine growth retardation: a fetus that is small in weight for the duration of pregnancy

Menarcheal age: age at the first menstruation

Neuroblastoma: Malignant tumor consisting mainly of immature nerve cells

Non-Hodgkin lymphomas: A group of malignant diseases affecting the lymph tissues (lymph nodes and others) excluding one particular type of lymphoma (Hodgkin's Disease)

Polythelia: multiple nipples

Precocious puberty: puberty occurring abnormally early in life

Sex ratio: male to female ratio at birth

Sperm concentration: the number of spermatozoa in one milliliter of semen

Sperm morphology: the shape of spermatozoa as seen under the microscope

Total motile sperm count: the total number of motile spermatozoa in the ejaculate

Total sperm count: the total number of spermatozoa in the ejaculate

Umbilical cord: the cord that carries blood, oxygen and nutrients to the baby from the placenta during pregnancy

Xenoestrogens: synthetic chemicals with female hormone (estrogen-like) actions

3 Introduction

As defined by the European Workshop on the impact of endocrine disrupters on human health and wildlife, an endocrine disrupter is an exogenous substance that causes adverse health effects in an intact organism, or its progeny, secondary to changes in endocrine function (European commission environment DG, 2001).

Numerous studies have evaluated the effects of endocrine disrupting substances in wildlife, laboratory animals and in *in vitro* laboratory experiments. Many of these studies are summarized in recent reviews (see for example De Bont & van Larebeke, 2004; VMM, 2003).

However, much less is known about the impact of environmental exposure to endocrine disrupters on human health. The purpose of the present work is not to prove a link between endocrine disruption and human health but to summarize the possible impact of endocrine disruption in humans. Whenever available, priority is given to evidence on effects of exposure at environmental rather than occupational levels.

Based on the evidence gathered on the possible health impacts of endocrine disruption, we explored the availability of medical data on the relevant pathologies in Flanders through contacts with many organizations and experts and developed a strategy for the retrieval of these data and linking them to data on environmental pollution.

Further details on the possible effects of relatively new substances accumulating in the environment such as flame retardants (De Bont & van Larebeke, 2004), perfluorooctyl sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) (De Bont et al., 2004) are reviewed in recent reports from Flemish institutions. The neurotoxic effects of environmental factors in general have also been recently reviewed (Viaene, 2000). An extensive set of data is also available on pollutant levels in the eel in Flanders (Goemans et al., 2003; Roose et al., 2003).

Besides endocrine disruption, it is evident that other etiological factors are involved in the pathogenesis of diseases including lifestyle and genetic factors, nutrition and non-hormonal effects of pollutants. An exhaustive description of these factors is beyond the scope of this work. Also, one given substance may exert its effects both via endocrine disrupting effects as well as via other mechanisms, for example genetic damage. The separation between these effects is not always evident.

4 Materials and methods

Literature searches were performed using the Pubmed search engine. Keywords used were endocrine disruptors (or disrupters) and health. The combination of an individual pathology and an individual endocrine disruptor (for example breast cancer AND dioxin) was also used for the literature search. An internet search for articles not included in Pubmed was performed using the Google search engine and similar keywords. For very recent articles not yet included in Pubmed, a hand search in relevant scientific journals was performed (for example environmental health perspectives and 'the Belgian' archives of public health). Whenever possible, meta-analyses, reviews, well-designed studies containing a large number of participants and recent articles (year 2000 or beyond) were used. In addition, data on possible sources of medical information in Flanders were obtained from different Belgian and international institutions such as the Belgian national institute for sickness and

invalidity insurance (Rijks Instituut voor Ziekte- en Invaliditeits Verzekeringen, RIZIV) medical mutualities, the European concerted action on congenital anomalies and twins (EUROCAT), and many others.

5 Pathologies possibly related to endocrine disruption (literature review)

The pathologies discussed below represent a summary of the literature on the possible relationship between endocrine disruption and human health. They are discussed in chronological order starting with intra-uterine life through childhood, adolescence and adulthood.

5.1 Intra-uterine growth and pregnancy outcome

A study from Spain (Ribas-Fito et al., 2002) indicated that premature newborns had higher umbilical cord serum concentrations of hexachlorobenzene (HCB) [1.94 ng/mL among prematures versus 1.10 among non-prematures ($p < 0.10$)], dichlorodiphenyl dichloroethylene (*p,p'* DDE) [2.40 versus 0.80 ($p < 0.05$)], and polychlorinated biphenyls (PCBs) [0.70 versus 0.14 ($p < 0.10$)]. Those infants born with a small length for gestational age had higher levels of HCB in cord serum than those with an adequate length for gestational age [1.64 ng/mL versus 1.00 ng/mL ($p < 0.05$)]. In addition, HCB umbilical cord serum levels were negatively associated in a dose-response way with crown-heel length [for each doubling of the dose there was a mean decrease of 0.46 (standard error = 0.22) cm] after adjusting for smoking, gestational age, and other organochlorine compounds (Ribas-Fito et al., 2002). Significant associations were also reported between hexachlorocyclohexane and *p,p'*-DDE in maternal and umbilical cord blood at the one hand and intra-uterine growth retardation (IUGR) after adjustment for potential confounders (Siddiqui et al., 2003) at the other hand. Atrazine, metolachlor, and cyanzinc levels in contaminated drinking water were also found to be significant predictors of IUGR rates in the community (Munger et al., 1997).

Earlier studies indicate that organochlorines and PCB exposure may be associated with spontaneous and missed abortion (Bercovici et al., 1983; Leoni et al., 1989; Saxena et al., 1981). The association between HCB and abortion/miscarriage is controversial (Jarrell et al., 1998; Leoni et al., 1989). In Turkish women accidentally exposed to HCB, there was a strong relationship between serum HCB levels and risk for spontaneous abortion (Jarrell et al., 1998).

A study from the Ukraine indicated concentrations of seven organochlorine pesticides (dichlorodiphenyltrichloroethane "*p,p'*-DDT", *p,p'*-DDE, beta-hexachlorocyclohexane, HCB, trans-nonachlor, oxychlorodane, heptachloroepoxide "HCE") and eleven different polychlorinated biphenyl congeners measured in maternal milk, had no impact on weight of the infant at birth (Gladen et al., 2003).

5.2 Congenital anomalies

Some studies report on the relationship between endocrine disruptors and all congenital anomalies in general (described below under section 5.2.1). The possible relationship between endocrine disruption and specific congenital anomalies hypospadias as well as cryptorchidism are individually discussed (section 5.2.2).

5.2.1 Congenital anomalies in general

A multicentre case-control study of the risk of congenital anomalies associated with residence near hazardous-waste landfill sites in Europe (The EUROHAZCON study) involving many European countries including Belgium indicates an increased risk of chromosomal and non-chromosomal congenital anomalies for people living 3 km or less near hazardous-waste landfill sites in Europe (Dolk et al., 1998; Vrijheid et al., 2002).

Also, a questionnaire study from south Africa indicated that the use of plastic containers for transport of drinking water [odds ratio (OR) 6.5, 95% confidence interval (CI) 2.2, 27.9] and exposure to chemicals used in agriculture (OR= 7.18, 95% CI= 3.99-13.25) were associated with increased incidence of congenital anomalies (Heeren et al., 2003).

Another study indicated that a mother living near industrial facilities that emitted solvents (OR= 1.3, 95% CI= 1.0-1.7) or metals into the air (OR = 1.4, 95% CI = 1.0-1.8) had an elevated risk of giving birth to a child with central nervous system birth defects (Marshall et al., 1997).

5.2.2 Hypospadias and cryptorchidism

An increased risk of hypospadias has been reported in the sons of women exposed to diethylstilbesterol (DES) in utero (prevalence ratio 21.3 [95% CI 6.5-70.1]) (Klip et al., 2002). A similar tendency has been recently reported by Roelfs et al. (2004), although the increase in risk did not reach statistical significance (OR= 2.6, 95% CI= 0.8–9.1). Both studies indicate that hypospadias was strongly associated with low birth weight, twin or triplet pregnancy, preterm delivery and use of assisted reproductive techniques.

Another study reported that the risk of hypospadias was doubled when the mother was exposed to chemical hazards (pesticides) during gestation (Morera et al., 2004).

At the other hand, a significantly increased risk of cryptorchidism but not of hypospadias was found in sons of Danish women working in gardening (adjusted OR = 1.67; CI= 1.14-2.47). The risks were not increased in sons of men working in farming or gardening (Weidner et al., 1998). A Chinese study, however, indicated that paternal exposure to pesticides occupationally was associated with an increased risk of cryptorchidism (OR= 12.79, 95% CI= 2.90 - 56.43) (Wang & Wang, 2002).

Significantly higher levels of HCE and HCB, have been detected in fatty tissue of children with cryptorchidism compared to children undergoing other surgical procedures (Hosie et al., 2000).

The results of a recent nested case-control study on DDT in relation to hypospadias/cryptorchidism were inconclusive (Longnecker et al., 2002). Boys with maternal serum levels of DDE greater than or equal to 85.6 µg/L had adjusted OR of 1.3 (95% CI= 0.7, 2.4) for cryptorchidism, 1.2 (95% CI= 0.6, 2.4) for hypospadias, and 1.9 (95% CI= 0.9, 4.0) for polythelia (multiple nipples). For cryptorchidism and polythelia, the results were consistent with a modest-to-moderate association (Longnecker et al., 2002).

In a study involving 7928 boys born to mothers taking part in the Avon Longitudinal Study of Pregnancy and Childhood, mothers who were vegetarian in pregnancy, had an adjusted OR of 4.99 (95% CI= 2.10-11.88) of giving birth to a boy with hypospadias, compared with

omnivores (North & Golding, 2000). Since vegetarians have a greater exposure to phytoestrogens from food than do non-vegetarians, these results support the possibility that phytoestrogens (possibly also xenoestrogens or some unrecognized nutritional deficiency) have a deleterious effect on the developing male reproductive system.

5.3 Development and health during childhood and adolescence

The possible effects of endocrine disrupting substances on development and health during childhood and adolescence include delayed mental and psychomotor development, thyroid dysfunction, immunosuppression as well as other health effects.

5.3.1 Mental and Psychomotor development

The umbilical cord serum levels of p,p'DDE were found to be negatively associated with both mental and psychomotor development. For each doubling of a dose of p,p'DDE, a resultant decrease of 3.50 points (standard error: 1.39) on the mental scale and 4.01 points (standard error: 1.37) on the psychomotor scale has been reported (Ribas-Fito et al., 2003a). Adverse effects of prenatal exposure to PCBs were detected primarily in children who had not been breast-fed. These included greater impulsivity, poorer concentration, and poorer verbal, pictorial, and auditory working memory (Jacobson & Jacobson, 2003). Earlier studies indicated that the levels of polybrominated biphenyls (PBBs) in young children to be negatively associated with scores on some developmental tasks (Schwartz & Rae, 1983). A recent review on perinatal exposure to background levels of dioxins in Europe and the USA indicates this exposure may cause persistent effects into childhood including deficits in intelligence and behavior (ten Tusscher & Koppe, 2004)

Most studies agree that exposure of the offspring to endocrine disruptors and other chemicals mainly occurs transplacentally (Jacobson & Jacobson, 2003; Pronczuk et al., 2004; Ribas-Fito et al., 2003a; Walkowiak et al., 2001). Long-term breastfeeding was found to be beneficial to neurodevelopment, potentially counterbalancing the impact of exposure to these chemicals through breast milk (Jacobson & Jacobson, 2003; Ribas-Fito et al., 2003a), although an earlier study from Germany suggested a small additional negative effect of PCB exposure via breast milk on neuropsychological development, especially higher-order mental processes such as simultaneous and sequential information processing but found no effect on developmental milestones (Walkowiak et al., 2001). A recent editorial from the World Health Organization (WHO) summarizes its own and other safety studies on human breast milk (Pronczuk et al., 2004). Based on these safety studies and the beneficial effects of breastfeeding including immunological, developmental, and psychological advantages and the possible prevention of diabetes, heart disease, and other diseases in adulthood, the WHO promotes breastfeeding in all countries (Pronczuk et al., 2004). The WHO also stresses the need for decreasing the levels of contaminants in the environment rather than limiting the period of breastfeeding. The same editorial indicates that tobacco smoking deserves special consideration because it increases the exposure of mothers and infants to a large number of toxicants, including pesticide residues and known carcinogens (Pronczuk et al., 2004). Women who smoke should be therefore encouraged to breast-feed and to eliminate, or at least reduce, cigarette smoking during pregnancy and lactation. The WHO recommends that infants should be exclusively breastfed for their first 6 months of life then receive complementary foods while breast-feeding continues up to 24 months of age or beyond (Pronczuk et al., 2004).

5.3.2 Thyroid function

Exposure of newborns, infants and children to PCBs, dioxins, and/or co-contaminants (reviewed in van Larebeke et al., 2001) is associated with changes in thyroid hormone levels including increased or decreased plasma thyroid-stimulating hormone (TSH) levels and lower plasma tetraiodothyronine (T4) levels. In particular, the higher TSH levels are indicative for hypothyroidism (Koopman-Esseboom et al., 1994). No association was found between high exposure to HCB and TSH concentrations at birth (Ribas-Fito et al., 2003b). For the possible effects of endocrine disruptors on thyroid function in adults see page 23.

5.3.3 Immunosuppression

Studies in newborns show that subtle functional alterations of the developing human immune system may result from in utero exposure to organochlorines (and mercury) (Belles-Isles et al., 2002). Changes in cells controlling the immune system indicating immunosuppression have been also reported in Dutch infants. These include a shift in T-cell subpopulations in favor of immunosuppressive subtypes and lower monocyte and granulocyte counts in the blood (Weisglas-Kuperus et al., 1995).

A more recent study from the Netherlands indicated that prenatal PCB exposure was associated in later childhood with lower prevalence of symptoms suggestive of asthma (less shortness of breath with wheeze), and that current PCB body burden was associated with a higher prevalence of recurrent middle-ear infections and of chicken pox and a lower prevalence of allergic reactions (Weisglas-Kuperus et al., 2000b). A Belgian study in adolescents from Antwerp also indicated that the levels of both dioxin-like compounds and PCBs were negatively correlated with symptoms and immunological markers of asthma and allergic responses (Van Den Heuvel et al., 2002). These studies suggest that the immunosuppressive effects of exposure to PCBs and dioxins persist into childhood and adolescence and might be associated with a greater susceptibility to infectious diseases and a lower prevalence of allergic diseases (Van Den Heuvel et al., 2002, Weisglas-Kuperus et al., 2000b). Whether the immunosuppressive effect of some endocrine disruptors is related to hormonal alterations in corticosteroids is presently unknown. For the possible immunosuppressive effects of endocrine disruptors in adults see page 24

5.3.4 Other health effects

Exposure of newborns to PCBs, dioxins, and/or co-contaminants (reviewed in van Larebeke et al., 2001) may interfere with the vitamin K metabolism associated with a late form of hemorrhagic disease of the newborn (Koppe, 1995). This late form is due to vitamin K deficiency at the age of 1 month to 1 year (Lane & Hathaway, 1985). The effects of perinatal exposure to background levels of dioxins also include interference in haematopoiesis, reduced lung function and some transient influences on liver enzyme levels (reviewed in ten Tusscher & Koppe, 2004).

5.4 Puberty

In most European countries the age of onset of puberty and age at the first menstruation (menarcheal age) has been decreasing during the past few decades (review: Muinich Keizer & Mul, 2001). Disturbances in pubertal development including both puberty occurring

abnormally early in life (precocious puberty) as well as delayed puberty may possibly be related to exposure to endocrine disruptors.

5.4.1 Precocious puberty

The onset of puberty at an earlier age described above has been attributed to environmental factors, possibly man-made estrogen like compounds (xenoestrogens). Also, precocious puberty has been more frequently observed in immigrated or adopted foreign children living in Western Europe (Parent et al., 2003). This diagnosis is still often unrecognized. It is important not to delay diagnosis and treatment of precocious puberty so as not compromise the final height of the patient (review: De Monleon, 2001). Higher levels of p,p'-DDE have been reported in immigrated or adopted foreign children living in Belgium (Krstevska-Konstantinova et al., 2001). It has been hypothesized that withdrawal of xenoestrogens, due to lower levels of exposure in Western Europe compared to land of origin, may be the cause of precocious puberty in immigrated or adopted foreign children (Krstevska-Konstantinova et al., 2001). A recent doctoral thesis has discussed this subject in more detail (Parent, 2004) and Professor J. P. Bourguignon (Center for cellular and molecular neurobiology, Department of pediatrics and adolescent medicine, Faculty of medicine, University of Liège) has established a registry for such children. Further studies are needed.

A study in humans accidentally exposed to PBBs (Michigan, USA) indicated that breastfed girls exposed to high levels of PBB in utero ($>$ or $=7$ parts per billion) had an earlier age at menarche (mean age = 11.6 years) than breastfed girls exposed to lower levels of PBB in utero (mean age = 12.2-12.6 years) or girls who were not breastfed (mean age = 12.7 years) (Blanck et al., 2000).

5.4.2 Delayed puberty

A Belgian study indicated that exposure to polychlorinated aromatic hydrocarbons (PCAH) is associated with delayed sexual maturation (Den Hond et al., 2002; Staessen et al., 2001), although the methodology and conclusions of this study has been criticized (Dhooge et al., 2001; Molenberghs et al., 2003). The pubertal development of adolescents living in a 'contaminated' suburb near two waste incinerators (Antwerp) was compared with the other control (supposedly clean) agricultural area of Peer. Fewer boys of a certain age from the Antwerp area ($p < 0.001$) had reached the adult stages of genital development (62% vs. 92% and 100%, respectively) and pubic hair growth (48% vs. 77% and 100%). Also, fewer girls of a certain age from Antwerp ($p = 0.04$) had reached the adult stage of breast development (67% vs. 90% and 79%). In individual boys, a doubling of the serum concentration of PCB congener 138 increased the odds of not having matured into the adult stage of genital development by 3.5 ($p = 0.04$). Similarly for PCB congener 153 in relation to male pubic hair growth, the OR was 3.5 ($p = 0.04$). In girls, a doubling of the serum dioxin concentration increased the odds of not having reached the adult stage of breast development by 2.3 ($p = 0.02$). Left plus right testicular volume was lower in both polluted areas (Antwerp) than in the control area of Peer (42.4 mL vs. 47.3 mL, $p = 0.005$) but was not related to the current exposure of the adolescents to PCAHs. These findings regarding pubertal development are in apparent contradiction with data on sperm quality from the same areas (see male infertility page 18).

5.5 Infertility

There have been concerns about a low and decreasing birth rate in many industrialized countries where up to 5-6% of children today are born after assisted reproduction (Jensen et al., 2002). Whether this decline is due to social changes or environmental factors requires further investigation. The classification of infertility into male and female subcategories is artificial because infertility affects couples and not individuals. Time to pregnancy, for example is a parameter that evaluates the fertility of both partners (see below).

5.5.1 Male infertility

Based on a meta-analysis of publications mainly from Europe and North America, Carlsen et al. (1992) indicated that number of spermatozoa per milliliter of the ejaculate (sperm concentration) overall had declined by half over a 50-year period. In a re-analysis of this study, Swan et al. (Swan et al., 1997) found that the decline could have been even stronger among European men. It has been hypothesized that exposure to endocrine disrupters during fetal life is responsible for a group of diseases collectively called the testicular dysgenesis syndrome, which includes cryptorchidism, hypospadias and testicular cancer in addition to male infertility (Skakkebaek, 2002).

A steady decrease in the percentage of spermatozoa with normal shape (morphology) has also been observed in young healthy Flemish candidate sperm donors (Van Waeleghem et al., 1996). Data is available on candidate donors from 1977 till present (Professor F. Comhaire, Andrology Laboratory, University Hospital Ghent). A study comparing sperm quality in Antwerp and Peer also indicated lower sperm morphology and serum testosterone levels in young men from Peer were accompanied by frequent consumption of locally produced fruits and vegetables by the study participants in Peer (W. Dhooge, personal communication) and higher levels of DDT (toxic equivalence, TEQ) in women from the same area (Onderzoek Milieu en Gezondheid) (Vlietinck et al., 2000). This was a rather unexpected finding since Peer was selected as the control (clean) area to be compared to the presumably more polluted areas in Antwerp (see puberty page 16). However, this study shows that patterns of exposure vary locally, with higher exposure to PCAH in the urban areas of Antwerp associated with delayed sexual maturation, while exposure to pesticides in the agricultural area of Peer may be related to impairment of sperm quality.

Studies from other countries also indicate that exposure to pesticides may be associated with declining sperm quality. A population-based study from an agricultural area (Missouri, USA) identified several currently used herbicides including alachlor (30.0, 95% CI 4.3–210) and atrazine (OR= 11.3, 95% CI= 1.3–98.9) and the insecticide diazinon (OR= 16.7, 95% CI= 2.8–98.0) to be associated with decreased semen quality (Swan et al., 2003).

Men poisoned by PCBs and polychlorinated dibenzofurans in Taiwan (the Yucheng exposure) had increased abnormal morphology, a higher incidence of oligozoospermia, and reduced capacity to penetrate hamster oocytes compared to controls (Hsu et al., 2003).

Data from subfertile men indicated an inverse dose–response relationship between PCB-138 and sperm concentration, motility, and morphology. There was also a limited evidence of an inverse relationship of total PCBs and a particular group of PCBs (cytochrome P450 enzyme inducers) with sperm motility and morphology, as well as limited evidence of an inverse association between p,p'-DDE and sperm motility (Hauser et al., 2003).

PCBs were detected in the seminal plasma of a group of Indian infertile men but not in the controls, and the concentration of phthalate esters was significantly higher in the infertile men (Rozati et al., 2002). The same study indicated that the total number of motile

spermatozoa in the ejaculate (total motile sperm count) in infertile men were inversely proportional to their xenoestrogen concentrations in seminal plasma and were significantly lower than those in the respective controls (Rozati et al., 2002). Negative dose-response relations have been reported for monobutyl phthalate and monobenzyl phthalate in urine with one or more semen parameters in subfertile men (Duty et al., 2003a). Urinary monoethyl phthalate at environmental levels, was found to be associated with increased DNA damage in sperm (Duty et al., 2003b).

Other substances reported to be related to reduced sperm quality or fecundability include chloredecone (kepone), dimethmethamidophos, captan, 2,4-D, dibromochloropropane, ethylene dibromide and glyphosate (review: Cocco, 2002).

Occupational exposure to ethylparathion and methamidophos seems to have a moderately adverse effect on sperm concentration and motility (Padungtod et al., 2000).

Data from the Netherlands indicate paternal exposure to pesticides is associated with decreased fertilization and implantation rates during treatment by *in vitro* fertilization for infertility (Tielemans et al., 1999; 2000). However, time to pregnancy was not prolonged among couples with paternal exposure to di(2-ethylhexyl)phthalate (DEHP) at a mean exposure level of <0.5 mg/m³ (Modigh et al., 2002).

5.5.2 Female infertility

The New York State Angler Cohort Study indicated fish consumption from lakes contaminated with endocrine disrupters may cause anovulation (Mendola et al., 1997), although preliminary findings from the same population do not support an adverse effect of contaminated fish consumption on time to pregnancy (Buck et al., 1997).

A recent study evaluated the effects of prenatal exposure to pesticides on time to pregnancy. The daughters' probability of pregnancy (28-31 years later) fell by 32% per 10 µg/L p,p'-DDT increase in maternal serum, measured 1 to 3 days after delivery (95% CI 11-48). By contrast, the probability of pregnancy increased 16% per 10 µg/L p,p'-DDE (6-27) (Cohn et al., 2003).

More than 50% of Canadian women attending a fertility program have had exposure to environmental chemicals sufficient to produce detectable concentrations in their serum and ovarian follicular fluid (Younglai et al., 2002). Of the chemical contaminants detected in the serum and ovarian follicular fluid of women undergoing *in vitro* fertilization, p,p'-DDE was the most frequently detected, had the highest residue levels, and was associated with failed fertilization. The same study indicates pregnancy was positively correlated with follicular fluid PCB 49 (Younglai et al., 2002).

Data from women attending a gynecological clinic in Germany indicates pentachlorophenol may act centrally on a hypothalamic or supra-hypothalamic level, which may result in mild ovarian and adrenal insufficiency (Gerhard et al., 1999a). The same authors found that in women with benign uterine tumors (uterine fibroids) endometriosis, miscarriages, persistent infertility, and hormonal disturbances, elevated concentrations of chlorinated hydrocarbons with long half-lives were observed suggesting these substances may play a role in female infertility and may be an underlying factor in certain gynecological conditions (Gerhard et al., 1999b). The relationship of endometriosis, which is a common cause of female infertility, to endocrine disruption is discussed below (see page 20).

5.6 Sex ratio (male to female ratio at birth)

Recent data indicate a declining male proportion at birth in Europe (Martuzzi et al., 2001). Decreased male to female ratio at birth has been reported following high levels of exposure to HCB (Jarrell et al., 2002). Exposure of men to 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) in the Seveso incident in Italy (Pesatori et al., 2003) and occupational exposures (Ryan et al., 2002) were linked to a lowered male/female sex ratio in their offspring. No significant association was found between environmental pollution and the proportion of male births in Italy during the period 1989-1993 (Figa-Talamanca et al., 2003). An Analysis of sex ratio over 250 Years in Finland does not support the hypothesis that agricultural or industrial environmental estrogens play any significant role in the changes in sex ratio (Vartiainen et al., 1999).

5.7 Endometriosis and endometrial cancer

Significantly higher serum levels of DEHP have been reported in a small group of women with endometriosis (Cobellis et al., 2003). Exposure to polychlorinated biphenyls and chlorinated pesticides during adulthood was not associated with endometriosis in the general population (Lebel et al., 1998). It has been hypothesized that the high incidence of endometriosis in Belgian women with infertility or gynecological pain (60-80 %) may be related to dioxin pollution (opinion paper: Koninckx et al., 1994). However, two recent small Belgian studies found no association between dioxin and PCBs and endometriosis in infertile women (Fierens et al., 2003; Pauwels et al., 2001b).

Similar adjusted relative risks of endometrial cancer were reported in the highest quartile of exposure compared with women in the lowest quartile for p,p'-DDE, and total PCBs (Sturgeon et al., 1998). Other studies also indicate that organochlorine exposure does not increase the risk for endometrial cancer (Weiderpass et al., 2000).

5.8 Breast cancer (female)

Recent reviews of the literature indicated that although initial studies implicated DDT and its metabolite DDE in the etiology of female breast cancer, more recent studies found no association (reviews: DeBruin & Josephy, 2002; Snedeker, 2001). However, an adverse effect of these compounds on breast cancers expressing estrogen receptors (estrogen receptor positive) cannot be excluded.

Persistently high serum levels of DDT (upper quartile OR= 3.6, 95% CI= 1.1-12.2) and PCB congener 138 (upper quartile OR= 2.1, 95%, CI= 1.0-4.4) at repeated testing over a period of 5 years were significantly positively associated with breast cancer risk, and the risk increased with increasing serum concentration (Hoyer et al., 2000b).

Studies from Wallony (Charlier et al., 2004) indicate significantly higher serum levels of p,p'-DDE and HCB in patients than in controls. The presence of both residues was significantly associated with an increased risk of breast cancer development (OR= 2.21, 95% CI= 1.41-3.48 for p,p'-DDE and OR= 4.99, 95% CI= 2.95-8.43 for HCB). In the cancer group, no differences in serum levels of p,p'-DDE or HCB were found in relation with estrogen-receptor (ER) status, but the HCB level was moderately correlated with tumor size ($p = 0.026$).

Increasing duration of farming was inversely associated with breast cancer risk; OR (95% CI) were 1.2 (0.8-1.7), 0.8 (0.5-1.2), 0.7 (0.5-1.1), and 0.6 (0.4-0.9) for 1-10, 11-17, 18-23, and >23 years of farming, respectively, relative to non-farmers (Duell et al., 2000).

In Danish women, serum dieldrin concentration was associated with a significantly increased dose-related risk of breast cancer (OR= 2.05; 95% CI= 1.17-3.57; p for trend 0.01) (Hoyer et al., 2000a). The observed increased breast cancer risk associated with exposure to dieldrin derived from women who developed an estrogen receptor negative (ERN) tumor (OR 1st vs. 4th quartile, 7.6, 95% CI= 1.4-46.1). Tumors in women with the highest dieldrin serum level were larger and more often spread at the time of diagnosis than estrogen receptor positive (ERP) tumors. Moreover, Dieldrin had a significant adverse effect on overall survival and breast cancer specific survival [relative risk (RR)= 2.78, 95% CI= 1.38-5.59, P trend < 0.01; RR= 2.61, 95% CI= 0.97-7.01, P trend < 0.01] (Hoyer et al., 2001).

The risk of dying was higher among patients with ERP breast cancer when compared to those with ERN. In the highest quartile of polychlorinated biphenyls it was more than 2-fold increased (RR 1st vs. 4th quartile, 2.5, 95% CI= 1.1-5.7), but no dose-response relation was apparent (Hoyer et al., 2001). This association has not been confirmed in studies from the United States (Gammon et al., 2002)

Among women who farmed, ORs were elevated for those who reported being present in fields during or shortly after pesticide application (OR= 1.8, 95% CI= 1.1-2.8) and for those who reported not using protective clothing while applying pesticides (OR= 2.0; 95% CI= 1.0-4.3), but not among those who reported using protective clothing (OR= 0.8; 95% CI= 0.4-1.8) (Duell et al., 2000).

O'Leary et al., (2004) found an increased breast cancer risk for women residing within 1 mile of hazardous waste disposal sites containing organochlorine pesticides (OR= 2.8; 95% CI= 1.1-7.1), after adjusting for other risk factors. Others found that serum levels of organochlorines were not associated with increase breast cancer risk (Gammon et al., 2002).

One study found that the PCB congener 183 (2,2',3,4,4',5',6-heptachlorobiphenyl) was significantly associated with breast cancer risk, with an adjusted OR of 2.0 (95% CI= 1.2-3.4) in women with bodily fat (adipose tissue) levels higher than 5.67 ng/g (Stellman et al., 2000).

The concentrations of some other PCBs and pesticides in adipose tissue were also found to be associated with risk of recurrence of breast cancer. The risk for the highest tertile of the PCB congener Ballschmiter and Zell 118 was 4.0 (95% CI= 1.3-4.9). There was an increased risk for the middle level of the most abundant pesticide, 1,1-dichloro-2,2-di(4-chlorophenyl)ethylene (p,p'-DDE) (RR= 2.3; 95% CI= 0.9-5.7), and for beta-hexachlorocyclohexane, but not for their highest levels (Muscat et al., 2003). Similarly, Axillary lymph node involvement with high serum levels of p,p'-DDE; (OR= 2.54; 95% CI= 1.20-5.35 between the highest and the lowest tertiles) (Demers et al., 2000).

Poly-aromatic hydrocarbon (PAH)-DNA adducts measured in breast tumor tissue of 100 cases and in normal tissue from 105 controls were significantly associated with breast cancer (OR= 4.43, 96% CI= 1.09-18.01) (Rundle et al., 2000).

The results of occupational exposure to electro magnetic fields, analyzed by the estrogen receptor status, showed an increased risk of estrogen receptor (ER)-positive breast cancer in the younger women (<50 year), while the older age group (>50 year) had an elevated risk of ER-negative breast cancer (Kliukiene et al., 2003). Residential magnetic field exposure has been found not to correlate with breast cancer risk (London et al., 2003;

Schoenfeld et al., 2003) although one study reported increased relative risk (OR= 7.4, 95% CI= 1.0-178.1) in ER-positive women younger than 50 years at diagnosis (Feychting et al., 1998).

A statistically significant increase in breast cancer risk with medium and high levels of triazine exposure (OR = 1.14, $p < 0.0001$ and OR = 1.2, $p < 0.0001$, respectively) has been reported (Kettles et al., 1997).

A nested case-control study including 1,925 women examined the association between breast cancer and serum polybrominated biphenyls (PBBs). Women with serum PBB levels of 2.0-3.0 parts per billion (ppb) (OR = 3.5; 95% CI = 0.9-13) or 4.0 ppb or greater (OR = 3.1; 95% CI = 0.8-12) had a higher estimated risk for breast cancer than women with less than 2.0 ppb (Henderson et al., 1995).

A significantly elevated risk of breast cancer was observed among postmenopausal women who were ever potentially exposed to chemical facilities (Nassau County, adjusted OR = 1.61, 95% CI = 1.06-2.43; Suffolk County, adjusted OR = 1.58, 95% CI = 0.71-3.51). This elevated risk, however, was not observed among premenopausal women. Risk increased for post-menopausal subjects as the number of chemical facilities increased from one (adjusted OR = 1.45, 95% CI = 0.93-2.25) to two or more (adjusted OR = 3.47, 95% CI = 1.06-11.38) (Lewis-Michl et al., 1996).

Active and passive smoking may play a role in breast cancer etiology (review: DeBruin & Josephy, 2002; Reynolds et al., 2004). A Swiss study indicated a dose-dependant increased risk of breast cancer (Morabia et al., 1996). Women who smoke and who have a genetically determined reduced inactivation of carcinogens (GSTM1 null genotype or slow NAT2 genotype, especially very slow NAT2 genotype) were found to be at increased risk of breast cancer (van der Hel et al., 2003).

The risk of early-onset breast cancer was increased 1.25 times (95% CI 1.00-2.51) for birth weights above 4,000 g and 1.59 times (95% CI= 1.00-1.55) for birth weights below 2,500 g in comparison with birth weights of 3,000-3,499 g. (Mellemkjaer et al., 2003).

Moderate to high correlations were observed between pesticides sales in Brazil and breast cancer mortality (Koifman et al., 2002).

Among women with a first full-term birth at age 35 or older, fertility problems were associated with a twofold risk of breast cancer (Weiss et al., 1998).

5.9 Prostate cancer

Animal experiments indicate that peri-natal exposure to estrogenic compounds can result in alterations in the size of the adult prostate and increase the incidence of prostatitis (Stoker et al., 1999). Chronic inflammation of the prostate is considered a predisposing factor for prostate cancer (review: De Marzo et al., 2003).

A meta-analysis indicated that occupational exposure to pesticides is associated with an increased risk of prostate cancer among farmers (Keller-Byrne et al., 1997). Most of the more recent studies confirm this association.

Although the pesticide applicators from Florida were consistently and significantly healthier than the general population, prostate cancer mortality [standardized mortality ratio(SMR) 2.38, 95% CI 1.83 to 3.04) was significantly increased (Fleming et al., 1999).

Increased risks were found among farmers exposed to organochlorine insecticides and acaricides (OR = 2.5, 95% CI = 1.4-4.2), including DDT (OR = 2.1, 95% CI = 1.2-3.8), and dicofol (OR = 2.8, 95% CI = 1.5-5.0) (Settimi et al., 2003). A pilot case-control study indicated oxychlorodane and PCB 180 were associated with an increased risk of prostate cancer (Ritchie et al., 2003).

Prostate cancer mortality was found not to be related to the estimated environmental exposure to the p,p'-DDE in the USA (Cocco & Benichou, 1998).

Moderate to high correlations were observed between pesticides sales in Brazil and prostate cancer mortality (Koifman et al., 2002).

The used amounts of atrazine and captan in central California correlated positively with the incidence of prostate cancer in black but not in white males (Mills, 1998).

TCCD contamination after the Seveso accident in Italy had no effect on prostate cancer mortality (Bertazzi et al., 2001).

Hispanic farm workers with relatively high levels of exposure to organochlorine pesticides (lindane and heptachlor), organophosphate pesticides (dichlorvos), fumigants (methyl bromide), or triazine herbicides (simazine) experienced elevated risk of prostate cancer compared to workers with lower levels of exposure (Mills & Yang, 2003).

One study reported lower than expected incidence of prostate cancer among men environmentally exposed to PCBs (Standardized Incidence Ratio=0.83; 95% CI= 0.69-0.97)(Pavuk et al., 2004).

5.10 Testicular cancer

High levels of cis-nonachlordane have been reported in patients with testicular cancer (Hardell et al., 2003). Mothers of the same patients showed significantly increased concentrations of the sum of PCBs, HCB, trans- and cis-nonachlordane, and the sum of chlordanes. Among case mothers the sum of PCBs yielded an OR of 3.8 (95% CI= 1.4-10). Odds ratios were also increased for HCB, OR = 4.4 (95% CI= 1.7-12); for trans-nonachlordane, OR = 4.1 (95% CI= 1.5-11); and for cis-nonachlordane, OR = 3.1 (95% CI= 1.2-7.8) (Hardell et al., 2003). Testicular cancer mortality was found not to be related to the estimated environmental exposure to the p,p'-DDE in the USA (Cocco & Benichou, 1998). Unlike other pathologies, e.g. prostate cancer, the observed increase in the incidence of testicular cancer in recent decades cannot be accounted for by the fact that people are living longer or have better methods of detection. Testicular cancer is a disease of young men and is easily detectable (Aitken et al., 2004).

5.11 Thyroid gland diseases in adults

A recent study evaluated the effects of high environmental exposure to PCBs and other organochlorines on the thyroid gland. Very high serum levels of PCBs were found in the population from a polluted area (7300 +/- 871 ng/g lipids) compared with controls (2045 +/- 147 ng/g) (Langer et al., 2003). Their results also indicated that thyroid volumes in the polluted area were significantly higher (P < 0.001) than in the control area. In males from the polluted area, the frequencies of abnormalities of the thyroid gland detected by echography (thyroid hypoechogenicity), thyroid nodules, positive antithyroid peroxidase antibody (anti-TPO), and abnormal TSH level were higher than in males from the control

area, whereas such differences were not observed in females. Increased thyroid volume and indicators of potential thyroid dysfunction were associated with long-term environmental exposure to PCBs. These effects on the thyroid were confined to subjects with PCB levels above 10,000 ng/g of lipid (thyroid volume) and to males from the polluted area (thyroid hypoechogenicity, thyroid nodules, positive anti-TPO, and abnormal TSH) (Langer et al., 2003). Accidental exposure to HCB has been associated with thyroid gland abnormalities (review: VMM, 2003).

Polybrominated flame retardants have been associated with hypothyroidism (Bahn et al., 1980; review: De Bont & van Larebeke, 2004).

Trijodothyronine levels in serum were significantly higher while thyroid hormone binding ratio was significantly decreased in workers with the highest perfluorooctyl sulfonic acid (PFOS) serum concentrations (1.69-10.06 ppm) (reviews: De Bont et al., 2004; OECD, 2002).

5.12 Pancreatic diseases

Occupational exposure to high levels of PCBs is associated with a high prevalence of glutamic acid decarboxylase (anti-GAD) antibodies, which may predispose to the development of diabetes mellitus (Langer et al., 2002).

The median concentrations of p,p' DDE, (1290 versus 1030 ng/g lipid; P = 0.05), PCBs (330 versus 220 ng/g lipid; P<0.001), and transnonachlor (54 versus 28 ng/g lipid; P = 0.03) were significantly greater among cases with pancreatic cancer than controls. A significant dose-response relationship was observed for total PCBs (P for trend <0.001). Subjects in the highest tertile of PCBs (> or =360 ng/g lipid) had an OR of 4.2 (95% CI = 1.8-9.4) compared to the lowest tertile. The OR of 2.1 for the highest level of p,p'-DDE (95% CI = 0.9-4.7) diminished (OR = 1.1; 95% CI = 0.4-2.8) when PCBs were included in the model (Hoppin et al., 2000).

5.13 Immunosuppression in adults

High levels of immunotoxic PCBs has been linked to an increased risk for non-Hodgkin lymphomas (Hardell et al., 2001; Nordstrom et al., 2000). Whether the immunosuppressive effect of some endocrine disruptors is related to hormonal alterations in corticosteroids is presently unknown.

A particular type of non-Hodgkin's lymphomas with a chromosomal translocation (translocation or "t"(14;18)-positive) was associated with farming (OR= 1.4, 95% CI = 0.9-2.3), dieldrin (OR= 3.7, 95% CI= 1.9-7.0), toxaphene (OR= 3.0, 95% CI= 1.5-6.1), lindane (OR= 2.3, 95% CI = 1.3-3.9), atrazine (OR= 1.7, 95% CI= 1.0-2.8), and fungicides (OR= 1.8, 95% CI= 0.9-3.6), in marked contrast to the null or negative associations for the same self-reported exposures and t(14;18)-negative non-Hodgkin's lymphomas (Schroeder et al., 2001).

A large study from the United States (3417 patients) indicated that the reported use of several individual pesticides was associated with increased incidence of non-Hodgkin lymphomas, including organophosphate insecticides coumaphos, diazinon, and fonofos, insecticides chlordane, dieldrin, and copper acetoarsenite, and herbicides atrazine, glyphosate, and sodium chlorate. A subanalysis of these "potentially carcinogenic" pesticides suggested a positive trend of risk with exposure to increasing numbers of chemicals (De Roos et al., 2003).

Lymphoma risk showed a dose-response relation with polybrominated flame retardants (biphenyls) levels in serum in a cohort that was accidentally exposed (Michigan, USA) (Hoque et al., 1998).

5.14 Other diseases and abnormalities

The results of a recent meta-analysis of the literature suggest that living in a rural area, drinking well water, farming, and exposure to pesticides may be a risk factor for developing Parkinson's disease (Priyadarshi et al., 2001). A retrospective epidemiological case control study (Pals et al., 2003), performed in Flanders during a 3-year period investigated 423 prevalent patients and 205 spouse-controls for known and potential environmental risk factors for Parkinson's disease by means of questionnaires. Discrete clustering of patients was found in areas with intensive metallurgic activity and patients were more frequently employed in metallurgy than controls (95% CI= 1.04–9.20). Furthermore, patients were clearly more exposed to zinc (95% CI= 1.51-90.90) and toluene (95% CI= 1.03- 58.82). Male patients reported more prostatectomy-surgery (95% CI= 1.54-17.24).

Neuroblastoma, a malignant tumor consisting mainly of immature nerve cells, is the most common tumor in children under 1 year of age. Pesticide use in both the home and garden were modestly associated with neuroblastoma [OR= 1.6 (95% CI= 1.0-2.3) and OR = 1.7, (95% CI= 0.9-2.1) respectively] (Daniels et al., 2001).

Occupational exposure to styrene has been associated with cytogenetic damage (sister chromatid exchanges) (Teixeira et al., 2004).

Moderate to high correlations were observed between pesticides sales in Brazil and infertility, testis, and ovarian cancer mortality (Koifman et al., 2002).

An increasing dose-response relation for digestive system cancer risk with higher serum polybrominated biphenyl category was found in a cohort that was accidentally exposed (Michigan, USA) (Hoque et al., 1998).

Exposure to environmental agents has been reported as a risk factor for erectile dysfunction in Argentinean men (OR= 7.1, 95% CI= 1.5-33.0 for pesticides; OR= 12.2, 95% CI= 1.2-124.8 for solvents) (Oliva et al., 2002).

A study from Liège indicates that Andropause, otherwise termed the Partial Androgen Deficiency of Aging Male (P.A.D.A.M.), might in part be due to excessive organochloride pesticide accumulation (Legros et al., 2003). Males with pp'DDE > 5µg/l had lower mean calculated free testosterone (43.3 ± 14.1) than males with pp'DDE < 5µg/l (59.6 ± 23.2 µg/l) (Legros et al., 2003).

Various studies indicate that flame retardants, in particular the brominated varieties (BFRs) are rapidly accumulating in the environment and in the bodies of wildlife and humans (Eriksson et al., 2001) including the Flemish population (Covaci et al., 2002). A recent study *in vitro* has indicated these compounds activate the aryl hydrocarbon receptor, which may be due in part to contaminants present in commercial/technical mixtures (Brown et al., 2004). Animal studies have shown that developing mice exposed to BFRs suffered behavioral changes and impaired learning ability (reviewed in: Eriksson et al., 2001).

Epidemiological studies indicate a possible association between exposure to PFOS and bladder cancer (reviews: De Bont et al., 2004; OECD, 2002). A cohort of 2083 workers in

the Decatur factory, Alabama, USA, was followed since 1961. Workers who were highly exposed to PFOS had 13 times (SMR= 12,77, 95% CL= 2.63-37.35) more chance to die from bladder cancer than the general population in Alabama (USA). This increase was statistically significant, but it is still unclear whether this increase is due to exposure to PFOS because these workers are most probably also exposed to other chemicals. Further follow of this cohort is needed (Alexander et al., 2003). Data are available on PFOS serum levels in exposed workers from the 3M factory in Antwerp (Olsen et al., 1999; 2003).

A retrospective cohort mortality study demonstrated a statistically significant association between prostate cancer mortality and the duration of employment in a factory that produces perfluorooctanoic acid (PFOA). In a more recent update of this study, where PFOA levels were measured, no significant association was found between prostate cancer and exposure to PFOA. Another study reported an increase in the concentrations of the "female hormone" estradiol in workers with the highest PFOA serum concentrations. The same study found no association between PFOA and other hormones or cholecystokinin, cholesterol or other serum components (reviews: De Bont et al., 2004; EPA, 2003). Data are available on PFOA serum levels in exposed workers from the 3M factory in Antwerp (Olsen et al., 2003).

A recent study reported familial clustering of multiple sclerosis and young-adult-onset Hodgkin lymphoma, consistent with the hypothesis that the two conditions share environmental and/or constitutional etiologies (Hjalgrim et al., 2004).

A recent congress of the American national institute of environmental health sciences discussed the possible link between developmental exposure to endocrine disruptors and obesity (NIH, 2004). Studies in rats indicate perinatal exposure to DES and genestein are associated with significant weight gain later in life (Newbold, 2004). Developmental exposure to bisphenol A may result in either over or underweight depending on endogenous estrogen levels and exposure severity (Vom Saal, 2004). The type of animal feed used and its contamination with endocrine disruptors may have a large influence on the results of in-vivo studies investigating the impact of endocrine disruptors (Vom Saal, 2004). No clinical human data are available to date (NIH, 2004).

Weight loss following gastroplasty in obese persons has been shown to increase plasma concentration of organochlorine pesticides and PCBs, which could be a risk factor of endocrine disruption. Future longitudinal research will have to determine if the advantages of body weight loss are reduced by this potentially harmful effect (Charlier et al., 2002).

In a recent case report, Hauser et al. (2004) reported for the first time on medications as a potential source of exposure to phthalates in a man who took Asacol [active ingredient mesalamine (mesalazine)] for the treatment of ulcerative colitis. The concentration of monobutyl phthalate, a dibutyl phthalate metabolite was more than two orders of magnitude higher than the 95th percentile for males in the United States. The authors concluded that further research is necessary to determine the proportional contribution of medications, as well as personal care and consumer products, to a person's total phthalate burden.

Medically unexplained physical symptoms and related syndromes are associated with extensive morbidity, and have a large negative impact on human functioning (review: Richardson & Engel, Jr., 2004). For example, multiple chemical sensitivity syndrome (MCSS) is an ill-defined syndrome of which the etiological classification is uncertain (allergic, neurological or psychiatric). On contact with small doses of different chemical substances there are multiple respiratory, cardiovascular, neurological gastro-intestinal symptoms (reviewed in Viaene, 2000). A recent study indicated that a significant percentage of

patients with MCSS (27.5%) reported that their hypersensitivity was initiated by an exposure to pesticides, whereas an equal percentage (27.5%) attributed it to solvents (Caress & Steinemann, 2003). The same study indicated that only 1.4% had a history of prior emotional problems, but 37.7% developed these problems after the physical symptoms emerged. This suggests that MCSS may have a physiologic rather than a psychologic etiology (Caress & Steinemann, 2003). There is a weak evidence for an association between chronic fatigue syndrome (also called myalgic encephalomyelitis) and exposure to organophosphate sheep dip (Tahmaz et al., 2003).

6 Clinical indicators specific to relevant pathologies

The review of the literature indicated that the pathologies enlisted in table 1 may be related to endocrine disruptors. Some other pathologies mentioned in the review above are not included in the table because the authors are convinced that the evidence that endocrine disruption is associated with these diseases is currently insufficient.

Many of the pathologies below are asymptomatic at the early stages, especially cancers. Many symptoms are very non-specific and common to many cancers like fatigue, weight loss, and symptoms of metastasis.

6.1 Intrauterine growth retardation

Definition

Fetus small for gestational age (10 % less than predicted fetal weight for gestational age)

Symptoms

Problems of immaturity (see below) and short stature postnatally

Investigations

Echography

Treatment

See treatment of prematurity below; growth hormone for short stature postnatally

Possible biases

Positive: faults in calculating the duration of pregnancy and estimation of fetal weight

Negative: same as for positive

Note: risk factor for hypospadias

6.2 Prematurity

Definition

Birth of a child before 37 weeks of gestation (SPE, 2004)

Symptoms

Susceptibility to infections, feeding problems, respiratory distress, intraventricular hemorrhage

Investigations

Vary according to accompanying pathology

Treatment

Varies according to symptoms (incubation, antibiotics, ventilation etc)

Possible biases

Positive: induction of labour for medical or other reasons and faults in calculating the duration of pregnancy

Negative: faults in calculating the duration of pregnancy

Note: Risk factor for cryptorchidism

6.3 Congenital anomalies

6.3.1 Congenital anomalies in general

Definition

These are structural defects (congenital malformations, deformations, disruptions and dysplasias), chromosomal abnormalities, inborn errors of metabolism, and hereditary diseases of the embryo, fetus or newborn (EUROCAT definition)

Symptoms

Variable according to the type of the anomaly

Investigations

Prenatal (e.g. genetic studies), postnatal (e.g. echocardiography)

Treatment

Variable according to the type of the anomaly

Possible biases

Positive: comparing databases is difficult. Some pathologies are not included in certain databases (e.g. cryptorchidism is not included in EUROCAT). Also, the criteria for the inclusion of a certain diagnosis may vary even between 2 databases from the same country. One example is the recording of hypospadias from Antwerp and Namur in the EUROCAT database (see table 2).

Negative: same as for positive

6.3.2 Hypospadias

Definition (EUROCAT)

Hypospadias is a congenital abnormality of the male genitalia characterized by incomplete development of the urethra so that the external urethral opening (meatus) is on the ventral

surface of the penis or on the scrotum, rather than at the tip of the penis (Dolk et al., 2004).

Symptoms

The external urethral opening (meatus) is on the ventral surface of the penis or on the scrotum. This may lead to psychological problems later in life. Infertility may occur due to failure of intravaginal ejaculation (or a common cause of both hypospadias and infertility).

Investigations

Karyotyping (cryptorchidism + hypospadias and ambiguous genitalia)

Treatment

- Testosterone cream (rarely used in Belgium)
- Urethroplasty

Possible biases

Positive: urethroplasty for other reasons e.g. urethral stricture and urethral trauma and faulty classification of an incomplete prepuce as hypospadias

Negative: more severe variants will be detected (penoscrotal) and are less likely to be under reported, although the parents ask the urologists more and more to operate milder forms in recent years.

Note: because of these problems in establishing the diagnosis, EUROCAT organized a study to validate their data on hypospadias (Dolk et al., 2004). None of the two Belgian centers participated in the data validation study organized by EUROCAT (Dolk et al., 2004).

6.3.3 Cryptorchidism

Definition

Failure of the testis to descend along its normal path into the scrotum from the posterior abdominal wall to the scrotum. The testis maybe high scrotal, inguinal or impalpable

Symptoms

- Empty scrotum (uni- or bilateral)
- Torsion or malignant transformation of undescended testis
- Ambiguous genitalia (intersex disorders)
- Infertility or symptoms of testicular cancer later in life

Investigations

- Human Chorionic Gonadotrophin (HCG) test + testosterone measurement (for differentiating cryptorchidism from anorchia "absent testes")
- Ultrasonography: inguinal region, abdomen
- Magnetic resonance imaging (MRI) or Computerized axial Tomography "CAT scan or CT"(Abdomen)
- Laparoscopy
- Karyotyping (cryptorchidism + hypospadias or ambiguous genitalia)

Treatment

- HCG treatment (eventually plus Human menopausal gonadotropin, HMG) before puberty
- Orchiopexy
- Orchidectomy
- Testicular autotransplantation (very rarely performed in Belgium)

Possible biases

Positive: the faulty inclusion of cases with retractile or ectopic testis as cryptorchidism. Orchidectomy for other reasons e.g. trauma, testicular cancer, transexualism.

Negative: EUROCAT includes cases of cryptorchidism only if associated with other major anomalies (see note below).

Note: It is now widely accepted that registry data cannot be relied upon and that prospective studies that involve a structured and standardized diagnostic approach are essential if secular trends or between-country differences in incidence are to be demonstrated convincingly (Toppari et al., 2001). EUROCAT does not systematically collect data on cryptorchidism. It is among a list of exclusions that includes minor anomalies and anomalies that would not be well defined or reported - the cases of cryptorchidism are not validated as to whether they required surgery etc. EUROCAT does not exclude cryptorchidism if it is associated with other major anomalies, so their database will be biased towards those cases (Helen Dolk, EUROCAT Project Leader, personal communication, 25/05/04).

6.4 Disturbances in mental and psychomotor development

Definition

Disturbances in the progressive acquisition of skills involving both mental and motor activities

Symptoms

These include failure to achieve developmental milestones, various behavioral disturbances and learning problems. In many cases the manifestations are subtle and detected only by special tests.

Investigations

Psychomotor development assessment tools or scales for example, the Bayley scales of Infant Development, and intelligence scores such as the Kaufman Assessment Battery for Children

Clinical assessment of neurological and motor functions

Treatment

Varies according to the clinical diagnosis

Possible biases

Positive: in recent years, many children are labeled as having for example attention deficit hyperactivity disorder (ADHD) and treated as such without proper investigation.

Negative: changes due to exposure to environmental factors are sometimes subtle and may only be detected using special tests.

6.5 Puberty

6.5.1 Precocious puberty

Definition

Precocious puberty is the onset of the signs of puberty before age 7-8 years in girls and age 9 in boys

Symptoms

- The development of breasts or pubic hair or the onset of menstruation in girls
- The appearance of pubic or facial hair, a deepening of the voice, or enlargement of the penis or testicles in boys
- The onset of acne in both sexes can also occur

Investigations

- Blood hormones (follicle stimulating hormone "FSH", luteinizing hormone "LH", testosterone, estradiol, prolactin)
- X-rays of the wrist and hand can show whether the bones are maturing too rapidly (bone age)
- CT scans and MRIs (magnetic resonance imaging) can help rule out specific causes of precocious puberty, such as a tumor in the pituitary gland, hypothalamus, brain, adrenal, ovary, or testicle.

Treatment

- Treatment of the cause if possible
- Gonadotropin releasing hormone (GnRH) analogues and antiandrogens

Possible biases

Positive: GnRH analogues are used for a variety of other conditions (but the age group is different) including female infertility and prostate cancer.

Negative: underreporting

6.5.2 Delayed puberty

Definition

Delayed adolescence in phenotypic male or female

- Girls:

Delayed breast development

No breast development by age 14 years

No breast development 5 years after Menarche

No Menses by age 16 years (Primary Amenorrhea)

- Boys:

Testicular length under 2.5 cm by age 14 years

Genital growth not complete five years from start

Symptoms

Absence or delay of pubertal markers (genital and extra-genital)

Investigations

- Blood hormones (FSH, LH, testosterone, estradiol, prolactin)

- X-rays of the wrist and hand may show delayed bone maturation (delayed bone age)

- CT scans and MRIs (magnetic resonance imaging) can help rule out specific causes of delayed puberty, such as a tumor in the pituitary gland, hypothalamus and investigations for chronic illnesses.

Treatment

- Treatment of the cause if possible

- Estrogen (female), androgen (male)

Possible biases

Positive: the use of hormones to induce bone maturation in excessively tall individuals

Negative: underreporting

6.6 *Male infertility and sperm quality*

Definition (WHO)

Failure to conceive after 12 months of unprotected intercourse (Rowe et al., 2000)

Symptoms

Failure to conceive despite unprotected intercourse

Investigations

- Semen analysis: We think that the number of semen analyses performed (per year excluding repeats) may give a good estimation of the prevalence of infertility in the population. Semen analysis is performed for each patient at least once (unlike many other investigations for infertility).

- Other investigations are less specific for infertility

Possible biases

Positive:

- Control semen analysis for male contraceptive purposes (mostly after vasectomy)
- Semen analysis for sperm freezing (e.g. testis and other cancers in young men, cytotoxic drugs for non malignant diseases)
- Semen analysis in cases with prostatitis/pelvic pain

Negative: may arise from semen analysis performed in some *in vitro* fertilization (IVF) laboratories. The analysis is performed but many labs are not accredited for that because they do not participate in quality control programs (Institute Louis Pasteur, Brussels) and therefore the semen analysis is not reported to the RIZIV because it is not refunded.

6.7 Female infertility

Definition (WHO)

Failure to conceive after 12 months of unprotected intercourse (Rowe et al., 2000)

Symptoms

Failure to conceive despite unprotected intercourse

Investigations

- Detection of ovulation
- Hysterosalpingiography
- Laparoscopy

Treatment

- Treatment of the cause
- Ovulation induction (clomiphene, FSH, HCG, GnRH agonist, GnRH antagonist)
- Assisted reproductive technology (intra-uterine insemination, *in vitro* fertilization "IVF", IVF with intracytoplasmic sperm injection "ICSI", testicular sperm extraction with ICSI)

Since 1/7/03, registration of all IVF cycles with single embryo transfer for up to 6 cycles is compulsory (refunded by RIZIV).

Possible biases

Positive:

- Rumors of foreign patients coming to Belgium for IVF treatment, registered as an "emergency" treatment and refunded by RIZIV
- Many foreign patients are treated at Belgian IVF centers (good expertise in Belgium), especially Dutch patients (long waiting lists in the Netherlands). Therefore, data from IVF centers may be informative about the success rates of IVF but biased concerning prevalence unless stratified by nationality.

Negative: cycles not refunded by RIZIV (more than six cycles and multiple embryo transfer)

6.8 Time to pregnancy

Definition

Time to pregnancy is defined as the period from initiation or resumption sexual intercourse without use of contraception till the occurrence of pregnancy. Time to pregnancy (usually expressed in months) is a good indicator of the fertility status of the population.

Possible biases

Positive: Recall bias is possible but comparing data from well-validated questionnaires to medical records indicate that the recall is good.

Negative: same as for positive.

6.9 Sex ratio

Definition: Male to female ratio at birth

Possible biases

Positive: rarely, sex assignment at birth is faulty due to, for example, ambiguous genitalia

Negative: same as for positive

6.10 Endometriosis

Definition

Endometriosis is classically defined as the presence of endometrial glands and stroma outside the uterine cavity and musculature.

Symptoms

Dysmenorrhea, dyspareunia, and infertility in women of reproductive age (none are pathognomonic for the disorder)

Investigations

- Endovaginal ultrasonography
- MRI is more sensitive and specific
- Laparoscopy (gold standard)

Treatment

- GnRH-analogues, Danazol, or gestagens
- Surgical treatment

Possible biases

Positive: laparoscopy is used as a diagnostic and therapeutic procedure for a large variety of intra-abdominal pathologies.

Negative: since the diagnosis requires laparoscopy, most asymptomatic cases will be missed

6.11 Breast cancer (female)

Symptoms

- Breast or axillary lump, bleeding areola
- Symptoms of metastasis

Investigations

- Mammography, ultrasonography
- Histopathology
- Receptor markers

Treatment

- Lumpectomy (removal of the tumor mass)
- Radiotherapy
- Chemotherapy
- Tamoxifen (secondary prevention in estrogen receptor positive tumors)

Possible biases

Positive: lumpectomy for other reasons (benign tumors etc)

Negative: underreporting

Note: the receptor status is not reported in data for cancer registries. This is important not only for treatment, but also for epidemiological studies since the relation to endocrine disruptors may be determined by receptor status (see page 20).

6.12 Prostate cancer

Symptoms

- Urinary (urgency, frequency, hesitancy, hematuria, dripping, nocturia, acute urinary retention). Scoring systems for prostatic symptoms are available, for example the International Prostate Symptom Score (IPSS) is widely used (Barry et al., 1992). A validated Belgian Dutch version is available, courtesy of prof. J.M. Kaufman, Endocrinology, Gent University
- Symptoms of metastasis (low back pain and others)

Investigations

- Prostate specific antigen
- Transrectal ultrasound
- Prostatic biopsy

Treatment

- Radical prostatectomy
- Radiotherapy
- Surgical castration (rare nowadays)
- Hormonal castration (with GnRH analogues, anti-androgens or uncommonly with estrogens)

Possible biases

Positive:

- Medical/surgical castration in transsexuals and voluntary medical castration in (potential) sex offenders and pedophiles.
- The same RIZIV nomenclature is used for both orchidectomy and surgical castration
- The same RIZIV nomenclature for castration is used in some hospitals for testicular sperm extraction (TESE) for use in assisted reproduction in place of testicular biopsy (the honorarium for testicular biopsy is too low for the labor-intensive TESE)

Negative: underreporting

6.13 Testicular cancer

Symptoms

- History of cryptorchidism or infertility
- History of carcinoma in-situ
- Testicular swelling (possibly after trauma)
- Pain and symptoms of metastasis (late)

Investigations

- Serum markers of germ cell tumors:
- Alpha-fetoprotein (AFP)
- Human chorionic gonadotrophin (HCG)

- Lactate dehydrogenase (LDH isoenzyme 1)
- Intra-operative testicular biopsy with spermatic cord clamping
- Histopathology

Treatment

- Orchiectomy
- Cisplatin, bleomycin, and etoposide "gold standard" man (15-45 years of age)
- Radiotherapy
- Retroperitoneal lymph-node dissection (rare)

Possible biases

Positive: orchidectomy for other reasons (trauma, transexualism, cryptorchidism)

Negative: underreporting

6.14 Thyroid gland diseases

Definition

A heterogeneous group of diseases affecting the thyroid gland including decreased (hypothyroidism) or increased secretion of thyroid hormones (hyperthyroidism) and thyroid tumors.

Symptoms

- Enlarged thyroid
- Symptoms of hypothyroidism or hyperthyroidism
- Symptoms of thyroid cancer

Investigations

- Echography: reported anomalies in a population exposed to PCBs include enlarged thyroid, hypoechogenicity, thyroid nodules,
- Laboratory tests

TSH, T4
antithyroid peroxidase antibody (anti-TPO)
Calcitonin

Treatment

- Antithyroid drugs
- Thyroxin
- Thyroidectomy

Possible biases

Positive: the distinction between the different types of thyroid diseases based on the type of medication used in the absence of medical records is extremely difficult because the same medication is frequently used for different types of pathology.

Negative: same as positive

6.15 Immune system diseases (immunosuppression)

Definition

Changes in the immune system that suppress the bodily immune reactions

Symptoms

Symptoms are variable and include increased susceptibility to infections e.g. middle-ear infections and chicken pox and lower prevalence of allergic reactions. Non-Hodgkin lymphomas are regarded by some authors as a manifestation of immunosuppression (see below).

Investigations

Quantification of immune cells and immunoglobulins in blood and other investigations according to the presenting pathology

Possible Biases

Positive: the differentiation between infection and allergy may be difficult in the absence of special tests.

Negative: same as for positive

6.16 Non-Hodgkin lymphomas

Symptoms

Symptoms can vary widely, depending on the cancer site. The most common symptom is a noticeable, usually painless swelling of a lymph node.

Other symptoms include fever, night sweats, tiredness, weight loss and widespread itching, and reddened patches on the skin

Investigations

- Biopsies of the bone marrow and lymph nodes
- Histopathology
- Immunophenotyping (immunohistochemistry or flow cytometry)
- Chromosomal analysis: a particular type of non-Hodgkin's lymphoma (translocation or "T"(14;18)-positive) has been associated with exposure to endocrine disruptors.

Treatment

- Chemotherapy (chlorambucil, cyclophosphamide, doxorubicin hydrochloride, vincristine, mitoxantrone, fludarabine)
- Radiotherapy
- Anti-CD20 monoclonal antibody (rituximab)
- Stem cell transplantation and growth factors (bone marrow support after high dose chemotherapy)

Possible biases

Positive: none

Negative: underreporting

7 Relevant pathologies: Which data are available for Flanders?

The next step is to investigate whether information on the relevant pathologies discussed in section 6 is available for Flanders. Some details are first given on the institutions involved in collecting the data.

7.1 Sources of data

7.1.1 Study center for perinatal epidemiology (Studiecentrum voor Perinatale Epidemiologie, SPE)

The SPE gathers information and reports on all hospital deliveries in Flanders. The first (almost complete) registration of 1991 reports on 95,5 % of hospital deliveries in Flanders and since 1996 the reporting of hospital deliveries is complete (100%). The SPE has a large database, containing extensive data on both the mother and child, mode of delivery and complications (see pages 127, 134). These include parity, the method of conception, duration of pregnancy, twin pregnancy, pregnancy risk factors, position of the baby, the use of epidural analgesia and the method of labour induction and delivery. The child's birth weight, Apgar score, and congenital anomalies are reported. In the event of maternal or neonatal death, the cause is reported. The database also contains the postcode of the mother/child. This may be useful if geographical trends are to be investigated. The most recent report covers the perinatal activities in Flanders for the year 2003 (SPE, 2004). To obtain the data in a database format, a request has to be submitted and approved by the SPE steering committee.

Some hospital deliveries are also included in the SPE reports making the number of newborns not included in the reports very small, only between 200 and 500 deliveries are not reported in the SPE reports in the years 1997-1999. This is less than 1 % of the total deliveries in Flanders (Gezondheidsindicatoren 1998, 1999, 2000, <http://www.wvc.vlaanderen.be/gezondheidsindicatoren/>).

7.1.2 The EUROCAT Register of congenital anomalies

The EUROCAT (European Concerted Action on Congenital Anomalies and Twins) network of population-based congenital anomaly registers is the main source of epidemiological data on congenital anomalies in Europe since 1979.

EUROCAT registries annually send a file of individual case records corresponding to each new birth year to the EUROCAT Central Registry, along with appropriate denominators (number of live and stillbirths in the region). Case records include a standard dataset, with standard coding. All data sent to the Central Registry are anonymous, and any identification of cases in order to collect further information is done at local registry level. For Belgium, data are available for Antwerp and Hainaut-Namur (See table 2).

7.1.3 Centers for guiding pupils (Centra voor Leerlingenbegeleiding, CLB)

These centers perform repeated medical examinations of pupils (see table 3). **The NICO-project** (Netoverstijgend ICT-project voor CLB gegevens in samenwerking met

departement Onderwijs) is being developed to allow the CLBs to function more efficiently and effectively via automatisisation of information. Contacts with CLB indicated that the NICO project is still in "full" development and that its electronic module, called datawarehousing, is still to be developed and not expected to be operational this school year (2004-2005). This experimental phase of development does not allow for systematic registration of health data (Prof. Karel Hoppenbrouwers, Mrs. Yolande Schulpen and Dr B. Aggoune, CLB and NICO, personal communications).

7.1.4 Cancer registries

Till the **year 2000**, the data collected in The **Belgian National Cancer Registry** were far from complete, the quality and diversity of the information was limited and there was a considerable time delay. For this reason, **regional cancer registries** were set up which, together with the National Cancer Registry, constituted a **Flemish Network of Cancer Registries** (Van Hal et al., 2000).

The Flemish league against cancer (Vlaamse Liga tegen kanker, VLK) plays a coordinating role in the collection of data for the Flemish network of cancer registries.

The dataset of the Flemish network of cancer registries includes information on age, sex, residence (NIS and post codes) and the general condition of the patient (World health organization code). Data concerning the tumor include date of diagnosis, type of cancer and localization and behavior of the tumor.

Additionally, **screening databases** were initiated (SDB) for breast and prostate cancer (Nelen et al., 2003; Van Hal et al., 2000). The multidisciplinary oncological consultation (multidisciplinair oncologisch consult, **MOC**) has been recently established with the purpose of better medical management of patients with cancer. Reporting of all cases of cancer discussed in multidisciplinary oncology meetings is compulsory from 1/2/03. These data are forwarded to the mutualities. We decided to evaluate the trends in cancer incidence in the last few years only (see below) since data on earlier years are expected to be less complete. Long term follow-up for cancer trends is necessary.

7.1.5 Health interviews

These interview health surveys (Gezondheidsenquêtes) are regularly organized (1997, 2001, 2004) by the Belgian institute of public health (Buziarsist et al., 2002). More than ten thousand persons representative of the Belgian population are invited to participate with a response rate around 60 %. The surveys report on health status, trends, needs and problems and possible social (in)equality in health as well as access to the health services, health consumption and its determinants (for further details see <http://www.iph.fgov.be/epidemie/epien/>).

7.1.6 Electronic medical file

Some hospitals are in the process of completing the electronization of medical files. This is the case in, for example, the University hospital of Ghent. Prorec-be (<http://www.prorec.be/>) is a non-profit organization whose mission is to contribute to the widespread use of high quality electronic healthcare records in Belgium.

7.1.7 Global medical file (Gloabaal Medisch Dossier)

The global medical file (**Gloabaal Medisch Dossier**) project started in 1999 and aims at centralizing all the medical information available on a given patient under the supervision of his/her treating general practitioner (Onafhankelijke Ziekefonds, 2004). The project is promoted via paying file-handling fees to the general practitioners and reduction in costs of medical consultation for patients who agree to join the project. The number of patients joining the global medical file arrangement is increasing (table 4). This may provide an infrastructure for a better source of documented information in the future.

7.1.8 The National Institute for Sickness and Invalidity Insurance (RIZIV)

The National Institute for Sickness and Invalidity Insurance (Rijks Instituut voor Ziekte- en Invaliditeits Verzekeringen, RIZIV) is in charge of the administrative and financial control of the insurance for medical care and benefit for incapacity. Personal contact with the RIZIV (Dr. Menseart, 1/10/04) indicated that the RIZIV has data in aggregated form concerning diagnostic and therapeutic procedures but no data over individual persons. The source of the aggregated data is the intermutuality agency (InterMutualistisch Agentschap, IMA). See also Visit to the RIZIV 1/10/04 (page 55).

7.1.9 The intermutuality agency (InterMutualistisch Agentschap, IMA)

The intermutuality agency (Intermutualistisch Agentschap, IMA), is an agency organizing the cooperation between its 7 large Belgian member mutualities. IMA was established to allow for better organization of medical insurance and aid in the collection and analysis of high quality data. Some health reports are also published by the. Personal contact with IMA (Dr. R. Mertens, 11/10/04) indicated that data on individual patients (starting from 1996) could be aggregated from the different mutualities on a project basis (paid service). This includes age (birth year), social status, and residence in NIS sector. The address of the patient can be transformed into statistical sector. Information is available on diagnostic and therapeutic procedures and as well as medications refunded by the mutualities. The Christian mutuality has data on tape that can be eventually reloaded starting form 1989. For further details see pages 56 to 57.

7.1.10 The Flemish Support point for environment and health (steunpunt milieu en gezondheid)

In 2001 the Flemish community established 13 academic support points one of which is concerned with environment and health (steunpunt milieu en gezondheid). It is a consortium formed between different Flemish academic and health institutes laying the foundation for a multidisciplinary research group. In addition to laboratory and field studies, the group has also established a database called milieupath with the aim of collecting medical and environmental data (for more details see page 75).

7.1.11 Minimal clinical findings (minimale klinische gegevens, MKG)

The Minimal clinical findings (MKG) data collection was established as a system for the control of the financial costs for hospitalization. Although MKG registration is obligatory since 1990, the data are of good quality from June 1997. Before June 1997 legal problems resulted in incomplete registration of the data (office of Mrs. Ingrid Mertens, MKG FOD volksgezondheid, personal communication).

The MKG data include information on the hospitalization itself (MKG verblijf in het ziekenhuis, MKGVBZH) including type of hospitalization (classical hospitalization, day hospitalization and a special category for newborns), date of hospitalization and discharge of the patient (month and year) and whether the patient was rehospitalized more than once during a particular year. Also, the nationality, sex, age in years and the main clinical diagnosis of the patient are included. MKG uses the international classification of diseases (ICD) version 9 (clinically modified, year 2002) for the classification of diseases. Postcode and national institute of statistics (NIS) code of the patient's residence is also registered.

The second set of data included MKG reports on the clinical diagnosis (MKG diagnose, MKGDIAG). This includes additional clinical diagnoses and the department where the patient was hospitalized.

To protect the privacy of the patients, a 13 digit coding of the patients identity is performed by the hospitals before sending the data to MKG. This generates the hospitalization number (verblijfsnummer). The hospitalization number uses a code that is unique for each patient per hospitalization but each hospital is allowed to use its own coding system and to change the coding system each year. Therefore, at the present time, data from MKG are expected to suffer from the problem of double registration due to the lack of a standardized method for the coding of patient hospitalization number.

Some data from MKG are now included in the database of the steunpunt milieu en gezondheid (milieupath, see pages 75, 130). It has to be noted that the MKG dataset delivered to steunpunt milieu en gezondheid and now included in the database (milieupath, <http://www.milieupath.be/>) does not contain the patient hospitalization number because of privacy issues. Repeated registration was removed by MKG (FOD volksgezondheid) and milieupath as far as the patient identification system allows (Greet Van Kersschaever, personal communication).

7.2 Data available on relevant pathologies

7.2.1 Intrauterine growth retardation (IUGR) and low birth weight

Defined as fetus small for gestational age (10 % less than predicted fetal weight for gestational age) and diagnosed by echography. No data are directly available but can be calculated from birth weight and the duration of pregnancy. Data on (low) birth weight as well as duration of pregnancy in live-birth hospital delivered babies are available from the yearly SPE reports. The percentage of babies with low birth weight (<2500 gram) has increased from 6,5 % to 7,4 % between the years 1994-2003. The incidence of IUGR (actually the percentage of babies small for gestational age) can be calculated from these two parameters in the database. Possible biases include a change in the percentage of hospital deliveries and better survival of low birth weight babies over the years. To obtain the data a request has to be submitted and approved by the SPE steering committee.

7.2.2 Prematurity

The incidence of prematurity is available from SPE for live-birth hospital deliveries in Flanders. Statistics comparing 1994 to 2003 indicate an increase in the percentage of premature deliveries from 5,8 to 7,4 % over a period of 10 years. Possible biases may be due to a change in the percentage of hospital deliveries and better survival of premature babies over the years and the induction of labour for medical or other reasons including patient's and/or medical staff's convenience. It has to be investigated whether the medical induction of labour, which occurs in about 30 % of all hospital deliveries in Flanders (SPE, 2004), has an effect on the incidence of prematurity.

7.2.3 Congenital anomalies in general

Two sources of information have been identified. The SPE database (see addendum 1) and EUROCAT (see table 5).

Data from SPE reports indicate a more or less stable incidence of congenital anomalies (1,5-1,7 %) (SPE 1996, 1997, 1998, 1999, 2003). At the other hand, data from Antwerp (EUROCAT) indicate an average prevalence of 2,63 %. Whether this difference is due to the quality of reporting or a true difference between Antwerp and the rest of Flanders is not known. It should be investigated whether this difference is trivial or real.

7.2.4 Cryptorchidism

Due to difficulties in the diagnosis and classification, no data on cryptorchidism are present in the EUROCAT database (E-mail contact with Helen Dolk, EUROCAT Project Leader, 25/05/2004). The SPE reports on urogenital anomalies in general with a place for reporting the end clinical diagnosis, but cryptorchidism is not reported separately.

One old publication by Steeno concerning the incidence of cryptorchidism in school children in Brussels (Steen et al., 1967) has been found by title in Pubmed. It may be useful to reproduce the study by Steeno using the same protocol. This may help to identify possible time trends.

7.2.5 Hypospadias

Data are available for Antwerp and Hainaut-Namur via EUROCAT (See table 2). The criteria for registration differ between the participating centers making comparison between regions or countries unreliable (comparison is not recommended by EUROCAT). The SPE reporting form gathers information on urogenital anomalies in general, with a place for reporting the end clinical diagnosis (see addendum 1). The reported prevalence of hypospadias in Antwerp is given in table 6. The lower prevalence in last couple of years is due to a change in diagnostic criteria and delayed reporting. This is because EUROCAT now requires the diagnosis to be confirmed both by a pediatrician and a pediatric surgeon, which results in delayed reporting of about 3-4 years.

7.2.6 Mental and psychomotor development

One Belgian study comparing the mental and psychomotor development in children conceived using intracytoplasmic sperm injection (ICSI) and those born after a spontaneous conception has been identified (Bonduelle et al., 1998).

A 42 month follow-up of the neuropsychological development of 200 young children in Flanders is organized by the Flemish "Steunpunt milieu en gezondheid" (STMPG, Strategische Doelstelling 3 > Biomonitoring en Surveillance). Partial results are expected in 2006. Contacts with the center for developmental disturbances, university hospital Ghent (Centrum voor Ontwikkelingsstoornissen, COS) indicated that only cases with advanced and clinically manifest disturbances of psychomotor development presenting to COS are registered using the same software for all centers in Flanders. Therefore, combining data from different COS centers is technically possible. Otherwise there is no systemic registration of psychomotor development of Flemish children (Mr. L. Goossens, Director COS Ghent, personal communication).

7.2.7 Growth/puberty

The age of the establishment of the menarche and its evolution in Belgium in roughly the first half of the twentieth century has been reviewed in 1969 (Jeurissen, 1969). The secular trend in the years 1960-1980 is evaluated in an article by Vercauteren and Susanne (Vercauteren & Susanne, 1985). In 1985, Carlier and Steeno reported that the mean age at first ejaculation in Belgian boys was 13 years and 2 months, with a corresponding testicular volume of 10 ml measured using Prader orchidometer (Carlier & Steeno, 1985).

The research project "Flemish Growth Curves" is a study of the growth and development of Flemish children (both males and females). It aims at the development of new growth charts for height, weight, Body Mass Index and head, upper arm and waist circumference from birth to 19 years of age; and standards for pubertal development from 8 to 18 years of age. Secondary targets are the description of growth and development in terms of health parameters, and the socio- economic, demographic and geographic background (Roelants et al., 2001). The results are expected in 2005.

The determinants of onset of puberty have been studied in a cohort of 1100 girls between birth and age of 13 (Janssens et al., 2003). The study found that age at onset of puberty can be modified by lifestyle factors. Obese (and tall) children will reach the first signs of puberty earlier than children with a lower weight. Children with diseases had also a tendency for earlier puberty. Breast development was earlier when the weight of the father is high and the length of the mother is short. The duration of and weight increase during pregnancy predict for early puberty of the child. Some of these findings can be implicated in breast cancer prevention.

Other publications concerning growth and puberty in Belgian youth are available (Lefevre et al., 1993; review: Vercauteren et al., 1998).

7.2.7.1 Precocious puberty

The role of previous exposure to organochlorine pesticides and sexual precocity after immigration from developing countries to Belgium has been reported (Krstevska-Konstantinova et al., 2001; Parent, 2004). For further details see page 16.

7.2.7.2 Delayed puberty

Although a Belgian study indicated exposure to polychlorinated aromatic hydrocarbons (PCAH) is associated with delayed sexual maturation (Den Hond et al., 2002; Staessen et al., 2001), the methodology and conclusions of this study has been criticized (Dhooge et al., 2001; Molenberghs et al., 2003). For further details see page 16.

7.2.8 Male infertility and sperm quality

Data on sperm quality and serum reproductive hormones are available in healthy male individuals (small numbers) from a population study in Flanders (Onderzoek Milieu en Gezondheid)(Vlietinck et al., 2000), Flemish candidate sperm donors (Comhaire et al., 1995; Van Waeleghem et al., 1996) and control groups for studies evaluating the effect of occupational exposure to carbon disulfide (Vanhoorne et al., 1994) and inorganic lead (Bonde et al., 2002) in Flanders on sperm quality. See also female infertility.

7.2.9 Female infertility

The SPE reports indicate that the number of children born in Flanders in 2003 has decreased 14%, in comparison with 1991. Data from the national institute of statistics show a similar trend (figure 1), suggesting that the data from SPE is not biased by a change in the percentage of hospital deliveries. The decrease in the number of births was most remarkable in West Flanders (- 16 %) (SPE, 2004). The percentage of twins and triples born in Flanders gives an indication on the use of hormonal stimulation of the female partner and the use of assisted reproductive techniques for the treatment of infertility (SPE, 2004). The percentage of twins and triplets has in general shown an increasing tendency (1994-2002) reaching a record high in 2002 (2.02 %). The percentage has decreased in 2003 (SPE, 2004). Whether this decrease is due to the implementation of the federal law coupling the refunding of the costs of *in vitro* fertilization/intracytoplasmic sperm injection (IVF-ICSI) to single embryo transfer remains to be seen. In support of this explanation is the fact that the percentage of multiple birth following IVF-ICSI has decreased with 3 % in 2003 (22,4 %) compared to 2002 (25,9 %). The percentage of pregnancies following "therapy for infertility" increased from 3.2 % in 1994 to 4.1 % in 2003 (SPE, 2004).

7.2.10 Time to pregnancy (TTP)

Validation studies of TTP recall (review: Joffe, 2000) have shown that women's self-reports are unbiased as a measure of the true value, as assessed by a concurrent (follow-up) method. At a group level, the TTP distribution thus derived corresponded very closely to that obtained prospectively. Furthermore, recall was found to be stable: the degree of correspondence was as good for pregnancies that occurred 14-20 years before data collection as for those occurring within 14 years (review: Joffe, 2000).

Two studies have been identified where TTP has been reported in Belgian women, one after the removal of intrauterine device (Delborge et al., 2002) and a control group for a study evaluating the effect of male exposure to inorganic lead on TTP in partners of Flemish men (Joffe et al., 2003). A recent study indicated that a long TTP is associated with a reduced risk of spontaneous twinning (Sinclair, 2000).

Questionnaires concerning TTP can eventually be added in the next health interviews "Gezondheidsenquête".

7.2.11 Sex ratio

The male (51.1 %-51.6 %) to female (48.4 % to 48.9 %) ratio of newborn babies (hospital deliveries) remains more or less stable (1994-2003) (from SPE, 2004).

7.2.12 Endometriosis

A high incidence of endometriosis infertility or gynecological pain (60-80 %) has been reported in Belgian women with menstrual disturbances and infertility (opinion paper: Koninckx et al., 1994). Otherwise no data are available.

7.2.13 Breast cancer (female)

The estimates for individual countries in Europe for the year 2000 show the highest incidence rates in the Netherlands ($91.6/10^5$), Denmark ($86.2/10^5$), France ($83.2/10^5$), Belgium (**$82.2/10^5$**), and Sweden ($81.0/10^5$) (Tyczynski et al., 2002). With almost 6 000 new cases and about 2 400 deaths per year, Belgium (female population of 5.2 million) ranks among the most affected countries in the World (Arbyn et al., 2002).

Therefore, a nation-wide population screening for breast Cancer started in 2001, for women in Belgium (age groups 50-69) through offering a free mammographic examination every two years (Arbyn et al., 2002). This led to the establishment of a separate RIZIV numbers for this sponsored breast cancer screening (Degauquier et al., 2004). The percentage of women participating in the screening program is increasing as shown in table 7 (Degauquier et al., 2004).

The absolute numbers of invasive breast cancer in Flanders are available via the Flemish league against cancer (Vlaamse Liga tegen Kanker, VLK) (table 8). VLK attributes the increase in the number of breast cancer cases largely to a better registration. In 2000, 4879 new cases of breast cancer have been registered in Flanders. It took about 4 years to make the data available (data for the year 2000 were published in 2004). In the provinces Flemish-Brabant and Antwerp, more breast cancer cases have been reported than in other provinces. VLK suggests that the higher incidence in these regions may be, at least in part due to the earlier start of systematic screening for breast cancer in women aged 50-69 years in these regions. The age-adjusted mortality from breast cancer has been always the highest in West-Flanders (Arbyn et al., 2002).

Arbyn et al. (2002) analyzed Belgian data on breast cancer mortality for the period 1954-1996. The annual number of women that died from breast cancer increased with 75% over the four decades: from 1405 in the period 1954-59 to 2454 in the period 2 1990-96 (these data are available from the National Institute of Statistics). The age-standardized rate, using the European reference population, increased from 25-27 per 100 000 in the fifties to 35-36 per 100 000 in the mid-eighties. Since then, the adjusted rate remained stable. Currently, 3.0% of the total female population dies of breast cancer before the age of 75 years. The increase in mortality was limited in the age groups younger than 50 years and more pronounced in older age groups. In postmenopausal women, mortality was rising until

1986, there after it remained stable. An obvious increase was noted for women born between 1900 and 1925 (Arbyn et al., 2002).

The breast cancer age-adjusted mortality in the Flemish Region was systematically higher than in the Walloon region (a difference of about 10/100 000 women-years). This difference tended to disappear after 1990. Mortality was always highest in the province of West-Flanders (Arbyn et al., 2002).

The Belgian age-adjusted breast cancer mortality trend was intermediate between France and Germany that showed lower rates and The Netherlands and England & Wales that showed higher mortality. In these countries, the mortality rates did not further increase in the 1970s, while Belgian mortality was still increasing. A spectacular drop was noted in England and Wales after 1990 (Arbyn et al., 2002).

Although changes over time are limited in Belgium, they have important impact on the total number of deaths, since the neoplasia occurs so frequently and because of the ageing of the population (Arbyn et al., 2002).

Understanding the changes in factors that determine trends is important to explain passed trends and to predict future evolutions. The increased cohort effect observed in women belonging to the birth cohorts C1900-C1920 is probably due to decreased fertility observed in the women before the second world war. The recent fall in mortality in certain western countries is most often explained as the consequence of earlier diagnosis mediated by increased breast awareness and improved treatment. The impact of well-conducted screening program is expected to become observable only 5-7 years after the start of the campaigns. Meanwhile it is essential to set up data collection systems allowing monitoring of process parameters concerning participation of the target population and the quality of all technical procedures. Only when the quality at all steps can be assured a reduction in mortality from breast cancer up to 30% can be expected (Arbyn et al., 2002).

7.2.13.1 Linking a breast cancer screening database to a cancer registry

Van Hal et al. (2000) attempted to link a breast cancer screening database with a cancer registry in Antwerp, Belgium. The study population comprised women between 50 and 70 years of age who were living in the region of the river Rupel ("Rupelstreek") and were invited for the first and/or second round of the breast cancer screening program in 1991-1992 and/or 1994. The Rupelstreek consists of six municipalities south of the city of Antwerp: Aartselaar, Boom, Hemiksem, Niel, Schelle and Rumst. They complemented their screening program with data obtained from the general practitioner (GP) via phone contacts and letters. A summary of the detection rates via screening, Antwerp cancer registry, and GPs is presented in table 9. Only 75 patients known at the screening database were found in the Antwerp Cancer Register. Of the cases diagnosed before the screening mammography, 109 out of 147 cases (74.1 %) were registered in the Antwerp cancer registry. If 100 % (instead of 46 %) of the invited population would have responded, it seems likely that even more cases would be discovered that are not included in the Antwerp cancer registry.

Van Hal et al. (Van Hal et al., 2000) found that data collection from GPs was labor-intensive and very difficult, due to the following:

- It took a lot of time to bring the official list of medical doctors up to date and 3 GPs were still missed;

- Women belonging to the target population did not necessarily have a GP in one of the 6 municipalities of the Rupelstreek;
- The response of the GPs to the 1st telephone call and the ensuing mailing was low (10 GPs out of 57 reacted 17.5%);
- A second telephone call resulted in information from 41 out of 47 GPs (87.2%);
- The information gathered does not always reflect reality. Only 10 % of cases were reported. Maybe the GPs thought it was not necessary to report those patients
- Data collection from GPs was very labor-intensive for both the Centre for Cancer Prevention and the GPs themselves.

Linking of databases presupposes an identification up to the level of first names and surnames. The Belgian law safeguarding personal privacy in relation to the processing of personal details, makes it very difficult to start a database with personal details, even for health care purposes.

Because of the number of manual searches needed to check whether it is the same woman in a "couple" that does not completely fit, linking databases is a very labor-intensive process. This time consuming work is to a great degree due to the restrictions in working practices imposed by the privacy law.

7.2.14 Prostate cancer

Data on the absolute number of cases with prostate cancer are available for the VLK (table 10). The European randomized screening for prostate cancer (ERSPC) screening program contains data on almost 10000 men as shown in table 11 (Nelen et al., 2003). Prostate specific antigen (PSA), a marker of prostate function, is included in the biomonitoring program of the "Steunpunt milieu en gezondheid". The incidence of prostate cancer in Flanders has been reported to be very high (higher than in 15 European countries included in the Eurocan 1997) (Lousbergh et al., 2003).

7.2.15 Testicular cancer

Data on the absolute number of cases with testicular cancer show no consistent trend during the period 1997-2000 (VLK) (table 12).

7.2.16 Non-Hodgkin lymphomas

Data on non-Hodgkin lymphomas are available from VLK (table 13). The absolute numbers of cases does not show a consistent trend (years 1997-2000).

7.2.17 Other data related to cancer

Data on DNA integrity and markers of cell maturation/signal transduction in healthy female individuals (small numbers) are available from a population study in Flanders (Onderzoek Milieu en Gezondheid) (Vlietinck et al., 2000). The ongoing study of STMP studies these markers in a larger population in adults.

7.2.18 Thyroid diseases

Data on thyroid stimulating hormone levels in (male and female) healthy individuals (small numbers) is available from a population study in Flanders (Onderzoek Milieu en Gezondheid) (Vlietinck et al., 2000). It is also planned to measure thyroid hormones in 1600 adolescents (800 boys and 800 girls) as a part of biomonitoring for Steunpunt Milieu en Gezondheid.

The reporting of thyroid problems in the health interview of 2001 was spontaneous by the interviewed under the category other medications used (table 14). Therefore, underreporting is expected relative to other health problems. No information is available concerning thyroid problems in the health interview of 1997 (Buziarsist et al., 2002). Data on thyroid cancer are available from VLK (table 15).

7.2.19 Immune system diseases

Data on immunological markers in healthy female individuals (small numbers) is available from a population study in Flanders including gammaglobulins, lymphocytes and complement (Onderzoek Milieu en Gezondheid)(Vlietinck et al., 2000). A Belgian study in adolescents from Antwerp indicated that the levels of both dioxin-like compounds and PCBs were negatively correlated with symptoms and immunological markers of asthma and allergic responses (Van Den Heuvel et al., 2002).

8 Which endocrine disrupting substances are relevant?

Hundreds of chemicals and substances with endocrine disrupting activities have been documented either in wildlife, experimental animals or *in vitro* laboratory experiments (Damgaard et al., 2002). These include pesticides, food additives, natural steroids, plant products, industrial chemicals, and pharmaceuticals (see table 16).

Although the toxic effects of heavy metals are long known, recent literature indicates these metals, especially cadmium, and to a lesser extent tin, antimony, lithium, barium, and chromium, to possess estrogenic activity *in vitro* (Choe et al., 2003; Johnson et al., 2003). In addition, cadmium can also affect progesterone production in humans and in animal experiments (review: Henson & Chedrese, 2004). For a review on the health effects of cadmium see Satarug & Moore (2004).

Recent biomonitoring surveys of non-occupationally exposed volunteers in the United Kingdom indicate that every person tested was contaminated by a cocktail of organochlorine pesticides, PCBs and polybrominated flame retardants (WWF, 2003). This has been confirmed in another recent study in members of the European parliament and other volunteers from 17 countries in Europe. The study indicated that each of the volunteers tested positive for HCB, pp'-DDE, the PCB congeners 52 and 74, DEHP, perfluorinated chemicals (PFOS/PFOA) and the polybrominated flame retardant BDE 153 (WWF, 2004).

The relevant chemicals where information is available for Flanders are listed in table 16. Detailed information on the chemical properties, mechanisms of toxicity, levels of these substances in water, soil and food and effects on animals are available in recent reports (Covaci et al., 2002; De Bont et al., 2004; De Bont & van Larebeke, 2004; Viaene, 2000; VMM, 2003).

Due to its physiological properties, sedentary way of living and special feeding habits, the European eel (*Anguilla Anguilla*) seems to be a suitable fish for the bio-monitoring of environmental pollution (de Boer and Brinkman, 1994; Knights 1991; 1997; Sancho et al, 2000). Extensive information over the concentration of PCBs and other pollutants in the eel in Flemish waters is available via the Flemish eel pollutant measurement network (palingpolluëntenmeetnet) (Goemans et al., 2003).

On the basis of our literature study on the effects of endocrine disruptors in humans (section 5) and the availability of data for the Flemish environment (De Bont et al., 2004; De Bont & van Larebeke, 2004; VMM, 2003) (table 16), it is concluded that at this moment the most relevant substances to be further studied in Flanders are DDT (and metabolites), cyclodienes (drins), hexachlorobenzene, dimethoate, nitrogenous organic pesticides (mostly atrazine), organotin compounds, PCBs, dioxins, styrene, nonyl phenols, bisphenol A, phthalates, and ethinylestradiol. However, new research data provide continuously new insights, which makes this list provisional and under permanent construction. For example, further studies are needed to evaluate the possible endocrine disrupting potential of human exposure to carbamates, parabens, polybrominated flame retardants, PFOS, PFOA and cadmium at environmental levels since little is known about their possible endocrine disrupting properties. A risk analysis is available for dioxin, bisphenol A, Atrazine and ethinylestradiol for the Flemish population (van Larebeke et al., 2001; VMM, 2003) (see below).

In Flanders, organochlorine pesticides are still frequently detected in abnormal concentrations in waterbeds. Although the use of pesticides such as DDT (and its

metabolites) is forbidden since many years, it is still detected in high concentrations. Also, cyclodiens, which are forbidden since decennia, are still detected in high concentrations in many places. For these substances possible sources include the illegal use of still existing stocks, contamination coming from other countries where these substances are still used (legally or illegally), and persistent historical contamination of waterbeds and soil (De Smet & Steurbaut, 2001; VMM, 2003).

As part of a study performed under the auspices of the Flemish Environment Agency, the Andrology laboratory of Ghent university has recently investigated samples of surface water from 40 different sources in Flanders. High levels of estrogenic compounds were detected in water sampled from the High Scheld river (Dhooge & Comhaire, 2003). The major estrogenic compounds detected in water belonged to 3 groups: steroids, including natural estradiol and ethinyl-estradiol, alkylphenols, and parabenes. The high amounts of estradiol probably derive from intensive cattle breeding, whereas ethinylestradiol results from activation in wastewater treating plants because of deconjugation of the contraceptive pill estrogen. The contribution to the estrogen load of parabenes (mostly methyl parabene) is quantitatively similar to that of the alkylphenols (Dhooge & Comhaire, 2003).

8.1 Risk evaluation for dioxin, bisphenol A, Atrazine and ethinylestradiol for the Flemish population

The estimated human intake (EHDI) of dioxin for a person weighing 70 kg, in Flanders is between 2,56 en 14,81 pg TEQ/kg/day (TEQ = Toxic equivalent of 2,3,7,8-TCDD). When these values are compared to PEC-values (estimated environmental concentrations) it seems that, by a daily intake of the minimum concentration, the number of spermatozoa and their quality can decline and that women have a high risk of endometriosis. The daily intake of maximum concentrations by a mother would delay the development of the baby, and exposure of embryos, increases the risk of fetotoxicity and spontaneous abortion. Immunosuppression would occur at the minimum daily intake, appreciably increasing the susceptibility to viral infection (VMM, 2003).

For dioxin and dioxin-like PCBs, additional calculations for body burden after the accidental exposure in 1999 have estimated the stochastic incremental cancer risk associated with the incident to vary between 44 and 8,316 cancer deaths. This is an estimation based on a simple model in which a sudden increase in body burden was transformed in a lifelong daily exposure (van Larebeke et al., 2001).

The daily intake of atrazine, for a person weighing 70 kg, is estimated to be between 0,014 and 4,47 µg/kg. The daily intake of 0,77 µg/kg/day would decrease the number of oocytes in women and decrease testicular volume in men and therefore decrease fertility in respectively women as well as men (VMM, 2003).

The daily intake of bisphenol A is estimated to be between $3,18 \times 10^{-3}$ and 7,51 µg/kg for a person weighing 70 kg. From 1,07 µg/kg/day the daily sperm production can decrease and even infertility may issue. Also, precocious puberty, changes in reproductive functions, and increased weight of the prostate and uterus may occur. The maximum concentration of 7,51 µg/kg/day as daily intake can decrease testicular volume, can have an effect on survival, growth and reproduction and increase prolactin concentrations in serum. In women, where a median weight of 60 kg is calculated, there is a higher risk of effects on the mammary glands by an intake of 1,25 µg/kg/day or more (VMM, 2003).

For ethinylestradiol, an intake of 0,62 ng/kg/day or more for a person weighing 70 kg may decrease sperm production during adolescence and the success of fertilization in women as well as decreasing aggressive behavior. A maximum concentration of 28,63 ng/kg/day can possibly cause anorexia. For contraceptive pill users (estimated for a female weighing 60 kg) there is an additional increased risk of the above-mentioned effects because of the intake of higher doses of ethinylestradiol which would also increase the risk of breast cancer. At the other hand oral contraceptives would decrease the risk of ovarian cancer (VMM, 2003).

Further details on the risk calculations are available in the original report. These estimations are not definitive but rather indicative. Except for dioxin, further studies are needed for better risk estimations because too few data are available concerning environmental concentrations of these substances in Flanders. This obliged the authors to use data from other countries (VMM, 2003).

9 Development of strategy for the collection of clinical findings

The main purpose of this project is to investigate the possibility of linking environmental data on endocrine disruptors to clinical data which reflect the possible health effects of exposure to these substances. Before exploring a strategy for the collection of clinical findings, the first question to be answered is at which level should the population be defined in medical registries to allow for epidemiological studies and, at the same time, respect the personal privacy.

9.1 *The need for data registration in statistical sector code*

The investigation of the possibility to relate the increased incidence of a particular pathology (cluster, exposed population) to an environmental pollution profile includes the comparison of the exposed population to a non-exposed population. Because both the number of cases with the pathology of concern as well as the geographical area where the cluster is suspected are usually small, cumulative data on the demography and pathology incidence in the concerned area is desired. The current system of disease registration in Flanders, which is based on postal code or national institute of statistics (NIS) code, with some code areas enclosing up to 450.000 inhabitants, lacks the accuracy needed for small area analyses. The municipalities are subdivided into statistical units. Each unit or sector has a statistical code. Theoretically, one unit encloses at least 200 inhabitants. The maximum number of inhabitants of a sector is not determined and depends on the population density. It is the smallest geographic unit on which demographic data are available and the number of inhabitants is much smaller than those living in a NIS or Postal code area. Therefore, the most appropriate level of registration for the study of clusters seems to be the statistical sector code. This provides a balance between health concerns and protection against disease on the one hand and concerns regarding the protection of privacy on the other hand (reviewed in Van Herbruggen et al., 2000). Our contacts indicated that the use of statistical sector code is ethically acceptable, except for rare diseases where its use may be in conflict with personal privacy.

9.2 *Visit to the RIZIV 1/10/04*

Present: Nicolas Van Larebeke, Ahmed Mahmoud (UG), Dr Antoon Mensaert, Mv De Prins, Rijks Instituut voor Ziekte- en Invaliditeits Verzekeringen (RIZIV)

The meeting started with an introduction from N. Van Larebeke and A. Mahmoud about the project (endocrine disruptors, AMINAL) and its aim to connect endocrine disruptor-related pathologies to environmental data in a joint database.

9.2.1 Information available at the RIZIV

Dr Mensaert: the RIZIV receives aggregated data on diagnostic tests and treatment procedures (medication, operations etc) but does not possess any information of individual patients.

9.2.2 The procedure to obtain data from the RIZIV

In principle, a scientist can get aggregated information on for example mammectomy or treatment with pure FSH for free from the RIZIV, after submitting a request which has to be approved by the responsible committee.

For medication, the committee for the evaluation of medication practice (comitee voor de evaluatie van geneesmiddelenpraktijk, CEG) should be contacted. Their information source is Farmanet. Farmanet contains information on all medications prescribed to non-hospitalized patients. Less information is available on medication prescribed to in-patients (hospitalized).

For all medical procedures other than medication, the Profile department (profielen dienst) of the RIZIV is to be contacted (contact persons: Antony Figys 'Director', Dr. Vereecken de Leidend Ambtenaar van de Dienst Geneeskundige Verzorging)

9.2.3 The source of information available at the RIZIV

The sources of information available at the RIZIV are the mutualities. The intermutuality agency (Intermutualistisch Agentschap, IMA), an agency which has the 7 medical mutualities as members (Sporwegen, Christelijke Landsbond, Verbond Socialistische Mutualiteiten, Onafhankelijke, Liberale, Neutrale, Hulpkas) and can bring together all data from the 7 mutualities.

According to Dr. Menseart all the details needed for this project will be available at IMA. IMA has recently published two reports on breast cancer using their database. He also added that the IMA database can be consulted for a fee.

Dr. Menseart added that the persons to contact are Dr. Raf Mertens (Christian mutuality) or Mr. Joeri Guillaume (socialist mutuality). Both together have access to about 75 % percent of the data. The other mutualities control the remaining 25 %.

9.3 *The federal knowledge center*

The federal knowledge center (het Federaal Kenniscentrum) is not a source of data but acts as a "knowledge advisor", added Dr Menseart.

9.4 *Visit to the Christian mutuality (as a representative of IMA, 11/10/04)*

Present: Nicolas Van Larebeke, Ahmed Mahmoud (University Ghent), Dr. Raf Mertens (Christian Mutuality)

The meeting started with an introduction from N. Van Larebeke, A. Mahmoud about the project

9.4.1 Information available from the mutualities

Information from the RIZIV for the period 1993-2002 indicates that more than 99% of the Belgian population is covered by medical insurance. Further information on this subject is

available at the website of the RIZIV (<http://inami.fgov.be>). Data are available from all 7 mutualities from 1996-present.

In addition, the christian mutuality has data available in its database starting from 1994 and data on the years 1989-1993 (on cassette) that can eventually be reloaded.

The data includes all procedures reimbursed by the mutualities (including diagnostic procedures, medication, and therapeutic procedures such as operations and radiotherapy), gender, birth year, the national institute of statistics code (NIS code) and some data on social status (e.g. on pension). Coding of patients using statistical sectors is technically possible, starting from the place of residence. The mutualities cooperate with the Flemish network for cancer registration (see strategy details below). Suspected cases of cancer are monitored by the advising doctor who requests information from the patient's physician and reports the case to the Flemish network for cancer registration.

9.4.2 The procedure to obtain data from IMA

At the moment, IMA operates on project basis (figure 2). A request is submitted to IMA. If approved, data are collected from the 7 mutualities and each patient is given a unique ID number via a process of coding called keying (versleuteling). This is different from coding using hashing. With hashing, a person cannot be identified with a certainty of 100%. The collected data is passed to an intermediate organization. This organization performs a second coding (versleuteling) and then a database is generated which is available for analysis. Backward decoding of the identity number is technically possible but not allowed as stated in the contract between IMA and the intermediate organization. IMA charges about 5000 Euro per approved request. It is expected that the fee may be less if the requested information can be used by more than one organization, as for example data on cancers.

9.4.3 Projects in development

9.4.3.1 IMA cancer cell database

IMA is currently discussing (negotiating) the establishment of a cancer database (IMA cancer cell database). This database will contain information on cancer from different sources including data available at the mutualities, multidisciplinary oncological consultations (multidisciplinair oncologisch consult, MOC), histopathology reports (antatomopathologisch discussie, APD) etc. If things go well, Dr. Mertens expects this database to be operational in 2005. In this database, the patient will be identified with his national registry number « rijksregister nummer ». For this purpose, a draft royal decree (koninklijk besluit, KB) is submitted to the privacy committee. IMA is in contact with the Flemish Administration (Chris Vander Auwera, Pieter van den Bulcke and Peter Hooft).

9.4.3.2 Carenet

At present, Carenet is an electronic registration of hospital administration and billing. It is planned to add data about approval of treatment by the advising physician (adviserende geneesheer), data on MOC & more. This will probably not be fully operational before a couple of years.

9.4.3.3 Permanent Belgian population sample (permanente steekproef)

A database containing a permanent Belgian population sample will “probably” be established with cooperation between IMA, RIZIV, the federal knowledge center (Federaal Kenniscentrum) & the scientific institute of public health (Wetenschappelijk Instituut Volksgezondheid). This database is expected to contain information on about 300.000 persons.

10 A suggested strategy for collecting clinical data using RIZIV numbers

Based on the information described above, a strategy is suggested for collecting clinical data indicative of pathologies possibly related to endocrine disruptors using RIZIV numbers. These pathologies (for example breast cancer) are to be linked to endocrine disruptors and to environmental information (such as dioxin levels in soil, water, air, and food). The framework of the suggested strategy is illustrated in figure 3.

For each pathology, a list of relevant medical procedures (prestaties) and medications reimbursed by the mutuality is generated whenever available, based on a review of the literature and discussion with medical experts (described under strategy details, not in figure).

1. This list has to be submitted to IMA. After approving the study protocol and receiving a fee (\pm 5000 Euro per request), IMA will extract data on these procedures from the seven mutualities (database X).
2. The data are then coded twice (by IMA then by the intermediate organization, IO) to conceal the identity of the patient and then passed to scientists authorized to handle the data. These medical data, coded by NIS code or, if possible, statistical sector will be included in database containing information on environmental levels of for example dioxin, also coded by NIS code or, if possible, statistical sector (database Y). This will allow the scientists to study possible relationships between, as in this example, breast cancer and dioxin level by NIS code or statistical sector.
3. If more information is needed on for example dietary habits for research purposes, or to invite a patient to actively participate in a study, it is technically possible (although legally not allowed according to the contract between IMA and the intermediate organization) to send a request to intermediate organization to decode the patient’s ID number.
4. After a second decoding, IMA can contact the patient via his/her treating doctor asking the patient to fill in a form concerning his/her dietary habits or to ask the participation of the patient in a scientific study. This step is technically possible but legally not allowed.
5. The obtained information can be passed to the scientists after being coded twice (by IMA then by the intermediate organization) to be included in database Y. This step is technically possible but legally not allowed.

11 Strategy details per pathology

One of the major problems in developing the present strategy was that in many cases there are no RIZIV numbers that are indicative of the relevant pathology (examples include cancers and endometriosis). Therefore, it is recommended that the RIZIV numbers should be evaluated and modified to make them a better source for medical information on among others, diseases with possible relationship to endocrine disruption.

11.1 Cancer pathologies

From our evaluations and contacts with different organizations involved in disease registration, the data on cancer pathologies are best retrieved from the Flemish cancer registration network coordinated by the Flemish League against cancer (Vlaamse Liga Tegen Kanker, VLK). The cancer registration occurs partially via electronic channels as shown in figure 4 (A. Remacle, Christian Mutuality, personal communication). VLK uses the International Classification of Diseases, tenth revision (ICD 10). The VLK database identifies patients by Postcode and NIS code. Recoding of patients addresses into statistical sectors will not be possible for all the data, since some data were collected manually from patients' medical files as is the case with some cancer registries (Liesbeth van Eycken, coordinator Vlaams Kankerregistratienetwerk, personal contact). The database is controlled for quality both automatically and manually, making the chance of double registration almost negligible according to the commission for the protection of personal privacy (commissie voor de bescherming van de persoonlijke levenssfeer, verslag over de werkzaamheden, 1997).

At the present time, data from minimal clinical findings (Minimale klinische gegevens, MKG) suffer from the problem of double registration due to the lack of a standardized method for the coding of patient identification number (see page 75). MKG uses ICD 9 (clinically modified, year 2002) for the classification of diseases. The MKG database identifies patients by Postcode and NIS code. According to MKG (office of Mrs. Ingrid Mertens, MKG FOD volksgezondheid), the data are of good quality from June 1997. We compared the data available for female breast, prostate and testicular cancer in both MKG and the Flemish cancer registry included in the database of the steunpunt milieu en gezondheid (see page 75). It has to be noted that the MKG dataset delivered to steunpunt milieu en gezondheid and now included in the database (milieupath, <http://www.milieupath.be/>) does not contain the patient identification number because of privacy issues. Repeated registration is removed by MKG (FOD volksgezondheid) and milieupath as far as the patient identification system allows (Greet Van Kersschaever, personal communication).

11.1.1 Breast cancer (female)

- MKG: ICD 9-CM 2002:
174 Malignant neoplasm of female breast
- VLK: ICD 10: C50 Breast cancer (female)

11.1.2 Prostate cancer

- MKG: ICD 9-CM 2002:
185 Malignant neoplasm of prostate
- VLK: ICD 10: C61 Prostate cancer
- The European randomized screening for prostate cancer (ERSPC)

This database contains information over 10000 men randomized into two groups with about 5000 men in each group, a group screened for prostate cancer and a second group that is not screened. The addresses of the patient are available and can be converted to statistical sector code provided that the relevant commissions agree (Vera Nelen, personal communications).

11.1.3 Thyroid cancer

- MKG: ICD 9-CM 2002:
193 Malignant neoplasm of thyroid gland
- VLK: ICD 10: C73 Thyroid cancer

11.1.4 Non-Hodgkin lymphomas

- MKG: ICD 9-CM 2002:
200 (subcategories .0,.1,.2,.8) Lymphosarcoma and reticulosarcoma
202 (subcategories .0, .1, .2,.8) Other malignant neoplasms of lymphoid and histiocytic tissue
- VLK: : ICD 10: C82-85 Non-Hodgkin lymphomas

11.1.5 Testicular cancer

- MKG: ICD 9-CM 2002:
186 Malignant neoplasm of testis
- VLK: ICD 10: C62 Testicular cancer

11.1.6 Conclusions regarding cancer pathologies

The most reliable source of information on cancer at the present time is the Flemish cancer register. Additional data on prostate cancer are available from the ongoing European randomized screening for prostate cancer (ERSPC).

11.2 Non-cancer pathologies

into statistical sector code provided that the privacy commission agrees. It is not planned for the data from EUROCAT to be included in the database of steunpunt milieu en gezondheid.

EUROCAT and SPE are comparing their datasets for the province of Antwerp at present. Vera Nelen will inform this consortium on the results of the comparative study when they becomes available (Vera Nelen, personal communication).

- CLB (NICO)

Contacts with CLB indicated that the NICO project is still in "full" development and that its electronic module, called datawarehousing, is still to be developed and not expected to be operational this school year (2004-2005). This experimental phase of development does not allow for systematic registration of health data (Mrs. Yolande Schulpen and Dr. B. Aggoune, CLB and NICO, personal communication).

- Conclusion

The SPE and EUROCAT databases are the most complete source of information on congenital anomalies for respectively Flanders and Antwerp. A comparison of these two sources is underway. Validation of data quality and the adoption of one classification by all organizations reporting congenital anomalies are needed.

11.2.2 Cryptorchidism

- RIZIV Nomenclature

A nomenclature exists for the surgical and medical treatment of cryptorchidism. These are unilateral and bilateral orchidopexy.

260890	260901	Enkelv
260912	260923	Dubbe

- RIZIV medication number

Medical treatment of cryptorchidism

Human chorionic gonadotrophin (hCG) treatment in a male less than 10 years of age.

00147823	1500 IU/ml Choriongonadotropine	(Pregnyl, Organon Belgium / Organon Europe)
00147924	5000 IU/ml Choriongonadotropine	(Pregnyl, Organon Belgium / Organon Europe)
00190966	5000 IU/ml Humaan choriongonadotropine (HCG)	(Profasi 5000, Serono Benelux)

- MKG: ICD 9-CM 2002: 752.51 Undescended testis: this includes Cryptorchism and Ectopic testis

This source of information reports on patients that have been hospitalized only.

- SPE

The first (almost complete) registration of 1991 reports on 95,5 % of hospital deliveries in Flanders and since 1996 the reporting of hospital deliveries is complete (100%). The SPE reporting form gathers information on urogenital anomalies in general but not specifically for cryptorchidism, with a place for reporting the end clinical diagnosis. Follow-up of these infants for possible spontaneous testicular descent is not possible.

- EUROCAT

Because cryptorchidism is considered as a minor anomaly and is difficult to diagnose and classify correctly, it is not reported by EUROCAT (Helen Dolk, personal communication). Vera Nelen (EUROCAT Antwerp) is willing to arrange for the registration of cryptorchidism at birth and follow-up newborns with cryptorchidism up to the age of one year in the next surveys of EUROCAT in Antwerp if financial support is provided (Vera Nelen, personal communication).

- Conclusion

RIZIV nomenclature and medication numbers are expected to generate reliable data on cryptorchidism.

11.2.3 Hypospadias

- RIZIV Nomenclature:

A nomenclature exists for the surgical treatment of hypospadias in one session (3084) or in 2 sessions, a main session (3165) and a complementary session. Personal communications with urologists in Belgium indicate that most cases of hypospadias are surgically treated including mild varieties upon request of the parents. Therefore, only a minority of cases with very mild hypospadias will not be detected using this parameter.

261310	261321	Radicale volledige behandeling van hypospadias
261332	261343	Heelkundige bewerking wegens hypospadias, in verscheidene bewerkingen: hoofdbewerking
261354	261365	Heelkundige bewerking wegens hypospadias, in verscheidene bewerkingen: voorbereidende en aanvullende bewerkingen.

- MKG: ICD 9-CM 2002: 752.61 Hypospadias
- SPE

The first (almost complete) registration of 1991 reports on 95,5 % of hospital deliveries in Flanders and since 1996 the reporting of hospital deliveries is complete (100%). The SPE reporting form gathers information on urogenital anomalies in general but not specifically for hypospadias, with a place for reporting the end clinical diagnosis.

- EUROCAT

Data on hypospadias are available for the province of Antwerp starting from the year 1991. Only postcode is recorded. Retrospectively, the addresses are not available in any form but the names, birth dates and birth date of the mother is available. Eventually, these could be recovered from the "rijksregister" if ethically and legally allowed. Prospectively, the address can be translated in statistical sector provided that the privacy commission agrees (Vera Nelen, personal communication).

- Conclusion

RIZIV nomenclature is expected to generate reliable data on hypospadias. Data on hypospadias are available for the province of Antwerp starting from the year 1991 from EUROCAT

11.2.4 Prematurity

- SPE

The first (almost complete) registration of 1991 reports on 95,5 % of hospital deliveries in Flanders and since 1996 the reporting of hospital deliveries is complete (100%). Only postcode is recorded.

- MKG: ICD 9-CM 2002:

644.2[0-1] Early onset of delivery:

Onset (spontaneous) of delivery before 37 completed weeks of gestation

Premature labor with onset of delivery before 37 completed weeks of gestation

765 Disorders relating to short gestation and low birth weight

Postcode and NIS code are both recorded.

- CLB (NICO)

The project is still in an experimental phase

- Conclusion

SPE is the only reliable source of information on prematurity that could be identified

11.2.5 Intrauterine growth retardation

- RIZIV nomenclature

No RIZIV nomenclature exists for intrauterine growth retardation. The following RIZIV numbers may give an indication on the possibility of high-risk pregnancy, but many false positives will be included, i.e. those with proven high-risk pregnancy but no actual intrauterine growth retardation.

460530 460541 Functioneel echografisch onderzoek dat een biometrie en een biofysisch profiel van de foetus omvat, met of zonder het meten van de ombilicale bloedstroom in geval van gedocumenteerd hoog obstetrisch of foetaal risico

469910 469921 Functioneel echografisch onderzoek dat een biometrie en een biofysisch profiel van de foetus omvat, met of zonder het meten van de ombilicale bloedstroom in geval van gedocumenteerd hoog obstetrisch of foetaal risico

- MKG: ICD 9-CM 2002:

764 Slow fetal growth and fetal malnutrition

It is expected that MKG data will suffer from serious under-reporting due to the fact that most mothers of the cases of slow fetal growth and fetal malnutrition are treated on an out patient basis and are not hospitalized.

- SPE

Data are not directly available but can be calculated from birth weight and duration of gestation at delivery.

- Conclusion

SPE is the only reliable source of information on intrauterine growth retardation that could be identified

11.2.6 Mental and Psychomotor development

- RIZIV nomenclature

No RIZIV Codes are available for detecting this parameter.

- MKG: ICD 9-CM 2002:

783.40 Lack of normal physiological development, unspecified
 Inadequate development
 Lack of development

783.41 Failure to thrive
 Failure to gain weight

783.42 Delayed milestones
 Late talker
 Late walker

783.43 Short stature
 Growth failure
 Growth retardation
 Lack of growth
 Physical retardation

315 Specific delays in development

317-319 Mental retardation

It is expected that MKG data will suffer from serious under-reporting due to the fact that most of the patients with delayed psychomotor development are treated on an out patient basis and are not hospitalized.

- CLB (NICO)

The project is still in experimental phase

- Conclusion

No reliable source of data on psychomotor development is available at present.

11.2.7 Precocious puberty

- RIZIV nomenclature

455033 **455044** Radiografie van de middelhand met visualisatie van metacarpalen en handwortelbeenderen, minimum twee clichés

This RIZIV number is used for radiography of the hand to determine bone age, which is a standard diagnostic test in the evaluation of pubertal and stature disturbances. The same number is also used to report x-ray films of the hand for other purposes including for example fractures and rheumatic diseases (Radiology department, University Hospital Ghent, personal communication). To exclude these pathologies, an age limit of 16 years and this parameter has to be coupled to one of the treatments mentioned below.

- RIZIV medication number

Medication for precocious puberty

00206225: 7.5 mg/ml (Triptoreline Decapeptyl sustained release 11,25 mg, Ipsen)
00206326: 1.875 mg/ml (Triptoreline Decapeptyl sustained release 3,75 mg, Ipsen)
00261391: H.R.F. 0,5 (0.1 mg/ml Gonadoreline,-hydrochloride, Tramedico)
00263112: 1.875 mg/ml Leuproreline, -acetaat (Gyno-lucrin depot, Abbott)
00263617: 1.875 mg/ml Leuproreline, -acetaat (Lucrin depot, Abbott)
00251287: 5.625 mg/ml Leuproreline, -acetaat (Lucrin tri-depot 11,25 mg, Abbott)
00366778: 9.9 mg Busereline, -acetaat (Suprefact depot 3 mois-implant, Aventis Pharma)
De specialiteit is niet meer vergoedbaar sinds 01-11-2003
00291000: 0.105 mg/dosis Busereline, -acetaat 100 doses neusspray (Suprefact nasal, Aventis Pharma)
00291101: 0.105 mg/dosis Busereline, -acetaat 400 doses neusspray (Suprefact nasal, Aventis Pharma)
00298171: 3.6 mg Gosereline, -acetaat (Zoladex Astrazeneca)
00481663: 3.6 mg Gosereline, -acetaat (Zoladex (Aktuapharma), Aktuapharma)
00249065: 10.8 mg Gosereline, -acetaat (Zoladex Long Acting Astrazeneca)
00216228: 200 mg Danazol (Danatrol, Sanofi-Synthelabo)
00254119: 50 mg Cyproteron, -acetaat (Androcur, Schering)
00296959: 50 mg Cyproteron, -acetaat (Cyproplex 50 Mg, Teva Pharma Belgium)

- MKG: ICD 9-CM 2002:

259.1 Precocious sexual development and puberty, not elsewhere classified

Sexual precocity:
NOS (not otherwise specified)
constitutional
cryptogenic
idiopathic

It is expected that MKG data will suffer from serious under-reporting due to the fact that most of the patients with precocious puberty are treated on an out patient basis and are not hospitalized.

- Flemish Growth Curves

This project is a study of the growth and development of Flemish children (both males and females). It aims at the development of new growth charts for height, weight, Body Mass Index and head, upper arm and waist circumference from birth to 19 years of age; and standards for pubertal development from 8 to 18 years of age. Secondary targets are the description of growth and development in terms of health parameters, and the socio-economic, demographic and geographic background. The normal growth curves for Flemish children have been recently published and data are reported per NIS code (Professor R. Hauspie, Department of Anthropogenetics, VUB, personal communication). The curves are available on the web (<http://www.vub.ac.be/groeicurven/groeicurven.html>).

- Determinants of onset of puberty study

Data on the determinants of onset of puberty in a cohort of 1100 Belgian girls is available per NIS code only and it is not possible to retrieve the addresses or statistical codes of the participants (Dr. JPh Janssens, personal communication, European Cancer Prevention Organization, Hasselt).

- Conclusions

The use of RIZIV nomenclature and medication numbers is expected to generate reliable data on precocious puberty. Data on normal growth and puberty is available from Department of Anthropogenetics, VUB and the European Cancer Prevention Organization, Hasselt.

11.2.8 Delayed puberty

- RIZIV nomenclature

455033 455044 Radiografie van de middelhand met visualisatie van metacarpalen en handwortelbeenderen,
minimum twee clichés

In combination with medical treatment for delayed puberty

- RIZIV medication number

Medical treatment for delayed puberty

- Male patient

Human chorionic gonadotrophin (hCG) treatment in a male older than 16 years of age and younger than 21 years of age

00147823: 1500 IU/ml Choriongonadotropine (Pregnyl, Organon Belgium / Organon Europe)

00147924: 5000 IU/ml Choriongonadotropine (Pregnyl, Organon Belgium / Organon Europe)
00190966: 5000 IU/ml Humaan choriongonadotropine (HCG) (Profasi 5000, Serono Benelux)

Testosterone treatment: If testosterone is used to search for male patients with delayed puberty, it may lead to a serious underestimation of the incidence in some years. The cause of the problem is that the reimbursement was stopped for many preparations due financial disagreements between the RIZIV and the pharmaceutical companies producing testosterone preparations.

00209659: 100 mg/ml Testosteron, -decanoaat, 60 mg/ml Testosteron, -fenylpropionaat, 60 mg/ml Testosteron, -isocaproaat, 30 mg/ml Testosteron, -propionaat (Sustanon 250, Organon Belgie / Organon Europe) De specialiteit is niet meer vergoedbaar sinds 01-05-2002

00469438: 100 mg/ml Testosteron, -decanoaat, 60 mg/ml Testosteron, -fenylpropionaat, 60 mg/ml Testosteron, -isocaproaat, 30 mg/ml Testosteron, -propionaat (Sustanon 250, Organon Belgie / Organon Europe) 6 ampul

00209760: 40 mg Testosteron, -undecanoaat (Undestor Organon Belgie / Organon Europe). De specialiteit is niet meer vergoedbaar sinds 01-05-2002

- Female patient

The use of RIZIV medication numbers for the treatment of female delayed puberty is complicated by the fact that the treatment with estrogens is used for many other indications including for example female contraception.

- MKG: ICD 9-CM 2002:

259.0 Delay in sexual development and puberty, not elsewhere classified
Delayed puberty

256.39 Other ovarian failure
Delayed menarche
Ovarian hypofunction
Primary ovarian failure NOS

It is expected that MKG data will suffer from serious under-reporting due to the fact that most of the patients with delayed puberty are treated on an out patient basis and are not hospitalized.

- Flemish Growth Curves & determinants of onset of puberty: see precocious puberty
- Conclusion

No reliable source of data on delayed puberty is available at present.

11.2.9 Sex ratio (male to female ratio at birth)

- SPE

Data is on the gender of the newborns delivered at a hospital in Flanders. The first (almost complete) registration of 1991 reports on 95,5 % of hospital deliveries in Flanders and since 1996 the reporting of hospital deliveries is complete (100%).

- FOD Mineco

Data on births by gender is also available from FOD Mineco (economie, KMO, middenstand en energie).

Data from both sources show no consistent trends in sex ratio (see table 17). Data on sex ratio per municipality (gemeente) is available FOD Mineco. A detailed follow up of the sex ratio per municipality or preferably per statistical sector code may be useful. A local change in sex ratio may indicate environmental problems.

- Conclusion

Sufficient data are available on male to female (sex) ratio at birth both for infants delivered at a hospital (SPE) as well as for the whole Flemish population (Mineco).

11.2.10 Female infertility

- RIZIV nomenclature

Although many investigations and therapeutic procedures used to treat female infertility, it is difficult to recover all cases with female infertility without including too many false positive cases. The following RIZIV numbers would indicate hormonal induction of ovulation and treatment with *in vitro* fertilization.

203416	203420	Paracervicale anesthesie tijdens een follikelaspiratie met het oog op een in-vitrofertilisatie
432714	432725	Plaatsen van een embryo na in vitro fertilisatie
432434	432445	Follikelaspiratie door punctie onder echografische controle of door laparoscopie

- RIZIV medication number (ovulation induction)

- Follicle stimulating hormone (and combinations)

00428618: 600 IU/ml Follitropine-alfa (biosynthetisch follikelstimulerend hormoon) IU/1,75 ml (GONAL-F 1050 IUM 75 ml, Serono Benelux / Serono Europe Limited)

00220773: 75 IU/ml Follitropine-alfa (biosynthetisch follikelstimulerend hormoon) (Gonal-F 75 IU Serono Benelux / Ares Serono) 1 ampul

00220874: 75 IU/ml Follitropine-alfa (biosynthetisch follikelstimulerend hormoon) (Gonal-F 75 IU Serono Benelux / Ares Serono) 3 ampul

00265738: 400 IU/ml Follitropine-alfa (biosynthetisch follikelstimulerend hormoon) (Puregon 200 I.U., Organon Belgie / Organon) De specialiteit is niet meer vergoedbaar sinds 01-11-2003

00377084: 75 IU/ml menotrophin (hMG) equiv met FSH activiteit, 75 IU/ml menotrophin (hMG) equiv met LH activiteit (Menopur, Ferring)

- Clomifene citrate

00016164: 50 mg Clomifeen, -citraat (Clomid, Aventis Pharma)

00190865: 50 mg Clomifteen, -citraat (Pergotime, Serono Benelux)

- Human chorionic gonadotrophin (hCG)

00147823: 1500 IU/ml Choriongonadotropine (Pregnyl, Organon Belgium / Organon Europe)

00147924: 5000 IU/ml Choriongonadotropine (Pregnyl, Organon Belgium / Organon Europe)

00190966: 5000 IU/ml Humaan choriongonadotropine (HCG) (Profasi 5000, Serono Benelux)

- SPE

Data on the use of hormonal stimulation and *in vitro* fertilization is available from SPE for all hospital deliveries in Flanders.

- MKG: ICD 9-CM 2002:

628 Infertility, female

V23.0 Pregnancy with history of infertility

V26.1 Artificial insemination

It is expected that MKG data will suffer from serious under-reporting due to the fact that many patients with female infertility are treated on an out patient basis and are not hospitalized.

- Conclusion

Only data on hormonal induction of ovulation and treatment with *in vitro* fertilization is available (SPE) or can be extracted (RIZIV). Therefore, studies in the field of female in(fertility) are much needed. See also time to pregnancy and endometriosis

11.2.11 Male infertility and sperm quality

RIZIV Nomenclature

The number of semen analyses performed per year may be indicative of the incidence of male infertility of the population. Semen analysis for other indications such as prostatitis, fertility check-up and control for male contraception are also included (false positives).

Age: > 18 years this will exclude some semen analyses performed with sperm freezing for malignancies in young adults.

545016	545020	Doseren van fructose (sperma)
545031	545042	Doseren van zure fosfatasen (sperma)
550012	550023	Tellen en mobiliteit van spermatozoiden in sperma
550034	550045	Morfologisch onderzoek van sperma na kleuring

Exclude vasectomy

260794	260805	Onderbinden van een ductus deferens
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- Sperm quality

Data on sperm quality of candidate donors are available on candidate donors from 1977 till present (Professor F. Comhaire, Andrology Laboratory, University Hospital Ghent). Other centers are being contacted. Comparison of sperm parameters between different centers is expected to be difficult due to the large variations found between laboratories in quality control studies (Dr. JC Libeer, Wetenschappelijk instituut volksgezondheid, personal communication). For further details see page 75.

- MKG: ICD 9-CM 2002: 606 Infertility, male

It is expected that MKG data will suffer from serious under-reporting due to the fact that most patients with male infertility are treated on an out patient basis and are not hospitalized.

- Conclusion

Apart from a long-term follow-up of Flemish candidate sperm donors (University hospital Ghent), large studies on sperm quality in Flanders are lacking. The number of semen analyses performed in Flanders per year can be calculated from RIZIV data. This may give a rough estimation on the magnitude of infertility in the Flemish population, although semen analysis is performed for indications other than fertility evaluation. Therefore, studies in the field of male in(fertility) are much needed. See also time to pregnancy below.

11.2.12 Time to pregnancy

Although time to pregnancy is a reliable parameter used internationally for evaluation of fertility, data on this parameter in Flanders is largely lacking.

11.2.13 Endometriosis

- RIZIV nomenclature

431211 431222 Radicale kuur wegens pelvische endometriose

Only a small portion of severe cases of endometriosis requiring surgery can be detected using this parameter.

- MKG: ICD 9-CM 2002: 617 Endometriosis

Serious under-reporting is expected since the majority of cases with endometriosis are treated at the outpatient clinics.

- Conclusion

Only the most severe forms of endometriosis can be detected using RIZIV data

11.2.14 Thyroid diseases

- RIZIV nomenclature:

The following RIZIV nomenclature will recover data on patients with thyroid dysfunction or disease. Patients with thyroid disease can then be subdivided into non-cancer cases and thyroid cancer using data on thyroid cancer from the mutualities. Thyroid cancer is registered for VLK (VLK: ICD 10: C73 Thyroid cancer) by the advising physicians of the mutualities (adviserende geneesheren).

257596	257600	Biopsie van de schildklier (exclusief transcutane punctie)
355596	355600	Schildklierpunctie voor cytologisch onderzoek
355611	355622	Schildklierpunctiebiopsie met het oog op een pathologisch - anatomisch onderzoek
433171	433182	Doseren van schildklier-stimulerend immuunglobuline (TSI) in de evolutie van een medicamenteuze behandeling (Maximum 1) (Cumulregel 80) Klasse 22
257014	257025	Eenvoudige totale thyreoïdectomie of gedeeltelijke thyreoïdectomie
257036	257040	Totale of subtotale tweezijdige thyreoïdectomie met dissectie van de nervi laryngei recurrentes en de bijschildklieren

- RIZIV medication number

- Thyroid hormone: Levothyroxine and combination preparations.

00303427: 50 µg Levothyroxine, natrium (Elthyron, Abbot)
00303528: 25 µg Levothyroxine, natrium (Elthyron, Abbot)
00303629: 100 µg Levothyroxine, natrium (Elthyron, Abbot)
00303730: 150 µg Levothyroxine, natrium (Elthyron, Abbot)
00303831: 200 µg Levothyroxine, natrium (Elthyron, Abbot)
00117309: 150 µg Levothyroxine, natrium (Euthyrox, Merck)
00117410: 25 µg Levothyroxine, natrium (Euthyrox, Merck)
00117511: 50 µg Levothyroxine, natrium (Euthyrox, Merck)
00117612: 200 µg Levothyroxine, natrium (Euthyrox, Merck)
00117713: 100 µg Levothyroxine, natrium (Euthyrox, Merck)
00117814: 125 µg Levothyroxine, natrium (Euthyrox, Merck)
00060018: 100 µg Levothyroxine, natrium (L-Thyroxine Christiaens 100 µG, Nycomed Belgium) De specialiteit is niet meer vergoedbaar sinds 01-07-2003 (100 tablet)
00098212: 100 µg Levothyroxine, natrium (L-Thyroxine Christiaens 100 µG, Nycomed Belgium) (112 tablet)
00059715: 125 µg Levothyroxine, natrium (L-Thyroxine Christiaens 125 µG Nycomed Belgium) De specialiteit is niet meer vergoedbaar sinds 01-07-2003 (100 tablet)
00098313: 125 µg Levothyroxine, natrium (L-Thyroxine Christiaens 125 µG, Nycomed Belgium) (112 tablet)
00060321: 150 µg Levothyroxine, natrium (L-Thyroxine Christiaens 150 µG, Nycomed Belgium) De specialiteit is niet meer vergoedbaar sinds 01-07-2003 (100 tablet)
00098515: 150 µg Levothyroxine, natrium (L-Thyroxine Christiaens 150 µG, Nycomed Belgium) (112 tablet)
00476512: 175 µg Levothyroxine, natrium (L-Thyroxine Christiaens 175 µG, Nycomed Belgium)

00059614: 200 µg Levothyroxine, natrium (L-Thyroxine Christiaens 175 µG, Nycomed Belgium)

De specialiteit is niet meer vergoedbaar sinds 01-07-2003 (100 tablet)

00098616: 200 µg Levothyroxine, natrium (L-Thyroxine Christiaens 175 µG, Nycomed Belgium) (112 tablet)

00059816: 25 µg Levothyroxine, natrium (L-Thyroxine Christiaens 25 µG, Nycomed Belgium)

De specialiteit is niet meer vergoedbaar sinds 01-07-2003 (100 tablet)

00098414: 25 µg Levothyroxine, natrium (L-Thyroxine Christiaens 25 µG, Nycomed Belgium)

(112 tablet)

00060422: 50 µg Levothyroxine, natrium (L-Thyroxine Christiaens 50 µG, Nycomed Belgium)

De specialiteit is niet meer vergoedbaar sinds 01-07-2003 (100 tablet)

00098111: 50 µg Levothyroxine, natrium (L-Thyroxine Christiaens 50 µG, Nycomed Belgium)

(112 tablet)

00476613: 75 µg Levothyroxine, natrium (L-Thyroxine Christiaens 75 µG, Nycomed Belgium)

00118117: 100 µg Levothyroxine, natrium, 20 µg Liothyronine, -natrium (Novothyral, Merck)

00118218: 100 µg Levothyroxine, natrium, 20 µg Liothyronine, -natrium (Novothyral, Merck)

00148025: 0.1 mg Levothyroxine, natrium (Thyrax Duotab, Organon Belgie / Organon Europe)

- Anti-thyroid drugs

Thioamides: Strumazol and Propylthiouracile,

00062038: 10 mg Thiamazol (Strumazol 10 Mg Nycomed Belgium)

Propylthiouracile: Not reimbursed by the mutuality since 1992 (R. Sion, Nycomed Christiaens, personal communication). This medication is not used as a first line drug. Only when problems such as leucopenia or idiosyncrasy arise under treatment with strumazol, Propylthiouracile is used. Therefore, the lack of a RIZIV number for this medication may result in a small and probably non-significant underestimation of thyroid diseases.

- Radioactive iodine

698176 698180 Radioactive iodine in therapeutic doses (in millicurie, medication).

- **MKG: ICD 9-CM 2002:**

226 Benign neoplasm of thyroid glands

240 Simple and unspecified goiter

242 Thyrotoxicosis with or without goiter

243 Congenital hypothyroidism

244 Acquired hypothyroidism

794.5 Thyroid: Abnormal thyroid (Nonspecific abnormal results of function studies): scan

uptake

Drugs, medicinal and biological substances causing adverse effects in therapeutic use:

E932.7 Thyroid and thyroid derivatives

E932.8 Antithyroid agents

- Conclusion

RIZIV nomenclature and medication numbers will allow the retrieval of most cases with thyroid problems. Data on thyroid cancer from the advising physicians (adviserende geneesheren) of IMA can then be used to separate cancer from non-cancer thyroid problems. Further detailed classification of thyroid disorders using available data is not possible mainly because one single treatment modality is used for different pathological conditions.

11.2.15 Immune system diseases (immunosuppression)

The strategy for Non-Hodgkin's lymphomas is discussed under cancer pathologies. No reliable source of information is available on immune system diseases in children.

11.2.16 Use of laboratory test results for biomonitoring

It is difficult to use laboratory results from persons with unknown clinical status for biomonitoring. This is because the indication for testing is unknown (screening, diagnosis or follow-up).

To minimize the chance that a person under treatment with for example thyroid hormone substitution is included, one should only use results from the first time the patient was tested. Also, abnormally low or high values of the evaluated parameter should not be included for biomonitoring. At the other hand, the proportion of abnormally low or high values of the evaluated parameter may give an indication about the prevalence of disease.

Another problem is that the methodology used changes. One example is the measurement of testosterone. Recently developed kits for testosterone measurement are more specific and less cross-reactive with dihydrotestosterone, resulting in measured testosterone levels that are about 14 % lower than as measured by older methods. Therefore, the results should always be expressed in relation to the normal range of the testing method used (Professor F. Comhaire, Department of Endocrinology, University of Gent, personal communication).

For semen analysis, quality control data from the Belgian scientific institute of public health (table 18) indicate that the results of semen analysis may vary widely between laboratories (WIV, 2004). This makes combining data on semen quality from different laboratories scientifically unacceptable. Therefore, when planning studies on semen quality, semen analysis should preferably be performed by a single laboratory. If the participation of multiple laboratories is unavoidable in semen quality studies, a special training program has to be organized for the technicians involved.

11.2.17 Database steunpunt milieu en gezondheid (milieupath)

At present, the milieupath database contains data from MKG (1997-1998), SPE (1996-2003), VLK (1997-1999), cause of death (1996-2003) and some environmental data (1997-2003). The database is still in the testing phase and access to the data is limited to the Flemish administration and the participants in steunpunt milieu en gezondheid. See addendum 2 (in dutch) for details. It is remarkable that environmental data are recorded in NIS code and not in statistical code, although in contrast to personal data, there are no problems of privacy. Therefore, it is recommended that environmental data are reported in statistical sector codes.

11.2.18 Comparison of data available from different sources

We compared the data integrated already in the milieupath database on testis, female breast and prostate cancers for the year 1998 originating from VLK and MKG (table 19). The table shows that the number of patients with testis, female breast and prostate cancers are seriously overestimated in the MKG data relative to data originating from VLK as was expected. This was true for testis, female breast as well as prostate cancers for whole Flanders and was not related to residence of the patient. We attempted to eliminate double registration in the MKG data by removing cases that were rehospitalized in the same year (1998) but for more than one third of the patients the rehospitalization status was unknown (table 20).

We also compared the number of cases of cryptorchidism in the datasets of MKG and SPE for the year 1998 which are integrated in the Milieupath database (table 21). The table shows that SPE data contains very few cases of cryptorchidism, which is due to the fact that cryptorchidism is not reported as a separate entity. Also, reporting cryptorchidism at birth only is not useful since about 80 % of the undescended testis descend to a normal scrotal position by the age of one year. It seems that SPE data underestimate the number of cases with cryptorchidism while MKG data are expected to overestimate the number of cases with cryptorchidism.

12 Ethical aspects of the suggested strategy

None of the persons or organizations contacted was opposed to the use of statistical sector codes for patient identification on ethical grounds. Cases with a rare pathology are one notable exception because the identification of a certain individual is possible due to the rarity of his (her) disease. Examples from our list of relevant pathologies include testicular cancer and some congenital anomalies with a small absolute number of cases per year. A possible solution to this problem is to group the patients into age groups instead of year of birth, combine a similar group of diseases together (e.g. cardiac congenital anomalies) or combine the statistics of several years on an uncommon disease together (Prof. B Rubins head of the ethical committee, Faculty of medicine, Ghent and Dr. R. Mertens, Christian mutuality; personal communications).

13 Ranking of relevant pathologies and the motivation behind the ranking

13.1 Criteria used to establish the priority for monitoring

Based on the information available on the pathologies concerned and our expertise, the descending order of priority of the relevant pathologies and the motivation behind the ranking are summarized in table 22.

The criteria used to establish the priority for monitoring a pathology were as follows:

1. Relevance to the Flemish/Belgian environment

The relevance to the Flemish/Belgian environment was evaluated as high when one of the following conditions were met:

a. A Flemish/Belgian study indicating a positive relationship between the pathology and the environmental agent.

b. High levels of the relevant pollutant in the Flemish environment, high or increasing prevalence of the pathology in Flanders and studies indicating a high risk (high odds ratios) associated with the exposure.

When no Belgian studies were available, preference has been given to European studies showing high risk especially studies from near-by countries including the Netherlands, Germany and France (geographic and population factors). Priority is given to an increased risk to the whole Belgian population over risk to a limited population (for example occupational exposure and people living around hazardous-waste landfill sites).

2. Availability of data and follow-up:

Pathologies where the data are available and the follow-up is relatively easy making use of the present infrastructure (databases etc) were given a higher priority.

3. Diagnostic accuracy:

Pathologies where the diagnosis can be established with high accuracy and the least possible confounding were given a higher priority.

4. Public concern

Public surveys in Flanders indicate that environmental pollution is persistently one of the five most important concerns of the Flemish population and is gaining increased priority moving from the third place in 1996 to second place in 2000 (APS, 2002). The Flemish population regards environment as the second most important factor affecting their health (after lifestyle factors). About 80 % of the population is convinced that the environment in Flanders is very polluted. Ninety six percent of the Flemish population regards university institutions as a trustworthy source of information on the environment. The Flemish people rank the spread of dangerous substances in their environment as the most threatening environmental issue (APS, 2002).

5. Scientific interest:

It is evident that all the relevant pathologies are of scientific interest. Exceptional points of scientific interest are discussed for two pathologies only, namely non-Hodgkin lymphomas and testicular cancer.

13.2 Ranking

Based on the criteria described above the pathologies are ranked in decreasing order of priority as follows:

1. breast cancer,
2. female infertility,
3. male infertility and sperm quality,
4. non-Hodgkin lymphomas,
5. prostate cancer,
6. delayed puberty,
7. male to female (sex) ratio at birth,
8. congenital anomalies,
9. intrauterine growth retardation,
10. prematurity,
11. testicular cancer,
12. mental and psychomotor development,
13. cryptorchidism,
14. hypospadias,
15. precocious puberty,
16. thyroid diseases,
17. immune system diseases (immunosuppression),
18. endometriosis and
19. time to pregnancy.

13.3 Motivation behind ranking detailed per pathology

13.3.1 Breast cancer (female)

1. Relevance to the Flemish/Belgian environment

Several studies indicate that environmental and occupational exposures to endocrine disruptors are associated with a significantly increased risk of breast cancer (see literature review). For example, a study from **Wallony** indicated **high odds ratios** of 4.99 and 2.2 respectively for HCB and p,p' DDE (Charlier et al., 2004). A Danish study indicated that high levels of PCBs were associated with increased breast cancer mortality in patients with estrogen receptor positive breast cancer (Hoyer et al., 2001). The above-mentioned chemicals are widely present in the Flemish environment. Also, the number of cases of breast cancer in Flanders is increasing over the years (although this may be partially attributable to better registration).

2. Availability of data and ease of follow-up

Data on breast cancer are easily available from VLK.

3. Diagnostic accuracy

The accuracy of the diagnosis of breast cancer is high.

4. Public concern

The high participation rates of Flemish women in breast cancer screening programs indicate that the public concern for breast cancer is high (Van Hal et al., 2000).

13.3.2 Female infertility

1. Relevance to the Flemish/Belgian environment

The statistics from NIS and SPE indicate a **decrease in** the number of children born recently in **Flanders** compared to 10-15 years ago. This is accompanied by an increase in the use of infertility treatment and *in vitro* fertilization (SPE, 2004). The literature review suggests female infertility to be associated with endocrine disruptors. See also male infertility and sperm quality.

2. Availability of data and ease of follow-up

Few data are available on fertility of Flemish women.

3. Diagnostic accuracy

The diagnosis of female infertility is difficult since male factor infertility has to be excluded. If both partners are investigated, the diagnostic accuracy is high.

4. Public concern

The public concern for female infertility is high (expert judgment).

13.3.3 Male fertility and sperm quality

1. Relevance to the Flemish/Belgian environment

A **decline in sperm quality**, more specifically sperm morphology has been demonstrated in sperm candidate donors in Flanders. In addition, a pilot study **in Flanders** has shown a possible **link between exposure at environmental levels and sperm quality** (Onderzoek Milieu en Gezondheid) (Vlietinck et al., 2000). Lower sperm quality and serum testosterone have been reported in the agricultural area of Peer compared to Antwerp (Hoboken and Wilrijk). Recent studies indicate a negative effect of exposure to PCBs and pesticides, which are widely spread in the Flemish environment on sperm quality. Recent studies also show that damage to sperm genetic material (DNA) may be related to environmental exposures (Duty et al., 2003b). This may carry the risk of transmission of mutations to the offspring. Data from the Netherlands indicates paternal exposure to pesticides is associated with decreased fertilization and implantation rates during infertility treatment by *in vitro* fertilization (Tielemans et al., 1999; 2000).

2. Availability of data and ease of follow-up

Data are available on sperm quality of Flemish candidate sperm donors (Prof. F. Comhaire, University Hospital Ghent) but no information on residence is available because sperm donors are anonymous. The results of a small pilot study on sperm quality in Flanders are also available (Onderzoek Milieu en Gezondheid) (Vlietinck et al., 2000). Otherwise very few data on male infertility are available.

3. Diagnostic accuracy

The high variations in the results of semen analysis between different laboratories prevents combining data from different sources. If both partners are investigated, the diagnostic accuracy is high.

4. Public concern

The public concern for male infertility is high (expert judgment).

13.3.4 Non-Hodgkin lymphomas

1. Relevance to the Flemish/Belgian environment

A **large study** by De Roos et al. (2003) including **3417 patients** from the United States as well as other studies, indicated that exposure to pesticides may be associated with a significant increased risk for non-Hodgkin lymphomas. Data from Flanders (VLK) show no consistent trend in the years 1997-2000.

2. Availability of data and ease of follow-up

Data on non-Hodgkin lymphomas are easily available from VLK.

3. Diagnostic accuracy

The accuracy of the diagnosis of non-Hodgkin lymphomas is high (expert judgment).

4. Public concern

The public concern for cancer in general is high (expert judgment).

5. Scientific interest

From a scientific point of view, non-Hodgkin lymphomas are particularly interesting cancers. Non- Hodgkin lymphomas possibly related to environmental exposures have been recently found to be associated with a marker chromosomal translocation, possibly allowing for future screening for Non- Hodgkin lymphomas possibly related to environmental exposures.

13.3.5 Prostate cancer

1. Relevance to the Flemish/Belgian environment

The **incidence** of prostate cancer **in Flanders is very high** (higher than in 15 countries included in the Eurocan 1997) (Lousbergh et al., 2003). **The number of cases of** prostate cancer in Flanders (see data available in Flanders) **is increasing over the years** (although this may be partially attributable to better registration). Evidence from the literature suggests that the risk of prostate cancer is mainly increased in men occupationally exposed to pesticides.

2. Availability of data and ease of follow-up

Data on prostate cancer are easily available from VLK. The European randomized screening for prostate cancer (ERSPC) screening program contains data on almost 10000 Flemish men as shown in table 11 (Nelen et al., 2003). Prostate specific antigen (PSA), a marker of prostate function is included in the biomonitoring program of the "Steunpunt milieu en gezondheid".

3. Diagnostic accuracy

The accuracy of the diagnosis of prostate cancer is high.

4. Public concern

The public concern for cancer in general is high (expert judgment).

13.3.6 Delayed puberty

1. Relevance to the Flemish/Belgian environment

A **Belgian study** indicated that exposure of the **general population** to polychlorinated hydrocarbons is associated with an increased risk of delayed puberty (Den Hond et al., 2002; Staessen et al., 2001).

2. Availability of data and ease of follow-up

Except for the study mentioned above, no data is available on delayed puberty in Flanders at present.

The research project 'Flemish Growth Curves" (Roelants et al., 2001) reports on normal pubertal development in a large set of Flemish children and adolescents. Data on the determinants of onset of puberty in a cohort of 1100 girls is available (Janssens et al., 2003).

3. Diagnostic accuracy

Most of the parameters used to evaluate pubertal development are subjective and therefore suffer from a large inter-observer variation making the diagnosis less accurate. One notable exception is age at first menstruation in females (menarche).

4. Public concern

The public concern for delayed puberty is moderate (expert judgment).

13.3.7 Sex ratio (male to female ratio at live birth)

1. Relevance to the Flemish/Belgian environment

The literature suggests a decrease in sex ratio at birth to be associated with exposure to endocrine disruptors. The sex ratio seems to be stable in Flanders (SPE reports and national institute of statistics, NIS). This parameter is easy to follow-up (SPE, NIS) and the confounding is minimal.

2. Availability of data and ease of follow-up

This parameter is easy to follow-up (SPE, NIS). It is recommended that the data on sex ratio are analyzed in detail per NIS or preferably per statistics sector code. Sex ratio is a suitable parameter for further monitoring.

3. Diagnostic accuracy

The accuracy of this parameter is high and the confounding is minimal.

4. Public concern

The public concern for sex ratio at birth is low (expert judgment).

13.3.8 Congenital anomalies in general

1. Relevance to the Flemish/Belgian environment

The incidence of congenital anomalies remains stable in the last 10 years (SPE, 2004) and data from Antwerp (EUROCAT) do not show a consistent pattern. An increased risk of chromosomal and non-chromosomal congenital anomalies has been reported for people living 3 km or less near hazardous-waste landfill sites in Europe including Belgium (Dolk et al., 1998; Vrijheid et al., 2002).

2. Availability of data and ease of follow-up

Data on congenital anomalies are available for all hospital deliveries in Flanders and some home deliveries from the study center for perinatal epidemiology (SPE, 2004) and for Antwerp from EUROCAT.

3. Diagnostic accuracy

Different institutions follow different criteria for the registration of congenital anomalies in Flanders. For future studies, it is recommended that the registration of congenital anomalies follows the guidelines of EUROCAT. EUROCAT is supported by the EU-Commission public health directorate programmed of community action on rare diseases and is a WHO collaborating centre on the epidemiology and surveillance of congenital anomalies.

4. Public concern

The public concern for congenital anomalies in general is high (expert judgment)

13.3.9 Intrauterine growth retardation

1. Relevance to the Flemish/Belgian environment

Several studies link intrauterine growth retardation to higher levels of for example HCB.

2. Availability of data and ease of follow-up

Data are not directly available for Flanders but could be calculated for all hospital deliveries in Flanders (SPE database).

3. Diagnostic accuracy

Confounding may be an important factor, because not all home deliveries are included in the database of SPE although the number of hospital deliveries not reported in SPE is less than 1 percent in recent years (200-500 cases).

4. Public concern

The public concern for intrauterine growth retardation is high (expert judgment).

13.3.10 Prematurity

1. Relevance to the Flemish/Belgian environment

The literature indicates exposure to HCB, DDE and PCBs is associated with prematurity. Data on hospital deliveries in Flanders (SPE, 2004) indicate an increased incidence.

2. Availability of data and ease of follow-up

Data on all hospital deliveries and some home deliveries in Flanders are available from SPE.

3. Diagnostic accuracy

Whether the reported increase in the number of premature deliveries is due to better survival of prematures thanks to medical advances, prematures being more frequently delivered in hospitals than at home, or due to medical induction of delivery has to be investigated.

4. Public concern

The public concern for prematurity is high (expert judgment).

13.3.11 Testicular cancer

1. Relevance to the Flemish/Belgian environment

Little is known about the relationship between environmental exposure to endocrine disruptors and testicular cancer. One recent study indicates increased levels of PCBs, HCB and chlordanes in the mothers of men with testicular cancer (Hardell et al., 2003). The number of cases of testicular cancer does not show an obvious time trend (years 1997-2000) in Flanders (VLK).

2. Availability of data and ease of follow-up

Data on testicular cancer are easily available from VLK.

3. Diagnostic accuracy

The accuracy of the diagnosis of testicular cancer is high.

4. Public concern

The public concern for cancers in general is high (expert judgment).

5. Scientific interest

From a scientific point of view, testicular cancer is a particularly interesting cancer. Unlike other pathologies (e.g. prostate cancer), the observed increase in the incidence of testicular cancer in recent decades cannot be accounted for by longevity or better detection. Testicular cancer is a disease of young men and is easily detected.

13.3.12 Mental and psychomotor development

1. Relevance to the Flemish/Belgian environment

The literature review indicated perinatal exposure to p,p' DDE and dioxin is associated with delayed psychomotor development (Jacobson & Jacobson, 2003; Ribas-Fito et al., 2003a). Both endocrine disruptors are persistently present in the Flemish environment.

2. Availability of data and ease of follow-up

The results of the ongoing study by the steunpunt milieu en gezondheid are awaited.

3. Diagnostic accuracy

The accuracy of the diagnosis of delayed mental and psychomotor development is low since specialized tests are needed in many cases.

4. Public concern

The public concern for mental and psychomotor development of children is high (expert judgment).

13.3.13 Cryptorchidism

1. Relevance to the Flemish/Belgian environment

Exposure to pesticides and gardening have both been identified as risk factors for cryptorchidism in the offspring.

2. Availability of data and ease of follow-up

No data on cryptorchidism is directly available for Flanders. Personal contacts with the representative of the EUROCAT in Antwerp (Vera Nelen) indicated it is possible to include cryptorchidism in the future surveys of EUROCAT.

3. Diagnostic accuracy

It is important to note that the diagnosis and classification of cryptorchidism is difficult. For this reason, the EUROCAT decided not to include cryptorchidism in their database (Dolk, personal communication). We think that the best way to evaluate cryptorchidism is to periodically organize a prospective study every five years.

4. Public concern

The public concern for congenital anomalies in general is high (expert judgment).

13.3.14 Hypospadias

1. Relevance to the Flemish/Belgian environment

Maternal exposure to chemical hazards (pesticides) during gestation and a vegetarian diet are reported as risk factors for hypospadias. Data from EUROCAT on the prevalence of hypospadias in Antwerp does not show a consistent pattern. As with cryptorchidism, the diagnosis and classification is clinically difficult. For this reason EUROCAT recommends to periodically organize a prospective study every five years. This could be combined with a study on cryptorchidism.

2. Availability of data and ease of follow-up

Data from EUROCAT on the prevalence of hypospadias in Antwerp is easily accessible.

3. Diagnostic accuracy

4. Public concern

The public concern for congenital anomalies in general is high (expert judgment). Contacts with urologists indicated that the parents of children with hypospadias are increasingly concerned about this anomaly and they request surgical correction for even the mildest form of hypospadias.

13.3.15 Precocious puberty

1. Relevance to the Flemish/Belgian environment

Belgian data indicate precocious puberty to occur more frequently in **adopted and immigrated foreign children** compared to native Belgian children. This is accompanied by higher levels of p,p'-DDE in the former group (Krstevska-Konstantinova et al., 2001).

2. Availability of data and ease of follow-up

The research project 'Flemish Growth Curves' (Roelants et al., 2001) reports on normal pubertal development in a large set of Flemish children and adolescents. Data on the determinants of onset of puberty in a cohort of 1100 Flemish girls is also available (Janssens et al., 2003).

3. Diagnostic accuracy

Most of the parameters used to evaluate pubertal development are subjective and therefore suffer from a large inter-observer variation making the diagnosis less accurate. One notable exception is age at first menstruation in females (menarche).

4. Public concern

The public concern for precocious puberty is moderate (expert judgment).

13.3.16 Thyroid diseases

1. Relevance to the Flemish/Belgian environment

The literature indicates that environmental (high levels) and/or occupational exposure to endocrine disruptors (PCBs, polybrominated flame retardants and perfluorooctyl sulfonic acid) is associated with thyroid dysfunction (hyper or hypothyroidism). One of these studies was performed on workers at the 3M factory in Antwerp. Higher levels of thyroid hormone (Triiodothyronine) and lower thyroid hormone binding ratio in workers with the highest perfluorooctyl sulfonic acid (PFOS) serum concentrations were found. Also, exposure of newborns, infants and children to PCBs is accompanied by changes in thyroid function as indicated by an increase or decrease in thyroid stimulating hormone levels in blood.

2. Availability of data and ease of follow-up

Data on thyroid hormone levels in healthy individuals (small numbers) is available from a population study in Flanders (Onderzoek Milieu en Gezondheid). It is also planned to measure thyroid hormones in 1600 adolescents (800 boys and 800 girls) as a part of biomonitoring for "Steunpunt Milieu en Gezondheid". The reporting of thyroid problems in the health interview of 2001 was spontaneous. Therefore, underreporting is expected. Data on thyroid cancer are available from VLK.

3. Diagnostic accuracy

The diagnostic accuracy for thyroid cancer is high while the accuracy for the the diagnosis of other thyroid problems is low (expert judgment).

4. Public concern

The public concern for thyroid diseases is high, especially thyroid cancer (expert judgment)

13.3.17 Immune system diseases (immunosuppression)

1. Relevance to the Flemish/Belgian environment

In addition to non-Hodgkin lymphomas (see above), the literature indicates increased susceptibility to infection and decreased incidence of allergic reactions in children exposed to PCBs and dioxin. Studies from **Belgium** and the **Netherlands** indicated that current PCB body burden in children was associated with a higher prevalence of recurrent middle-ear infections and of chicken pox and a lower prevalence of allergic reactions.

2. Availability of data and ease of follow-up

One Belgian study involving adolescents has been identified. Otherwise, no data are available.

3. Diagnostic accuracy

Due to the multiplicity of the possible diseases associated with « immunosuppression », we are convinced that infection in children should be investigated in a separate prospective study.

4. Public concern

The public concern for the symptoms of immunosuppression e.g. recurrent infections is high (expert judgment).

13.3.18 Endometriosis

1. Relevance to the Flemish/Belgian environment

Although very common in Belgium (opinion paper: Koninckx et al., 1994), two (small) Belgian studies indicate no association between endometriosis and environmental exposure to dioxin/PCBs (Fierens et al., 2003; Pauwels et al., 2001a). Recently, high levels of DEHP have been reported in a small number of women with endometriosis (Cobellis et al., 2003). Follow-up of the literature is necessary.

2. Availability of data and ease of follow-up

A high incidence of endometriosis has been reported in Belgian women with menstrual problems and infertility. Otherwise, no data are available.

3. Diagnostic accuracy

The diagnosis of endometriosis requires laparoscopy, a diagnostic procedure that is invasive and ethically unacceptable in asymptomatic women.

4. Public concern

The public concern for endometriosis is high due to the high prevalence in Belgium and the association of endometriosis with menstrual disturbances and female infertility (expert judgment).

13.3.19 Time to pregnancy

1. Relevance to the Flemish/Belgian environment

Prenatal exposure to pesticides has been reported to be associated with longer TTP (Cohn et al., 2003). The evaluation of TTP is a reliable marker of fertility.

2. Availability of data and ease of follow-up

Except for data on control groups of two occupational studies and a TTP study after removal of intrauterine device, **few data are available for Belgium**. TTP is being recorded by steunpunt milieu en gezondheid (deelstudie pasgeborenen/moeders). It may be useful to add TTP questions to the next health questionnaire (gezondheidsenquête).

3. Diagnostic accuracy

Some recall bias is possible although studies indicate that the recall is good.

4. Public concern

The public concern for time to pregnancy is high (expert judgment).

14 Conclusions and recommendations

On the basis of our literature study on the effects of endocrine disruptors in humans and the availability of data for the Flemish environment, it is concluded that at this moment the most relevant substances to be further studied in Flanders are DDT (and metabolites), cyclodiens (drins), hexachlorobenzene, dimethoate, nitrogenous organic pesticides (mostly atrazine), organotin compounds, PCBs, dioxins, styrene, nonyl phenols, bisphenol A, phthalates, and ethinylestradiol. However, new research data provide continuously new insights, which makes this list provisional and under permanent construction. For example, further studies are needed to evaluate the possible endocrine disrupting potential of human exposure to carbamates, parabens, polybrominated flame- retardants, PFOS, PFOA and cadmium at environmental levels since little is known about their possible endocrine disrupting properties. A risk analysis is available for dioxin, bisphenol A, Atrazine and ethinylestradiol for the Flemish population. A recent case-report suggests medication (enteric coated tablets) as a potential source of exposure to high levels of phthalates. Further research is necessary to determine the proportional contribution of medications, as well as personal care and consumer products, to a person's total phthalate burden.

Based on the relevance to the Flemish environment, availability of data and ease of follow-up making use of the present infrastructure in Flanders (databases etc), public concern and possible confounding, the pathologies possibly related to endocrine disruption are ranked in descending order of priority as follows:

1. breast cancer,
2. female infertility,
3. male infertility and sperm quality,
4. non-Hodgkin lymphomas,
5. prostate cancer,
6. delayed puberty,
7. male to female (sex) ratio at birth,
8. congenital anomalies,
9. intrauterine growth retardation,
10. prematurity,
11. testicular cancer,
12. mental and psychomotor development,
13. cryptorchidism,
14. hypospadias,
15. precocious puberty,
16. thyroid diseases,
17. immune system diseases (immunosuppression),
18. endometriosis and
19. time to pregnancy.

From a scientific point of view, non-Hodgkin lymphomas and testicular cancer are particularly interesting cancers. Non- Hodgkin lymphoma related to environmental exposures has been recently found to be associated with a marker chromosomal translocation, possibly allowing for future screening. Unlike other pathologies (e.g. prostate cancer), the observed worldwide increase in the incidence of testicular cancer in recent decades cannot be accounted for by longevity or better detection. Testicular cancer is a disease of young men and is easily detected. Further research is needed or ongoing on the relationship of endocrine disruption to diabetes mellitus, obesity, erectile dysfunction and low serum androgens in the male, pancreatic cancer and Parkinson's disease.

According to information available in Flanders, a detailed strategy is described for collecting information on the pathologies described above, including RIZIV nomenclature and medication numbers. Possible biases and the expected degree of completeness of the retrieved data are also described in the present report. One of the major problems in developing the present strategy was that in many cases there are no RIZIV numbers that are indicative of the relevant pathology (examples include cancers and endometriosis). Therefore, it is recommended that the RIZIV numbers should be evaluated and modified to make them a better source for medical information on among others, diseases with possible relationship to endocrine disruption.

For each relevant pathology, we delineated possible biases of the current strategy based on the literature and discussions with the experts. Data from many Belgian/Flemish sources of information included in this report lack external quality validation. Therefore, the reliability of the data collected using the present strategy has to be evaluated. It is also advised that different sources of information are compared and that the registration criteria are harmonized through better co-operation between different institutions. We compared the number of cases of female breast, prostate and testicular cancers reported by MKG and VLK for the year 1998. These data are included already in the database of steunpunt milieu en gezondheid (milieupath). The comparison indicated that the number of these cancers was seriously overestimated in the MKG data relative to data originating from VLK. We attempted to eliminate double registration in the MKG data by removing cases that were rehospitalized in the same year (1998) but for more than one third of the patients the rehospitalization status was unknown.

Therefore, our evaluation indicates that the Flemish cancer registry is the most reliable source of information for cancer pathologies at the present time. Additional data on prostate cancer are available from the ongoing European randomized screening for prostate cancer (ERSPC). As recently recommended by a European working group, hisopathological characterization of a tumor should be included in cancer registries (European commission environment DG, 2004). In particular, because recent studies indicate that the effect of endocrine disruptors on breast cancer may be affected by the receptor status of the tumor, it is recommended that the receptor status of breast cancers should be added to the data collected by the Flemish institutions.

The SPE and EUROCAT databases are the most complete sources of information on congenital anomalies for respectively Flanders and Antwerp. The two organizations are currently comparing their datasets.

The use of RIZIV nomenclature and medication numbers is expected to generate reliable information on hypospadias and cryptorchidism. Additional data on hypospadias is available from EUROCAT for the province of Antwerp. One old publication by Steeno in 1967 concerning the incidence of cryptorchidism in school children in Brussels has been found in Pubmed. It may be useful to reproduce the study by Steeno using the same protocol. This may help to identify possible time trends. The SPE is advised to include cryptorchidism and hypospadias each as a separate entity in their reporting form. Infants with cryptorchidism at birth should be followed one year later since most undescended testes descend into the scrotum by the age one year. The representative of EUROCAT in Antwerp (Vera Nelen) is willing to collect data on cryptorchidism at birth and follow-up information at the age of one year provided that financial support is available.

SPE is the only reliable source of information on prematurity and intrauterine growth retardation that could be identified.

None of the sources evaluated will generate reliable data on psychomotor development or delayed puberty. A 42 month follow-up of the neuropsychological development of 200 young children in Flanders is organized by the Flemish "Steunpunt milieu en gezondheid". Partial results are expected in 2006. Contacts with centers for developmental disturbances, (Centra voor Ontwikkelingsstoornissen, COS) indicated that only cases with advanced and clinically manifest disturbances of psychomotor development presenting to COS are registered using the same software for all centers in Flanders. Therefore, combining data from different COS centers is technically possible. Otherwise there is no systemic registration of psychomotor development of Flemish children (Mr. L. Goossens, Director COS Ghent, personal communication).

The use of RIZIV nomenclature and medication numbers is expected to generate reliable data on precocious puberty.

Data on normal growth and puberty in both sexes is available from the department of anthropogenetics, Free University Brussels (VUB). Data on the determinants of puberty in girls are available from the European cancer prevention organization, Hasselt. One Belgian study comparing the mental and psychomotor development in ICSI children and children born after a spontaneous conception has been identified.

As a potential future source of data on health parameters in children and adolescents, the progress of the NICO project has to be followed up closely. Our personal contacts with CLB/NICO indicated that at the present time, there is a delay in the progress of the NICO project, and that it is still in the development (experimental) phase. This does not allow the systematic registration of medical data for the time being.

Sufficient data are available on male to female (sex) ratio at birth both for infants delivered at Flemish hospitals (SPE) as well as for the whole Belgian population (FOD Mineco). A detailed follow up of the sex ratio per municipality or preferably per statistical sector code may be useful as a rapid screening tool since a local change in this parameter may indicate environmental problems.

With regards to female infertility, only data on hormonal induction of ovulation and treatment with *in vitro* fertilization are available (SPE) or can be extracted (RIZIV). Only the most severe forms of endometriosis, a condition common in females with infertility or gynecological pain, can be detected using RIZIV data. Apart from a long-term follow-up of candidate sperm donors (Prof. F. Comhaire, University hospital Ghent), large studies on sperm quality in Flanders are generally lacking. The number of semen analyses performed in Flanders per year can be calculated from RIZIV data. This may give a rough estimation on the magnitude of infertility in the general population, although semen analysis is performed for indications other than fertility evaluation. Therefore, studies in field of in(fertility) are much needed.

Time to pregnancy (TTP) is one parameter that evaluates the fertility of couples (male and female). Two studies have been identified where TTP has been reported in Belgian women, one after the removal of intrauterine device and a control group for a study evaluating the effect of male exposure to inorganic lead on TTP in partners of Flemish men. TTP is being recorded by steunpunt milieu en gezondheid (deelstudie pasgeborenen/moeders). Due to the paucity of data on TTP in the Flemish population, it may be useful to include a TTP questionnaire in the next health interviews (Gezondheidsenquêtes).

RIZIV nomenclature and medication numbers will allow the retrieval of most cases with thyroid problems. Data on thyroid cancer from the advising physicians (advieserende geneesheren) of IMA can then be used to distinguish cancer from non-cancer thyroid problems. Further detailed classification of thyroid disorders using available data is not possible mainly because one single treatment modality is used for different pathological conditions. Data on thyroid stimulating hormone levels in (male and female) healthy individuals (small numbers) is available from a population study in Flanders (Onderzoek Milieu en Gezondheid). It is also planned to measure thyroid hormones in 1600 adolescents (800 boys and 800 girls) as a part of biomonitoring for Steunpunt Milieu en Gezondheid. The self-reported incidences of thyroid problems in the health interview of 2001 are probably underreported.

Except for a study indicating that exposure to dioxins and PCBs is associated with immunosuppression in Flemish adolescents, no reliable source of information is available on immune system diseases (immunosuppression) in children. Data on immunological markers in healthy adult female individuals (small numbers) is available from a population study in Flanders including gammaglobulins, lymphocytes and complement (Onderzoek Milieu en Gezondheid).

It is to be noted that the present strategy does not allow for the evaluation of other etiological factors, for example smoking habits and genetic factors, involved in the pathogenesis of the relevant pathologies. Due to time and budget limitations, it was not planned to collect detailed data on health parameters of workers occupationally exposed to endocrine disruptors within the frame of the current study. It is recommended however, that a similar strategy for collecting data on occupational exposures should be developed in the near future. The generated data from both strategies should end up in the same database.

The use of statistical sector code for each patient registered in hospitals, cancers registries and all other organizations involved in health care as well as its use for registration of environmental data is the key to a better evaluation of the possible role of environmental factors on human health.

Different health authorities use different coding systems to conceal the patient's identity. This makes combining or comparing data from different sources impossible. Coding of a patient's identity at different places has to use a unique identification number. One possible solution is that the government supplies a single coding system (or software) for use in all Flanders (or at a federal level). For this purpose, a software is used by all the member mutualities of IMA. The Flemish cancer registration network also distributes a software to its collaborating centers for the generation of a unique code. IMA performs an additional coding by an intermediate organization before data are delivered to a user outside IMA.

The authors wish to report that access to medical data in Flanders is not always easy. We are grateful to organizations that follow an open policy and make their data available in an interactive form on their websites such as EUROCAT, and MINECO. This facilitates recalculation of data needed for scientific purposes. It is hoped that others will follow the same policy in the future. It is also recommended that more details on ongoing Flemish projects are made easily available, for example, the number of cases to be sampled and types of measurements planned.

Due to the multifactorial nature of diseases, environmental, wildlife and human data from different sources should be combined in one database. This would allow more robust conclusions on the "possible" relationship between health and the environment to be made.

In this regard, the database of the steunpunt milieu en gezondheid (milieupath) is a step in the right direction. Many additional data sources should be included in the database. We recommend that the data on congenital anomalies for hospital delivered children in the province of Antwerp (EUROCAT) should be included in the database of steunpunt milieu en gezondheid. This would allow the comparison between three sources of information on congenital anomalies (EUROCAT, SPE, MKG). Also, the extensive dataset on pollutant levels in the eel from the Flemish eel pollutant measurement network (palingpolluentenmeetnet) would be a useful addition to the database.

For access to data from mutualities (IMA), a foreseen amount of 5000 Euro for each query is expected to paralyze future investigation and management of health related issues. Therefore, it is suggested that such essential information is made accessible to scientists and health authorities for the sake of health of the Flemish population for a limited fee, or maximally a fixed yearly amount. As issues that transcend every "proprietary" aspect of mutuality data are dealt with here, it is important that authorities start negotiating such access as soon as possible, and if needed through higher political levels.

Last but not least, a strategy has to be developed for communicating the results of scientific studies including possible risks to the Flemish public.

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