Hormone disruptors in humans

Aanbiedingsbrief

Hormone disruptors in humans

Health Council: Committee on Hormone disruptors and
human reproduction and development

to:

the Minister and State Secretary of Health, Welfare and Sport

the Minister of Housing, Spatial Planning and Environment

the Minister of Agriculture, Nature Management and Fisheries

the State Secretary of Social Affairs and Employment

No. 1997/08, Rijswijk, 10 April 1997

Preferred citation:
Health Council of the Netherlands: Committee on Hormone disruptors and human reproduction and development. Hormone disruptors in humans. Second printing with corrections. Rijswijk: Health Council of the Netherlands, 1997; publication no. 1997/08.

ISBN: 90-5549-156-X

Contents

Summary

There is at present an intense discussion about the possible effects on human reproduction and development of substances which affect hormonal regulation. At the request of the President of the Health Council, a Health Council Committee has looked at two questions relating to the presence of endocrine disruptors in the Netherlands:

Is there cause for concern about the influence of endocrine disruptors on human reproduction and development, particularly in the Netherlands?

Should specific research be conducted in the Netherlands in order to trace endocrine disruptors, to quantify exposure to endocrine disruptors and to assess the effects of exposure on health?

The Committee answers that there are no indications that exposure to endocrine disruptors constitutes a direct, acute threat to public health. However, the entire population of the Netherlands is exposed to substances of this kind and effects on reproduction and development are, albeit possibly subtle, biologically plausible. The Committee is therefore of the opinion that the possible effect of endocrine disruptors on health merits serious attention. Given the gaps in knowledge and the lack of data this view leads to the advice to support specific research into the risks of endocrine disruptors for public health. Since the Netherlands does not occupy an unusual position in terms of exposure to endocrine disruptors and sensitivity to them, considerations of efficiency mean that internationally-coordinated research is preferable. The Committee makes a number of recommendations in that respect.

Chapter 1

Introduction

1.1 Background

Certain substances present in the environment can influence human and animal hormonal regulation. However, do these *endocrine disruptors** also have undesirable effects on reproduction and development? There is at present an intense discussion in scientific and lay circles about this question. A range of scientific reports and reviews have been published on the subject recently (Bro95, Kav96, MEE95, MRC95, RIVM96a, Top96). Public interest has been provoked by, among other things, the BBC documentary 'Assault on the male' (BBC93) and a book published in the United States in early 1996 entitled 'Our stolen future' (Col96).

The President of the Health Council decided to include the subject of endocrine disruptors in the Council's Work Programme in 1995 and to break down the subject into a section on risks to humans and a section on risks to eco-systems. This advisory report deals with risk to humans and concentrates in particular on the situation in the Netherlands. The President of the Council has appointed a separate Committee to assess the effects of endocrine disruptors on reproduction and development in animals and eco-systems.

* The term 'endocrine disruptor' is used in this report in the following sense: a substance in the environment which can induce disturbances in hormonal regulation, in particular that part of the endocrine system which is involved with sexual development and the functioning of the reproductive system, in intact organisms or their offspring.

Many substances have been thought to interfere with the endocrine system. Endocrine disruption has been linked to human exposure to lipophilic substances of anthropogenic origin such as PCBs and DDT and their metabolites, as well as to lipophilic substances of natural origin — such as phyto-oestrogens* — which are commonly consumed in food. Incidentally, some of these substances are thought to provide protection against certain forms of cancer. There are, for example, indications that in groups which consume food which is relatively rich in phyto-oestrogens, the incidence of breast and prostate cancer is lower than in other populations (Cow93, Lee91).

It is suspected that most endocrine disruptors may have a negative effect on human reproduction and development. Indications of this have been found in animal studies and studies of cells and organ systems (*in vitro* studies). Other indications have been found in animals living in the wild, examples being an increase in the production of the protein vitellogenin in male and female fish, the masculinization of female fish, abnormalities in the development of the reproductive system in reptiles, deviant clutch size and female-female pairing in gulls and imposex in molluscs** (MRC95). In addition, parallels have been drawn in the literature with health problems caused by the use of diethylstilbestrol (DES), a synthetic hormone.

Epidemiological changes and changes in health characteristics have also been linked to endocrine disruptors. These include increases in the incidence rates of breast, prostate and testicular cancer, a possible decrease in sperm concentration and quality***, more congenital anomalies of the reproductive organs such as failure of the testes to descend (cryptorchidism) and malformation of the penis (hypospadias and epispadias****) and possibly smaller testes and microphallus. However, other factors may be the cause of these phenomena or contribute to them. It is impossible to say on the basis of the observed changes which factors have played more or less important roles.

1.2 Report subject and method

The preparations for this advice included discussions with specialists in the fields of andrology, gynaecology, epidemiology, endocrinology, toxicology, pharmacology, teratology and paediatric medicine (see annex A). These discussions were rounded off with a workshop on 25 June 1996 attended by the specialists referred to here and other

* Phyto-oestrogens: compounds with an oestrogenic action which occur naturally in plants.
** Imposex in molluscs: male genitalia in female molluscs.
*** Sperm quality is related to morphology and motility of the sperm cells.
**** Hypospadias: an anomaly in which the urethra opens on the under-side of the penis or the perineum. Epispadias: an anomaly in which the urethra opens on the dorsum of the penis.

experts (see annex A). The discussion during this workshop related to the question of whether there is any cause for concern in the Netherlands about the consequences of exposure to endocrine disruptors. The President of the Health Council then appointed a Committee which was asked to answer the following questions on the basis of the results of the workshop:

Is there cause for concern about the influence of endocrine disruptors on human reproduction and development, particularly in the Netherlands?

Should specific research be conducted in the Netherlands in order to trace endocrine disruptors, to quantify exposure to endocrine disruptors and to assess the effects of exposure on health?

This report contains the Committee's answers to those questions. The members of the Committee are listed in annex B. The literature search method is described in annex C.

1.3 Report design

Chapter 2 discusses hormonal regulation, the suspected effects of endocrine disruptors on reproduction and development and the modalities of exposure to endocrine disruptors. It also contains a survey of the natural and synthetic substances which can influence hormonal regulation. The publications in the international scientific literature about links between effects and exposure to endocrine disruptors which the Committee considers to be the most important are presented in a table (annex D). Chapter 3 is devoted to data about exposure and the possible consequences insofar as they are of direct importance for the Dutch situation. Chapter 4 provides a summary of the data available in the Netherlands about illnesses and disorders which can be associated with a disturbance in hormonal regulation. Chapter 5 contains the Committee's answers to the questions put to it and the Committee's recommendations for further research.

Chapter 2

Endocrine disruptors and their suspected effects on reproduction and development

In this chapter, the Committee discusses the natural and synthetic substances which can interfere with human reproduction and development as a result of their effect on hormonal regulation.

2.1 Hormonal regulation

An organism's physiological functions, such as cell and organ development, reproduction and behaviour, are regulated by hormones. The endocrine system coordinates the work of the hormones. It consists of a complex whole of regulatory systems and mechanisms involving numerous organs. This complexity affords many openings for interference from substances as well as for compensation of such interference.

The basic building blocks of the endocrine system are hormones [H] and receptors [R] - see figure 1. Hormones are made as required (G) and act as messengers. Receptors act as receivers of the signals by forming complexes [HR] with the hormone molecules and as transmitters to other parts of cells, including the DNA in the nucleus. This results in a series of changes in the cell, including activation of the hormone receptor complex {HR}, followed by an action A. Endocrine processes are closely regulated by feedback mechanisms. This process is shown diagrammatically in figure 1. It is a part of the homeostatic system which, in humans and vertebrates, maintain physiological functions under changing external circumstances.

Interactions between substances and the endocrine system can result in changes in hormonal regulation. The substances can act at different stages of hormone actions. As

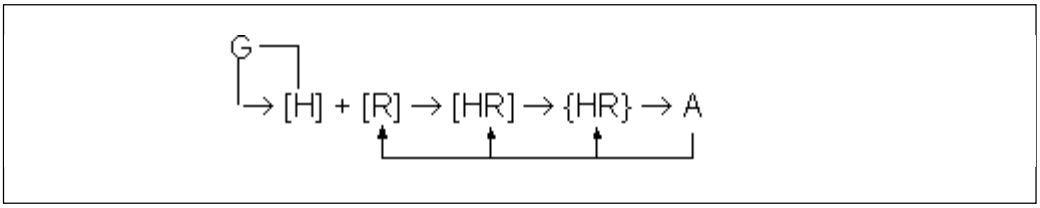

Figure 1 Diagrammatic representation of the process of hormone production and actions.

a result, hormone concentrations can change and receptor functions will not be available. The effectiveness of hormones can also be altered so that the result of hormone action can be abnormal. In addition, the influence of substances can depend on the stage of development of the individual (foetus, child, adult).

2.2 Suspected effects of endocrine disruptors

The effects which are linked with exposure to endocrine disruptors are described in this report as 'suspected effects'. As often as not, no causal links have been established with any certainty between exposure on the one hand and effects on reproduction and development on the other. It is also possible that mechanisms other than endocrine disruption cause the reported effects on reproduction and development.

The risk that exposure to an endocrine disruptor will result in an effect on reproduction and development depends on a variety of factors. Examples are: the level of exposure, the endocrine disruption potential of the substance, the persistence of the substance and the time frame in which exposure can have a negative effect. Effects on reproduction and development can result from a disturbance of the developing foetus (*in utero*) and from influences during youth and adulthood.

Possible effects of *in utero* exposure to endocrine disruptors which are stated in the literature are:

- Abnormal development of the reproductive system. The literature contains references to symptoms in males, such as decreases in sperm concentration and quality, decrease of spermatogenesis, cryptorchidism, hypospadias and epispadias, feminization, and testicular cancer, and symptoms in females, such as the occurrence of clear-cell carcinoma of the cervix or vagina, masculinization.
- Abnormal development of the central nervous system. The literature contains references to neurological, cognitive and behavioural disorders (including sexual behaviour), smaller head size at birth, feminization and masculinization.

- More general developmental abnormalities. The literature contains references to shorter pregnancies, lower birth weight, disturbed hormonal regulation (thyroid gland), arrested growth and changes in sex ratio*.

Exposure later in life could lead to the following effects:

- Abnormalities in the functioning of the reproductive system. The literature contains references to symptoms in males, such as impotence and loss of libido, disturbance of hormonal regulation, drop in testis size and weight, decreases in sperm concentration and quality and spermatogenesis, as well as problems in females, such as difficulties with breast-feeding, disturbance of hormonal regulation, menstrual or menopausal problems, alterations in fertility and an increased rate of spontaneous abortion.
- A higher incidence of tumours related to disturbance of hormonal regulation. The literature contains references in this respect to breast, endometrial, prostate, testicular, ovarian, adrenal and thyroid cancer**.

2.3 Endocrine disruptors

The Committee makes a distinction between two groups of substances with an endocrine disruptive effect: hormones themselves, whatever their origin, and chemicals of anthropogenic origin:

Natural and synthetic hormones such as:

- medicines which contain hormones
- phyto-oestrogens
- growth stimulants used in livestock farming.

Synthetic chemicals (other than hormones), such as some:

- pesticides
- detergent components and breakdown products
- monomers and additives used in the plastics industry
- organometals
- persistent environmental contaminants from the past.

The endocrine disruptive effects which are ascribed to various substances in the scientific literature were observed in a variety of laboratory tests with laboratory

* Sex ratio: the ratio between the number of births of girls and boys.

** These forms of cancern concern tumours in the sexual organs or in organs which play an important role in human reproduction and development through, for example, the production of specific hormones.

animals or cell cultures. The following substances and groups of substances are expected to be endocrine disruptors:

- *pesticides*: such as p,p'-DDT, p,p'-DDE and o,p'-DDT, chlordecone, beta-hexachlorocyclohexane, dibromochloropropane (DBCP), endosulfan, dieldrin, lindane (gamma-hexachlorocyclohexane), chlorotriazines (atrazine, simazine), vinchlozolin, mirex, methoxychlor and toxaphene
- *polychlorinated biphenyls (PCBs)*
- *dioxins*: polychlorinated dibenzo-para-dioxins (PCDD) such as TCDD and polychlorinated dibenzofurans (PCDF)
- *alkylphenol polyethoxylates (APEs) and decomposition products,* such as octylphenol and nonylphenol
- *bisphenol A*
- *phthalates,* such as diethylhexyl phthalate (DEHP), dibutyl phthalate and butyl benzyl phthalate
- *polycyclic aromatic hydrocarbons (PAHs)*, such as dimethyl benzanthracene and benzo[a]pyrene
- *phyto-oestrogens*, such as coumestrol, zearalenone, isoflavones (including genistein) and lignans
- *pharmaceuticals*, such as diethylstilbestrol (DES), ethinyl oestradiol (in contraceptives) and muscle builders (anabolic steroids).

Indications of possible effects of endocrine disruptors on human reproduction and development have been found in studies of animals living in the wild which were very probably exposed to endocrine disruptors, and have emerged from studies of laboratory animals and *in vitro* studies in cells and organ systems. Tables 1 and 2 (annex D) contain a list of the links described in the literature on the basis of those studies.

Other indications for a possible influence on human reproduction and development which are stated in annex D are the results of epidemiological studies. A difficulty with the interpretation of these data is the presence of other factors which may influence reproductive or developmental abnormalities, examples being genetic factors, diseases, radiation and the use of stimulants. It is not easy to structure epidemiological research in such a way that those other factors are eliminated or relegated to a subordinate role or to correct for their influence entirely.

Of major importance are the investigations into the side-effects of diethylstilbestrol (DES) use, about which a lot has been published. Between the forties and the seventies, DES was prescribed to prevent miscarriage and complications during pregnancy. Daughters of mothers who were treated with DES during their pregnancy have been found to have a variety of morphological abnormalities and

sexual organ dysfunction, abnormal pregnancies and disrupted menstrual cycle. An increased incidence has also been found in young adult ‘DES daughters’ of clear-cell carcinoma of the cervix or vagina. Above-normal incidence rates of cryptorchidism, micropenis and microphallus* and epidydymal cysts have also been found in the male offspring of ‘DES mothers’. In addition, indications have also been found of a reduction in sperm count and motility in ‘DES sons’.

There has been research in the Netherlands into the link between effects on health and exposure of groups of people to endocrine disruptors. A review can be found in table 3 (annex D) and the data will be discussed in the next chapter. The Committee will discuss observed changes in the Dutch population relating to reproduction and development in Chapter 4.

* Micropenis: anatomically normal penis which is too short. Microphallus: abnormal smallness of the penis. in combination with hypospadias, etc.

Chapter 3

Results of exposure and effect studies in the Netherlands

There is little Dutch data about exposure to endocrine disruptors and about a possible link between such exposure and effects on reproduction and development. Most of the available information relates to the intake of particular endocrine disruptors via food. In this chapter, the Committee will discuss the data available for the Netherlands.

3.1 Exposure

People can be exposed to endocrine disruptors in various ways. The following exposure situations are possible:

- iatrogenic*, examples being the use of DES, hormonal contraception or other hormone treatments
- via food and drinking water (including breast milk)
- at work
- in the immediate living and home environment
- in other ways, e.g. the use of anabolic steroids (sport).

Iatrogenic exposure

The main examples of exposure to endocrine disruptors in a medical context are:

* Iatrogenic exposure: exposure to substances as a result of medical intervention (including the side-effects of medicines).

- the use of hormonal contraceptives: approximately 45% of women aged between 16 and 49 in the Netherlands use 'the pill' at present (30-35 μg ethinyloestradiol a day; CBS96)
- use of menopausal hormone replacement: 4% of women aged between 40 and 69 take replacement hormones during menopause (30-35 μg ethinyloestradiol a day; Odd94)
- use of ovarian stimulants: there is an increasing demand in the Netherlands for ovarian stimulants (LH/FSH preparations).

Food and drinking water

Humans can be exposed via food and drinking water to the following endocrine disruptors:

- phyto-oestrogens which occur naturally in plant foods (isoflavones, for example)
- traces of pesticides which are used in food production and persistent substances in the environment which accumulate in food (breast milk, cow milk, meat and fish)
- substances which escape from packaging material (e.g. phthalates)
- substances which are formed during the preparation of food (e.g. PAHs in barbecues)
- traces of growth stimulants (such as anabolic steroids in meat)

Table 4 in annex E provides an overview of the information about the intake of endocrine disruptors via food in the Netherlands. The study results relate primarily to exposure to PCBs and dioxins.

The intake of *phyto-oestrogens* is considerably greater than that of synthetic chemicals with an endocrine-disruptive effect (Pri85, Saf94). This does not mean that these substances are more of a danger to health since phyto-oestrogens are metabolized quickly after absorption in the body. There is no data available about the intake of phyto-oestrogens in the Netherlands. Various greens and vegetables, e.g. peas, beans, cabbage, sprouts and spinach, contain phyto-oestrogens. A rich source is soya, that is increasingly found in food products, and mainly consumed in the Netherlands by vegetarians, vegans and devotees of Asian cuisine. It is reasonable to assume that the intake of phyto-oestrogens will be considerably higher among these groups than in the population as a whole.

Pesticides are used on a large scale in the Netherlands. There is therefore a risk that they will be present for longer or shorter periods in an environmental compartment. The data from the Surveillance Programme Man, Nutrition and

Environment* provides some information about exposure to pesticides via food (Sta95). As part of this programme, approximately 10,000 samples of vegetables and fruit are examined for traces of pesticides every year. The measurement data shows that these substances can be present in foodstuffs and that, in a small number of cases, the residue limit is exceeded. The Committee would wish to point out here that the simple fact that the limit is exceeded need not necessarily mean that there will be effects on public health. In addition, as far as the Committee is aware, undesirable effects on hormone metabolism were not explicitly taken into account when the residue limits were being set (or at least not in all cases).

In terms of exposure to persistent environmental contaminants, exposure to *PCBs and dioxins* via food has been best documented. Using data from the first national food consumption survey (1987/88) and the results of analyses for a large number of foodstuffs, the burden of dioxins and planar PCBs with dioxin-like effects via food have been calculated (see RIVM91a and table 4, annex E). The dioxin and dioxin-like PCB levels can be relatively high, particularly in breast milk. Results of the studies coordinated by the WHO show that the levels of dioxins and PCBs in breast milk in the Netherlands are relatively high (WHO89). The dioxine levels are on the decrease, the levels of PCBs in breast milk remain more or less constant (Lie96). Major sources of these substances in the food supply are milk and dairy products, fish and fish oil and, to a lesser extent, meat (RIVM96b). RIKILT DLO** too estimated the burden of these compounds. The results corresponded reasonably closely to the values reported by the National Institute of Public Health and Environment (RIVM).

Atmospheric deposition of *PAHs* on grain, vegetables with large leaf surfaces, fruit and plants used to produce oil is a major source of PAHs in our food. Direct heating (desiccation) of raw materials with gaseous fuels is another way in which PAH contamination can take place (malt, milk powder, oil-bearing seeds etc.). Environmental pollution resulting from the discharge of waste water and the deposition of PAHs into water cause contamination of shellfish in which PAHs can accumulate (mussels, oysters, see Sch88). The burden via food in table 4 is estimated on the basis of a total diet study.

Phthalates may be present in food packaging material and can enter food from that material (Wam87). These substances can also enter food from conveyor pipelines and storage containers during manufacture or processing. Exposure to phthalates can also

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* The Surveillance Programme Man, Nutrition and Environment is a project run by the Health Protection Inspectorate, the Veterinary Inspectorate of Health and the Health Care Inspectorate. In this monitoring programme, sampling is carried out by the Commodity Inspectorate. On occasion, during certain periods of the year, certain products are subjected to extra examinations because there is a suspicion that they contain more traces of pesticides at those times.

** RIKILT DLO: Government Institute for Quality Control of Agricultural Products of the Agricultural Research Service.

occur in the health sector, for example during kidney dialysis when PVC tubes are used or during blood transfusion using plastified blood bags (SZW93).

As a result of the ban on the use of *growth hormones in livestock farming*, the risk of exposure to these substances via the consumption of meat and meat products in the Netherlands should be small. However, these substances may be present in imported meat and illegal use cannot be excluded.

In addition to food, drinking water can also be a source of exposure to endocrine disruptors (Faw94). Endocrine disruptors can enter drinking water from surface water and groundwater (Kiwa97). Given the nature of the compounds and surface water purification, the risk of this happening is small. Unlike a number of other countries, the Netherlands has an extensive drinking water purification system. In Germany, low concentrations of oestrogens have been measured in drinking water (less than 0.5 ng/l, Rad79, Rur79). Oestrogens have also been found in drinking water in Israel (12-20 ng/l; Sho93). In both cases, the water in question have not been purified using activated carbon filtration. Activated carbon filtration was gradually introduced in the Netherlands from 1977 onwards.

Work

In agriculture and horticulture, workers can be exposed to endocrine disruptors in the form of pesticides (Coc94). The Netherlands is a country with intensive agricultural and horticultural industries and there is therefore a greater risk of exposure to pesticides than in surrounding countries. In other industries — the paper, plastics and food industries, for example — workers can come into contact with endocrine disruptors. There is no data available about exposure of this kind in the Netherlands.

Home and living environment

There can also be exposure to endocrine disruptors in the home and living environment. Examples are the use of pesticides in gardens and allotments, direct hand-to-mouth contact with polluted soil (children) and exposure to PAHs in traffic. There can be indirect exposure via the pollution of surface water and groundwater by waste water from homes and industry (Kiwa97).

Other types of exposure to endocrine disruptors

The Committee will limit itself here to stating one important example: the use of doping in sport. 35,000 practitioners of sports which mainly test physical strength or

appearance (e.g. body-building) aged between 18 and 35 use substances of this kind (Boe96, CBS96,)

Conclusion

The degree of exposure to endocrine disruptors via food depends very much on eating habits. Here, it is not only the amounts consumed which are of importance but also the nature and composition of the food. The persistent lipophilic environmental contaminants are concentrated mainly in the fat of foods such as milk, dairy products, meat and fish. In terms of the answers to the questions put to the Committee, it is important to know whether eating habits in the Netherlands are so different from those in surrounding countries that the degree of exposure to endocrine disruptors via food is higher there than elsewhere. Table 5 (annex E) gives for that reason an overview of the average consumption of different types of food per capita of the population in the member states of the European Union. The table shows that the Netherlands is average in terms of eating habits in the European Union. One could conclude from this that the Netherlands will also not be exceptional in any positive or negative sense in terms of the intake of endocrine disruptors. The Committee would also wish to point out that table 5 also indicates that eating habits can vary considerably from region to region, while little or nothing is known about geographical variations in concentrations of endocrine disruptors in food.

In order to establish an overall picture, it would be helpful to classify the various substances in one way or another under a single denominator. Safe has proposed a conversion into oestrogen equivalents (Saf94). The Committee finds this approach too limited because it is based solely on intake and does not take into account all the stages of hormonal regulation. In addition, it is quite feasible that interactions between endocrine disruptors play a role when there is combined exposure (Arn96, Sim96). Safe does not take this into account. In general, exposure to different endocrine disruptors is difficult to compare since each substance undergoes a different metabolic process. That also means that predictions about the effects of endocrine disruptors cannot be made on the basis of information about other substances — contraceptives, for example — when nothing is known about the exposure-effect relationship.

The conclusion of the Committee is that there is a reasonable level of qualitative understanding of exposure of the Dutch population to endocrine disruptors. However, quantitative information is scarce.

3.2 Effect studies

There have been two studies in the Netherlands into the effect of exposure to particular endocrine disruptors on human reproduction and development, one with infants and one with workers in fruit farming.

Infant study

A study has been conducted into the effect on Dutch infants of exposure to dioxins and dioxin-like PCBs via breast milk. The study concentrated on the neurological and psychomotor development of young children. It found minor effects on the results of neurological and psychomotor tests which depended on the age of the child. The tests covered neonatal responses, muscle tone, spontaneous posture and motor function as well as mental and behavioural functions. Even after corrections were made for a range of interfering variables, there was still an effect resulting from exposure to dioxins or dioxin-like PCBs via breast milk (Bro95, Hui95a, Hui95b, Koo96). Prenatal and post-natal exposure were negatively correlated in this study to test scores at two months. At eighteen months, a link of this kind was only found for prenatal exposure. For more details about this study such as the effects on plasma levels of thyroid hormone of dioxins and dioxin-like compounds via breast milk, the reader is referred to the Health Council advisory report entitled ‘Dioxins’ (GR96).

Worker study*

In a study of fruit farmers in the Netherlands, the influence was studied of exposure to pesticides on offspring. The researchers used the variables ‘time to pregnancy’** and ‘sex ratio in offspring’. The results suggest that exposure at work to pesticides results in an increase in ‘time to pregnancy’ and a shift in the sex ratio to more female offspring (Coc94). However, taken in combination with foreign studies, the results fail to produce a consistent picture, in part because of methodological shortcomings in the various studies. The results also do little to increase our understanding of the role of exposure to endocrine disruptors. Nothing is known, for example, about the degree of internal exposure. In addition, it is not known whether other factors are involved (and,

* Many studies are currently under way into exposure at work to endocrine disruptors and the effects. For example, some years ago, the European Asclepios project began. One of the areas it covers is sperm quality among workers in the polyester-processing industry and the agrarian sector in EU member states (including the Netherlands).

** ‘Time to pregnancy’ is used in epidemiological research in order to determine the effects of exposure on fertility. It is the period between the decision to have children and conception.

if so, how) or which of the pesticidess may play a causal role or whether the effects result from an interaction with hormone actions.

Conclusion

The Committee notes that there is some Dutch data about exposure-effect relationships. The infant study showed that exposure to dioxins and dioxin-like PCBs could influence neurological and psychomotor development. The results of the study of fruit farmers suggest that exposure to pesticides at work results in an increase of the time to pregnancy and a change in the sex ratio. However, this study does not provide any information about the nature or extent of exposure and, in the opinion of the Committee, other factors may have resulted in the effects observed. More studies have been started in the meantime.

Chapter 4

Hormone-related illnesses and disorders in the Netherlands

Observed changes in reproduction and development may, in the opinion of the Committee, provide a direction for research into causal factors. In this chapter, the Committee discusses the Dutch data about illnesses and disorders associated with disturbed reproductive and developmental functions, including data about birth parameters.

4.1 General

Table 6 in annex F provides a list of reports in the international literature about changes in time in the incidence rates of illnesses and disorders associated with reproduction and development. Table 7 in annex F provides a list of Dutch reports on these changes.

Cancer registration is centrally coordinated and standardized in the Netherlands. Additional data can be found in a variety of locations about premature birth, birth weight, sex ratio at the time of birth and about children with behavioral disorders and psychosocial problems. There is no data available about sperm concentration and quality of adults or about sexual organ defects at birth.

4.2 Cancer

The Committee would expect the possible adverse effect of exposure to endocrine disruptors to become manifest after 10 to 20 years as an increase in the incidence of hormone-related forms of cancer. Some nuance is in order. Indications have been

found of a negative effect of exposure to endocrine disruptors on the incidence of breast and prostate cancer (Cow93, Lee91). The time-lag between exposure and effect implies that present day trends in cancer incidence do not provide information on factors which have only recently gained in importance.

There has been national registration of cancer in the Netherlands since 1989. Figures are now available for the period 1989 to 1993 inclusive (NCR96). This period of five years is too short as a basis for conclusions about changes in cancer incidence rates. In the Eindhoven region, there has been cancer registration since 1955 and this is therefore the only source at present of figures for determining trends in cancer incidence (ECR95).

The Committee considers the following forms of cancer to be affected by disturbances in hormonal regulation: breast cancer, testicular cancer, prostate cancer, thyroid cancer, adrenal cancer, endometrial cancer and clear-cell carcinoma in the cervix or vagina. These are tumours in the sexual organs or in organs which play an important role in human reproduction and development. The Committee will now discuss the available data about the incidence rates of these forms of cancer in the Netherlands.

Breast cancer: The incidence of breast cancer among women increased between 1989 and 1993 from 100 per 100,000 (10^5) in 1989 to 118 per 10^5 in 1993. During this period, the number of deaths resulting from breast cancer fluctuated around 39 per 10^5 women a year (NCR96). Breast cancer incidence in males between 1989 and 1992 was between 0.6 and 0.8 per 10^5 a year. Death from breast cancer in men during that period remained stable and was approximately 0,3 per 10^5 a year (NCR96). The register for the Eindhoven region shows that the incidence of breast cancer in women in the period 1988-1992 had doubled in all age categories compared to the period 1958-1962 (annex F, table 8). The rate of the increase in the incidence rate is lower for women born after 1949 than for women born before then (ECR95, Nab94). Mortality in the Eindhoven region remained virtually unchanged.

Testicular cancer: Testicular cancer is relatively rare in the Netherlands. The incidence rate increased slightly in the period 1989-1993 from 4.2 per 10^5 men in 1989 to 4.7 per 10^5 men in 1993. Deaths from testicular cancer remained stable during this period at approximately 0.4 per 10^5 men a year (NCR96). Cancer registration in the Eindhoven region shows a slight increase in the incidence of testicular cancer in the period 1958-1992 (annex F, table 9). This increase was found in seminoma and non-seminoma in the 15-29 age group (ECR95).

Prostate cancer: During 1989-1993, the national incidence of prostate cancer increased from 62 per 10^5 men in 1989 to 76 per 10^5 men in 1993. This increase was found in all age categories. It is striking that the incidence rate in young men increased and that this was accompanied by a worsening of the prognosis, possibly because of the occurrence of more poorly-differentiated tumours (Coe97). Mortality remained constant during this period (approximately 32 per 10^5 men a year) (NCR96). The data from the Eindhoven Cancer Registry also shows an increase in prostate cancer (annex F, table 10) (ECR95).

*Endometrial cancer**: The national incidence of endometrial cancer between 1989 and 1993 was stable at 15 to 16 per 10^5 women a year (NCR96). Mortality also remained stable during the same period at approximately 4 per 10^5 women a year (NCR96). The data from Eindhoven in table 11 (annex F) supports this picture (ECR95).

Thyroid cancer: There has been little change on the national level between 1989 and 1993 in the incidence of thyroid cancer (NCR96). The incidence rate for men varied between 1.0 and 1.4 and the rate for women between 2.4 and 3.0 per 10^5 a year. Mortality remained constant during this period (approximately 0.7 per 10^5 a year for women and 0.4 per 10^5 a year for men). The data for Eindhoven presented in table 12 in annex F shows that incidence has been low since 1958 fluctuating at about 0.7 per 10^5 person-years (ECR95). Incidence is lower in men than in women.

Adrenal cancer: The incidence of this extremely rare form of cancer remained virtually unchanged during the registration period both in the Eindhoven region and in the Netherlands as a whole.

Clear-cell carcinoma in the cervix or vagina: The national incidence of clear-cell carcinoma in the period 1989-1993 was quite stable (annex F, table 13, see NCR96). It varied between 0,7 and 1,6 per 10^5 person-years for clear-cell carcinoma in the cervix and between 0,1 and 0,5 per 10^5 person-years for clear-cell carcinoma in the vagina. Approximately 60% of these clear-cell carcinomas occurred in DES daughters (Han91). In the Eindhoven region, there have been no noteworthy changes in the incidence rate since 1970.

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* Endometrium: the mucous membrane lining the uterus.

Assessment

The data from the cancer register in Eindhoven indicates an increase in the incidence of testicular, breast, and prostate cancer between 1958 and 1992. It is not known to what extent these trends are representative for the Netherlands as a whole. As stated, national cancer registration has not been in place long enough to justify any conclusion about changes in incidence over time. However, surrounding countries have found trends in cancer incidence rates which correspond to the Eindhoven findings (MRC95).

The Committee believes that the increase in the number of registered cases of cancer — such as prostate cancer in older men and breast cancer in women — should in all probability be seen as the result of improved diagnosis and screening. In other words, it is doubtful whether these illnesses are actually more common. Most of the increase in prostate cancer can be explained by the more widespread use of diagnostic tests such as those for prostate-specific antigen (PSA test). The observed increase in the incidence of breast cancer is, in part, caused by the extension in 1990 of the national screening programme for breast cancer to women aged between 50 and 70.

The Committee believes that the increase in the incidence of prostate and testicular cancer among younger men is a genuine phenomenon. In practice, young men receive relatively little attention from urologists. The Committee does not therefore believe that it is plausible in this case that earlier detection is one of the causes of the observed increase in the number of cases of cancer among young men.

In addition to improved detection, a number of other factors may account for the increase in the number of registered cases of cancer. The increase in the age at which women have their first child, low numbers of children and the length of the period of breast-feeding are risk factors for breast cancer. It is possible that the increased access to health care in the Netherlands is one of the causes of improved detection.

4.3 Birth data

Since 1983, the incidence of severe forms of premature birth* has increased from 0.63% in 1983 (Ver83) to 0.77% in 1993 (WBC97). The incidence of the severe form of low birth weight (less than 1,500 grams) has increased during that period from 0.68% (Ver83) to 0.73% (WBC97).

As in Denmark (Mol96), there has been a very slight alteration in the sex ratio in the Netherlands at birth since the Second World War. Data from Statistics Netherlands shows that the proportion of boys has dropped from 0.516 in 1950 to 0.513 in 1994 and has now virtually dropped back to the pre-war level (Pal97, Bro97).

* less than 7 months (32 weeks) pregnancy

Assessment

The increased incidence of premature births and the increased number of babies with low birth weight can partly be explained by reference to changes in obstetric* policy. The improved chance of survival of babies born prematurely or with a low birth weight means that gynaecologists will tend to intervene selectively earlier by, for example, carrying out a Caesarean operation or inducing birth prematurely. In the National Midwifery Registration, the number of Caesarean operations before the 32nd week of pregnancy has increased from 14.4% in 1989 to 17.7% in 1993 (SIG96). Other factors, such as the increased age at which women bear their first child, the increase in fertility treatments and the use DES (Bui93a) may partly explain the increased incidence of premature birth (Bui93b)

4.4 Behavioural disorders

The number of pupils in schools for special education increased considerably in the Netherlands until the beginning of the nineties (Orl90). In recent years, there appears to have been a stabilization. There was a drop in the number of pupils in special education in the 1996-1997 academic year which is explained by current government policy directed towards keeping children with special educational needs in normal schools. Foreign studies have found slight indications of an increase in behavioural disorders and emotional problems (Pro96). Dutch studies were unable to confirm these findings (Ver96, Ver97). Nor does Attention-Deficit Hyperactivity Disorder** seem to occur more than it used to be in the Netherlands (Gun96).

Assessment

The Committee considers it difficult to state causes for any possible increase in the incidence of behavioural disorders. For example, differences in opinion about what constitutes a disorder play a role here, as do changes in the tolerance of deviant behaviour at school and in society as a whole.

4.5 Sperm quality

A report by Carlsen *et al.* (Car92) suggested a possible global decrease in sperm concentration. The authors conducted a meta-analysis of 61 studies involving 14,947

* Obstetrics: midwifery.

** ADHD: hyper-activity in children, lack of attention, easily distracted, irritability, impulsiveness, low frustration tolerance, poor school performance, sleep disorders.

men from 23 different countries. They found that sperm concentration had dropped from $113x10^6$ spermatozoa per millilitre of ejaculate in 1940 to $66x10^6$ spermatozoa per millilitre in 1990. However, there has been a great deal of criticism of this analysis in scientific circles.

There is no central registration in the Netherlands of data from standardized studies relating to sperm concentration and quality. Data is available from other countries. Sperm concentration in Toulouse (France) has remained stable (Buj96) but it has dropped over time in Paris (Aug95). In Finland, sperm concentrations increased (Suo93) while remaining stable in Belgium (Wae96) and the United States (Fis96) and decreasing in the United Kingdom (Irv96). Cf. annex F, table 6.

Assessment

The Committee is of the opinion that it is difficult, if not impossible, to make general statements about changes in sperm concentration and quality over time. A major problem is that the reproducibility of sperm studies is generally low. For example, a national quality control study using one sample of sperm resulted in a variation coefficient of 70% for the sperm concentration measured in 70 different laboratories (Web96). Because some laboratories are not sufficiently strict in their observation of the WHO guidelines for determining sperm concentration and quality, it is often impossible to compare research results.

Even if trends in certain areas prove to be a reflection of reality, then it is impossible, without further research, to state the cause of the observed changes. In addition to the possibility of substances in the environment, other factors such as stress and testicular temperature can also influence sperm concentration and quality.

4.6 Sexual organ defects at birth

Changes in the prevalence of cryptorchidism, hypospadias and epispadias are difficult to establish because incidence data are not centrally registered in the Netherlands and diagnostic examination is not standardized. The diagnosis of cryptorchidism depends very much on the environment (temperature of the room in which the examination takes place) and the doctor. In addition, the distinction between hypospadias and epispadias is often not made, with both being described as hypospadias.

Chapter 5

Conclusions and recommendations

5.1 Answer to the questions posed

Many factors can exert an influence on hormonal regulation and, as a result, affect reproduction and development. Exposure to endocrine disruptors is one of the possible factors. It is biologically plausible that these substances can have an effect on reproduction and development. Studies of animals in the wild, as well as of laboratory animals and people who have accidentally been subjected to high exposure levels, have yielded results pointing in that direction.

However, it is not an easy matter to determine whether — and, if so, to what extent — there is a threat to public health in the Netherlands as the result of exposure to endocrine disruptors. The sparse research data allows for no unambiguous conclusion. There is no doubt that there is exposure to these substances but the extent of exposure can only be partially determined. In the Netherlands, exposure to dioxins, PCBs and pesticides via food is documented best. Data about exposure to other endocrine disruptors and exposure via other routes is too summary to facilitate exposure estimates. An exception to this is the ‘voluntary’ exposure to hormonal contraceptives and menopausal hormone replacement.

There are ways in which endocrine disruptors can affect bodily processes. Endocrine disruptors are often lipophilic compounds which can accumulate in the body and affect health over time, possibly acting in combination. That effects on health cannot be excluded is clearly shown by the consequences of iatrogenic exposure to DES: clear-cell carcinomas in the cervix or vagina in female offspring of the women

exposed during pregnancy. A second example in the Netherlands is exposure of babies via breast feeding to dioxins and PCBs with a dioxin-like action.

Indications of a threat to public health from endocrine disruptors might be found in an increase in hormone-related illnesses and in changes for the worse in health characteristics associated with reproduction and development. The Committee has made a meticulous examination of the data available in the Netherlands (chapter 4). It can find no indications in the data about cancer, behavioural disorders and births that there have been negative developments in these illnesses or any increase in incidence rates. Exceptions are the increases in the incidence of prostate and testicular cancer in young men and breast cancer in women. However, there has been no research which can clarify the causes of those increases. It cannot therefore be stated whether exposure to endocrine disruptors plays a role in this respect.

The President of the Health Council asked the Committee 'whether there was cause for concern about the influence of endocrine disruptors on human reproduction and development, particularly in the Netherlands'. The Committee's answer is that there are no indications that exposure to endocrine disruptors constitutes a direct, acute threat to public health. However, the entire population of the Netherlands is exposed to substances of this kind and effects on reproduction and development are, albeit possibly subtle, biologically plausible. The Committee is therefore of the opinion that the possible effect of endocrine disruptors on health merits serious attention. Given the gaps in knowledge and the lack of data this view leads to the advice to support specific research into the risks of endocrine disruptors for public health. Since the Netherlands does not occupy an unusual position in terms of exposure to endocrine disruptors and sensitivity to them, considerations of efficiency mean that internationally-coordinated research is preferable.

5.2 Recommendations for research

The conclusions of the Committee imply that there is every reason to seriously monitor the exposure to endocrine disruptors. It cannot be stated without further research which substances pose the greatest risk for endocrine disruptive acton and by which mechanism, which substances qualify for restrictive measures first, what the minimum restriction of exposure to those substances should be and how this can be achieved most effectively. Below the Committee lists research subjects; however, the list should not be considered to be a complete research programme. The subjects are either of special importance for the Netherlands, or do fit in ongoing Dutch research programmes.

Substances

The Committee recommends a coordinated approach for tracing substances with endocrine disruptive properties. This should cover both new substances and substances which are already on the market ('existing chemicals') and natural substances. The following are required for this purpose:

- the further development of *in vitro* screening methods for the tracing of endocrine disruptors in the environment and food
- stimulating research with laboratory animals in order to allow for more well-founded appraisals of the endocrine-disruptive effects of a substance
- the establishment of relationships between the structure and the endocrine disruptive activities of substances (both qualitative and quantitative structure-activity relationships) in order to be able to predict endocrine-disruptive effects.

Exposure

The Committee recommends the encouragement of research in order to establish a picture of the exposure of population groups to endocrine disruptors via food and drinking water. It is possible that the periodical food consumption survey may be of significance in this respect. In addition to the above mentioned *in vitro* screening methods, the development of methods for determining the concentration of endocrine disruptors or the hormonal activity in biological samples (*inter alia* biomarkers) is necessary, to obtain a greater understanding of internal exposure of humans.

Effects

Although data on humans (experiments with volunteers and epidemiological studies) are of prime importance, the Committee is of the opinion that these data should be supplemented with information from animal experiments, in order to arrive at a definitive appraisal of the effects of substances on reproduction and development. It believes that, in this context, the following research efforts are required:

- the development of *in vivo* measuring methods for quantifying hormone-related effects on reproduction and development.

The discussion about the possible influence of endocrine disruptors on health is in part the result of observed or putative trends in disorders and health characteristics related to reproduction. That discussion would benefit from more understanding of the reliability of diagnoses and measurement methods. The Committee therefore

recommends to further the standardization of the diagnosis of cryptorchidism, hypospadias and epispadias and the introduction on a national and international scale a standardized method for determining sperm concentration and quality.

In addition, the Committee urges to improve the registration in the Netherlands of data about illnesses and disorders which may be, or which actually are, associated with disorders of the endocrine system. The Committee is particularly concerned about data relating to:

- cryptorchidism, epispadias and hypospadias, registered by infant health centres
- duration of pregnancy, birth weight and head size as part of the National Midwifery Registration
- fertility, registered by fertility clinics
- sperm concentration and quality.

An improved registration would offer opportunities for the analysis of trends in the incidence of the diseases and birth and fertility parameters referred to above. Furthermore, the Committee is of the opinion that it is possible to perform studies using existing cohorts in the Netherlands, as well as the monitoring of trends in the incidence of specific hormone-related tumours. The results of such studies would form a basis for further investigations into the effects of exposure to endocrine disruptors (*inter alia* chronic occupational exposure) and clarify the sensitive age period for such exposures (pregnancy and period shortly after birth).

It is not known what form is taken by the exposure-effect relationship for endocrine disruptors. This is particularly true of the exposure levels which occur in day-to-day life. Furthermore, there are doubts about the applicability of the ‘classic’ threshold model (which postulates that there is no effect on health below a certain threshold value). Also there are indications that the exposure-effect relationship does not have that traditional ‘S-shape’. In particular, the time of life at which exposure takes place would seem to be of major importance. In order to take into account the effects on hormonal regulation under discussion here in the risk assessment of substances, the Committee recommends the following:

- the encouragement of research into the development of methods for estimating the risks of endocrine disruptors
- epidemiological studies with groups at risk using biomarkers to characterize the exposure
- further research into effects in specific population groups in the Netherlands, such as people with relatively low or high exposure levels. Here, the Committee has in mind groups with high levels of exposure to pesticides (e.g. farmers) and groups with increased dietary exposure to phyto-oestrogens (vegetarians or vegans).

Given the potential importance of exposure to endocrine disruptors for public health and given the gaps in our knowledge, the Committee recommends that the scientific data will be periodically reviewed and evaluated.

Rijswijk, 10 April 1997
For the Committee,

signed

S Bosman-Hoefakker,	JH van Wijnen,
scientific secretary	chairman

Literature

Alb94 Alberman E. Prematurity: epidemiology, prevalence and outcome. In: Pless IB. The epidemiology of childhood disorders. New York: OUP, 1994.

Ald75 Aldyreva MV, Klimora TS, Izyumova AS, *et al.* The influence of phthalate plasticizers on the generative function. Gi Trud Prof Zool 1975; 12: 25-9.

Ara83 Arai Y, Mori T, Suzuki Y, *et al.* Long-term effects of perinatal exposure to sex steroids and diethylstilbestrol on the reproductive system of male mammals. Int Rev Cytol 1983; 84: 235-68.

Arn96 Arnold SF, Klotz DM, Collins BM, *et al.* Synergistic activation of estrogen receptor with combinations of environmental chemicals. Science 1996; 272: 1489-92.

Aug95 Auger J, Kunstmann JM, Czyglik F, *et al.* Decline in semen quality among fertile men in Paris during the past 20 years. N Engl J Med 1995; 332: 281-5.

BBC93 Horizon. Assault on the male. London: British Broadcasting Company, 1993.

Ber96 Bergström R, Adami HO, Möhner M, *et al.* Increase in testicular cancer incidence in six european countries: a birth cohort phenomenon. J Natl Cancer Inst 1996; 88: 727-33.

Ber93a Berkowitz GS, Lapinski RH, Dolgin SE, *et al.* Prevalence and natural history of cryptorchidism. Pediatrics 1993; 92: 44-9.

Ber93b Bertazzi PA, Pesatori AC, Consonni D, *et al.* Cancer incidence in a population accidentally exposed to 2,3,7,8-tetrachlorodibenzo-para-dioxin. Epidemiol 1993; 4: 398-406.

Boe96 de Boer A, van Haren SF, Hartgens F, *et al.* Praktijkpublicatie; Onderzoek naar het gebruik van prestatieverhogende middelen bij body-builders in Nederland. Rotterdam: Nederlands Centrum voor Dopingsvraagstukken (NECEDO), 1996.

Bou95 Bouwman CA, Fase KM, Ine DH, *et al.* Cytochrome P450 induction in rats after pre- and postnatal exposure to PCB#126, PCB#118, PCB153 or 2,3,4,7,8-PnCDF. Organohalogen Compounds 1995; 25: 39-44.

Bow89a Bowman RE, Schantz SL, Gross ML, *et al.* Behavioral effects in monkeys exposed to 2,3,7,8-TCDD transmitted maternally during gestation and for four months of nursing. Chemosphere 1989; 18: 235-42.

Bow89b Bowman RE, Schantz SL, Weerasinghe NCR. Chronic dietary intake of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) at 5 or 25 parts per trillion in the monkey: TCDD kinetics and dose-effect estimate of reproductive toxicity. Chemosphere 1989; 18: 243-52.

Bro97 van den Broek JM. Change in male proportion among newborn infants. Lancet 1997; 349:805.

Bro95 Brouwer A, Ahlborg UG, van den Berg M, *et al.* Functional aspects of developmental toxicity of polyhalogenated aromatic hydrocarbons in experimental animals and human infants. Eur J Pharmacol 1995; 293: 1-40.

Bru93 Brussaard JH, Schneijder P, van Aken AMMAM, *et al.* Dietary intake of food contaminants in the Netherlands. Input for TNO Total Diet Study 1988-1989 Part 1. Cadmium, lead, organochlorine compounds, nitrate and malathion. Zeist: TNO-Voeding, 1993; (Report V93.3567).

Bui93a Buitendijk SE, Verloove-Vanhorick SP, Beets G. Bijdrage van het DES-probleem aan het totaal aantal vroeggeboorten in Nederland. Ned Tijdschr Geneeskd 1993; 137: 1622-4.

Bui93b Buitendijk SE, Verloove-Vanhorick SP. Vroeggeboorten. In: Ruwaard D, Kramers PGN, red. Volksgezondheid Toekomst Verkenning. Den Haag: SDU uitgeverij, 1993: 486-489.

Buj96 Bujan L, Mansat A, Pontonnier F, *et al.* Time series analysis of sperm concentration in fertile men in Toulouse, France between 1977 and 1992. Br Med Journal 1996; 312: 471-2.

Bul88 Bull JJ, Gutzke WHN, Crews D. Sex reversal by estradiol in three reptilian orders. Gen Comp Endocrinol 1988; 70: 425-8.

Bus86 Bush B, Bennett A, Snow J. Polychlorinated biphenyl congeners, p,p'-DDE, and sperm function in humans. Arch Environ Contamin Toxicol 1986; 15: 333-41.

Car92 Carlsen E, Giwercman A, Keiding N, *et al.* Evidence for decreasing quality of semen during past 50 years. Br Med J 1992; 305: 609-13.

Cas93 Cassidy A, Bingham S, Setchell K. Biological effects of plant estrogens in premenopausal women. FASEB J 1993; 7: A866.

Cas94 Cassidy A, Bingham S, Setchell K. Biological effects of a diet of soy protein rich in isoflavones on the menstrual cycle of premenopausal women. Am J Clin Nutr 1994; 60: 333-40.

CBS96 Centraal Bureau voor de Statistiek, Statistisch Jaarboek 1996. Voorburg: CBS, 1997.

Che92 Chen YC, Guo YL, Hsu CC, *et al.* Cognitive development of Yu-cheng ("oil disease") children prenatally exposed to heat degraded PCBs. J Am Med Assoc 1992; 268: 3213-8.

Che94 Chen YC, Hsu CC. Effects of prenatal exposure to PCBs on the neurological function of children: A neuropsychological and neurophysiological study. Dev Med Child Neurol 1994; 36: 312-20.

Coc94 de Cock J, Westveer K, Heederik D, *et al.* Time to pregnancy and occupational exposure to pesticides in fruit growers in The Netherlands. Occup Environ Med 1994; 51: 693-9.

Coe97 Coebergh JWW. Personal communication, 1997.

Col96 Colborn T, Peterson Myers J, Dumanoski D. Our stolen future-Are we threatening our fertility, intelligence and survival? New York: Duton, 1996.

Cow93 Coward l, Barnes NC, Setchell KDR, *et al.* Genistein, daidzein, and their b-glycoside conjugates: antitumor isoflavones in soybean foods from American and Asian diets. J Agric Food Sci 1993; 41: 1961-7.

Des89 DeStefano F, Annest JL, Kresnow M, *et al.* Semen characteristics of Vietnam veterans. Reprod Toxicol 1989; 3: 165-73.

Dav94 Davis BJ, Maronpot RR, Heindel JJ. Di-(2-ethylhexyl) phthalate suppresses estradiol and ovulation in cycling rats. Toxicol Appl Pharmacol 1994; 128: 216-23.

ECE94 ECETOX. Assessment of non-occupational exposure to chemicals. Brussel: Ecotox, 1994; (Technical report no: 58).

ECR95 Eindhoven Cancer Registry. Cancer incidence and survival in the Southeast of the Netherlands 1955-1994. Eindhoven: Integraal Kanker Centrum Zuid, 1995.

Ege94 Egeland GM, Sweeney MH, Fingerhut MA, *et al.* Total serum testosterone and gonadotropins in workers exposed to dioxin. Am J Epidemiol 1994; 139: 272-281.

Egn80 Egnatz DG, Ott MG, Townsend JC, *et al.* DBCP and testicular effects in chemical workers: an epidemiological survey in Midland, Michigan. J Occup Med 1980; 22: 727-32.

Eld94 Eldridge JC, Fleenor-Heyser DG, Extrom PC, *et al.* Short-term effects of chlorotriazines on estrus in female Sprague-Dawley and Fischer 334 rats. J Toxicol Environ Health 1994; 43: 155-67.

Faw94 Fawell JK, Wilkinson MJ. Oestrogenic substances in water: a review. Aqua 1994; 43: 219-221.

Fei84 Fein GG, Jacobson JL, Jacobson SW, *et al.* Prenatal exposure to polychlorinated biphenyls: effect on birth size and gestational age. J Pediatr 1984; 105: 315-20.

Fis96 Fisch H, Goluboff ET, Olson JH, *et al.* Semen Analyses in 1,283 men from the United States over a 25-year period: no decline in quality. Fertil Steril 1996; 65: 1009-14.

Gar96 Garcia-Rodriguez J, Garcia-Martin M, Nogueras-Ocana M, *et al.* Exposure to pesticides and cryptorchidism: geographical evidence of a possible association. Environ Health Perspect 1996; 104: 1090-5.

Gil78 Gill WB, Schumacher GFB, Bibbo M. Genital and semen abnormalities in adults males two and one-half decades after in utero exposure to diethylstilbestrol. In: Herbst AL. Intrauterine exposure to diethylstilbestrol in the human. Chicago: American College of Obstetricians and Gynecologists, 1978: 53.

Gil79 Gill WB, Schumacher GFB, Bibbo M, *et al.* Association of diethylstilbestrol exposure in utero with cryptorchidism, testicular hypoplasia and semen abnormalities. J Urol 1979; 122: 36-9.

GR96 Health Council of the Netherlands: Committee on risk evaluation of substances. Dioxins. Rijswijk: Health Council of the Netherlands, 1996; publication no. 1996/10E.

Gra82 Gray LEJr. Neonatal chlordecone exposure alters behavioral sex differentiation in female hamsters. Neurotoxicology 1982; 3: 67-80.

Gra94 Gray LE, Ostby JS, Kelce WR. Developmental effects of an environmental antiandrogen: the fungicide vinclozolin alters sex differentiation of the male rat. Toxicol Appl Pharmacol 1994: 129: 46-52.

Gun96 Gunning WB. Personal communication, 1996.

Guo94 Guo YL, Lin CJ, Yao WJ, *et al.* Musculoskeletal changes in children prenatally exposed to polychlorinated biphenyls and related compounds (Yu-cheng children). Toxicol Environ Health 1994; 41: 83-93.

Guz82 Guzelian PS. Comparative toxicology of chlordecone (Kepone) in humans and experimental animals. Ann Rev Pharmacol Toxicol 1982; 22: 89-113.

Han91 Hanselaar AGJM, van Leusen NDM, Wilde PCM, *et al.* Clear cell adenocarcinoma of the vagina and baarmoederhals. Cancer 1991; 67: 1971-8.

Hsu89 Hsu CC, Chen YC, Soong WT, *et al.* A six-year follow up study of intellectual and behavioral development of Yucheng ("oil-disease") children: cross-sectional findings of the fourth year field work. Chin Psychiatr 1989; 3: 101-5.

Hen76 Henderson BE, Benton B, Cosgrove M, *et al.* Urogenital tract abnormalities in sons of women treated with diethylstilbestrol. Pediatrics 1976; 58: 505-7.

Hui95a Huisman M, Koopman-Esseboom C, Fidler V, *et al.* Perinatal exposure to polychlorinated biphneyls and dioxins and its effect on neonatal neurological development. Early Hum Dev 1995; 41: 111-27.

Hui95b Huisman M, Koopman-Esseboom C, Lanting CI, *et al.* Neurological condition in 18-month-old children perinatally exposed to polychlorinated biphenyls and dioxins. Early Hum Dev 1995; 43: 165-76.

Irv96 Irvine S, Cawood E, Richardson D, *et al.* Evidence of deteriorating semen quality in the United Kingdom: birth cohort study in 577 men in Scotland over 11 years. Br Med J 1996; 312: 467-71.

Jac85 Jacobson SW, Fein GG, Jacobson JL, *et al.* The effects of PCB exposure on visual recognition memory. Child Dev 1985; 56: 853-60.

Jac88 Jacobson JL, Jacobson SW. New methodologies for assessing the effects of prenatal toxic exposure on cognitive functioning in humans. In: Evans M. Toxic Contaminants and Ecosystem Health: A great Lakes Focus. New York: John Wiley and Sons, 1988: 374-88.

Jac90a Jacobson JL, Jacobson SW, Humphrey HEB. Effects of exposure to PCBs and related compounds on growth and activity in children. Neurotox Terat 1990; 12: 319-26.

Jac90b Jacobson JL, Jacobson SW, Humphrey HEB. Effects of in utero exposure to polychlorinated biphenyls and other contaminants on cognitive functioning in young children. J Pediatr 1990: 116; 38-45.

Jon89 Jones GRN. Polychlorinated biphenyls: where do we stand now? Lancet 1989; ii: 791-4.

Kav96 Kavlock RJ, Daston GP, DeRosa C, *et al.* Research needs for the risk assessment of health and environmental effects of endocrine disruptors: a report of the U.S. EPA-sponsored workshop. Environ Health Perspect 1996; 104: 715-40.

Kel95 Kelce WR, Stone CR, Laws SC, *et al.* Persistent DDT metabolite p,p' DDE is a potent androgen receptor antagonist. Nature 1995; 375: 581-5.

Key94 Key T, Reeves G. Organochlorines in the environment and breast cancer. Br Med J 1994; 308: 1520-1.

Kiwa97 van Dijk-Looijaard AM. Personal communication, 1997.

Koo94 Koopman-Esseboom C, Huisman M, Weisglas-Kuperus N, *et al.* Dioxin and PCB levels in blood amd human milk in relation to living areas in the Netherlands. Chemosphere 1994; 29: 2327-38.

Koo96 Koopman-Esseboom C, Weisglas-Kuperus N, de Ridder MAJ, *et al.* Effects of PCB/dioxin exposure and feeding type on the infants mental and psychomotor development. Pediatrics 1996; 97: 700-6.

Lee91 Lee HP, Gourley L, Duffy SW, *et al.* Dietary effect on breast cancer risk in Singapore. Lancet 1991; 337: 1197-200.

Lie96 Liem AKD, Ahlborg UG, Beck H, *et al.* Levels of PCBs, PCDDs and PCDFs in human milk. Results from the second round of a WHO-coordinated exposure study. Organohalogen Compounds 1996; 40: 268-73.

Lin88 Linn S, Lieberman E, Schoenbaum SC, *et al.* Adverse outcomes of pregnancy in women exposed to diethylstilbestrol in utero. J Reprod Med 1988; 33: 3-7.

Lio88 Lione A. Polychlorinated biphenyls and reproduction. Reprod Toxicol 1988; 2: 83-9.

Luc91 Lucier GW. Humans are a sensitive species to some of the biochemical effects of structural analogs of dioxin. Environ Toxicol Chemistry 1991; 10: 727-35.

Mab92 Mably TA, Bjerke DL, Moore RW, *et al.* In utero and lactational exposure of male rats to 2,3,7,8-Tetrachlorodibenzo-p-dioxin. Toxicol Appl Pharmacol 1992; 114: 118-26.

Mac79 MacLeod J, Wang Y. Male fertility potential in terms of semen quality: a review of the past, a study of the present. Fertil Steril 1979; 31: 103-16.

Mat85 Matlai P, Beral V. Trends in congenital malformations of external genitalia. Lancet 1985; i: 108.

MEE95 Ministry of Environment and Energy, Danish Environmental Protection Agency: Male reproductive health and environmental chemicals with estrogenic effects. Copenhagen: Ministry of Environment and Energy, 1995.

Moc96 Mocarelli P, Brambilla P, Gerthoux PM, *et al.* Change in sex ratio with exposure to dioxin. Lancet 1996; 348: 409.

Mol96 Moller H. Change in male:female ratio among newborn infants in Denmark. Lancet 1996; 348: 829.

MRC95 Medical Research Council Institute for Environment and Health, University of Leicester. IEH assessment on environmental oestrogens: consequences to human health and wildlife. Leicester: Institute for Environment and Health, 1995.

Mur79 Murray FJ, Smith FA, Nitschke KD, *et al.* Three-generation reproduction study of rats given 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the diet. Toxicol App Pharmacol 1979; 50: 241-52.

Nab94 Nab HW, Mulder PGH, Crommelin MA, *et al.* Is the peak in breast cancer incidence in Sight? A study conducted in the Southeastern Netherlands. Eur J Cancer 1994; 30A: 50-52.

NCR96 Netherlands Cancer Registry. Incidence of cancer in the Netherlands 1993. Utrecht: Vereniging van Integrale Kankercentra, 1996.

New87 Newbold RR, Bullock BC, McLachlan JA. Testicular tumors in mice exposed in utero to diethylstilbestrol. J Urol 1987; 138: 1446-50.

Odd94 Oddens BJ, Boulet MJ, Lehert P, *et al.* A study on the use of medication for climacteric complaints in Western Europe-II. Maturitas 1994; 19: 1-12.

Ols90 Olsen GW, Lanham JM, Bodner KM, *et al.* Determinants of spermatogenesis recovery among workers exposed to 1,2-dibromo-3-chloropropane. J Occup Med 1990; 32: 979-984.

Orl90 Orlebeke JF, Das-Smaal EA, Boomsma DI, *et al.* De groei van het speciaal onderwijs: een volksgezondheidsprobleem? Ned Tijdschr Geneeskd 1990; 134: 1315-19.

Paj97 Paj J, Laippala P, Penttila A, *et al.* Incidence of disorders of spermatogenesis in middle aged Finnish men, 1981-91: two necropsy series. Br Med J 1997; 314: 13-8.

Pal96 Palmlund I. Exposure to a xenoestrogen before birth: the diethylstilbestrol experience. J Psychosom Obstet Gynecol 1996; 17: 71-84.

Pal97 van der Pal-de Bruin KM, Verloove-Vanhorick SP, Roeleveld N. Change in male:female ratio among newborn babies in Netherlands. Lancet 1997; 349: 62.

Pau96 Paulsen CA, Berman NG, Wang C, *et al.* Data from men in greater Seattle area reveals no downward trend in semen quality: further evidence that deterioration of semen quality is not geographically uniform. Fertil Steril 1996; 65: 1015-20.

Pet93 Peterson RE, Theobald HM, Kimmel GL, *et al.* Developmental and reproductive toxicity of dioxins and related compunds: cross-species comparisons. Crit Rev Toxicol 1993; 23: 283-335.

Pow95 Power C. Children's physical development. In: Botting B. The health of our children. London: HMSO, 1995.

Pri85 Price KR, Fenwick GR. Naturally occurring oestrogens in foods-A review. Food Additives Contaminants 1985; 2: 73-106.

Pro96 Prosser J, McArdle P. The changing mental health of children and adolescents: evidence for a deterioration? Psychol Med 1996; 26: 715-25.

Rad79 Radmet M, Sonneborn M. Biologically active oestrogens in potable water and effluents. Forum Stadic Hygiene 1979; 30: 45-59.

Reij86 Reijnders PJH. Reproductive failure in common seals feeding on fish from polluted coastal waters. Nature 1986; 324: 456-7.

RIK96a van Klaveren JD, van Dooren-Flipsen MMH. Blootstelling van de Nderlandse bevolking aan dioxinen en planaire PCB's via de voeding. Wagenigen: RIKILT DLO, 1996; (report project no. 7071106)

RIK96b van Klaveren JD. Personal communication, 1996.

RIVM84 Vaessen HAMG. Gehalten aan polycyclische aromatische koolwaterstoffen van enkele levensmiddelen en duplicaten van 24-uurs voeding. Bilthoven: RIVM, 1984; (report no. 648203001).

RIVM88 Liem AKD, Marsman JA, Berkhoff CJ, *et al.* Polychloorbiphenylen in duplicaat 24-uurs voedingen. Bilthoven: RIVM, 1988; (report no. 388474008).

RIVM91a Liem AKD, Theelen RMC, Slob W, *et al.* Dioxinen en planaire PCB's in voeding. Gehalten in voedingsproducten en inname door de Nederlandse bevolking. Bilthoven: RIVM, 1991; (report no. 730501034).

RIVM91b Vermeire TG, van Apeldoorn ME, de Fouw JC, *et al.* Voorstel voor de humaan-toxicologische onderbouwing van C-(toetsings)waarden. Bilthoven: RIVM, 1991; (report no. 725201005).

RIVM94 Janus JA, Hesse JM, Rikken MGJ, *et al.* Aandachtstoffen in het Nederlandse Milieubeleid. Bilthoven: RIVM, 1994; (report no. 601014006).

RIVM96a Mennes W, Piersma AH. Volksgezondheidsaspecten van oestrogene stoffen in het milieu. Bilthoven: RIVM, 1996; (report no. 613320001).

RIVM96b Liem AKD, Theelen RMC, Hoogerbrugge R. Dioxinen en PCB's in voeding. Resultaten van aanvullend onderzoek. Bilthoven: RIVM, 1996; (report no. 639102.005).

Roe91 Roegner RH, Grubbs WD, Lustik MB *et al.* Air force health study: an epidemiologic investigation of health effects in air force personnel following exposure to herbicides. Serum dioxin analysis of 1987 examination results. Washington: NTIS, 1991; (NTIS# AD A-237-516 through AD A-237-524).

Rog87 Rogan WJ, Gladen BC, McKinney JD, *et al.* Polychlorinated biphenyls (PCBs) and dichlorodiphenyl dichloroethene (DDE) in human milk: effects on growth, morbidity, and duration of lactation. Am J Public Health 1987; 77: 1294-7.

Rog88 Rogan WJ, Gladen BC, Hung KL, *et al.* Congenital poisoning by polychlorinated biphenyls and their contaminants in Taiwan. Science 1988; 241: 334-6.

Rur79 Rurainski RD, Theiss HJ, Zimmermann W. The occurence of natural and synthetic oestrogens in drinking water. Gas-Wasserfach Wasser Abwasser 1979; 6: 288-291.

Saf94 Safe SH. Environmental and dietary estrogens and human health: Is there a problem? Environ Health Perspect 1995; 102: 346-51.

Sau94 Sauer PJJ, Huisman M, Koopman-Esseboom C, *et al.* Effects of polichlorinated biphenyls (PCBs) and dioxins on growth and development. Hum Exp Toxicol 1994; 13: 900-6.

Sch88 Schouten A. Polycyclische aromatische koolwaterstoffen in voeding. Zeist: TNO-Voeding, 1988; (report no. A88.507)

Sco64 Scorer CG. The descent of the testis. Arch Dis Childhood 1964; 39: 605-9.

Sha95 Sharpe RM, Fisher JS, Millar MM *et al.* Gestational and lactational exposure of rats to xenoestrogens results in reduced testicular size and sperm production. Environ Health Perspect 1995; 103: 1136-43.

Sho93 Shore LS, Gurevitz M, Shemesh M. Estrogen as an environmental pollutant. Bull Environ Contamin Toxicol 1993; 51: 361-366.

SIG96 SIG Zorginformatie. Verloskunde in Nederland. Grote lijnen 1989-1993. Utrecht: SIG, 1996.

Sim96 Simons SS Jr. Environmental estrogens: can two alrights make a wrong? Science 1996; 272: 1451.

Smi91 Smith AG. Chlorinated hydrocarbon insecticides. In: Hayes WJ, Laws ER. Handbook of pesticide toxicology. London: Academic Press, 1991; 2: 731-915.

Sta95 Staarink T, Kleter G, Visser G, *et al.* Bewakingsprogramma mens, voeding en milieu. Rijswijk: Ministerie VWS, 1995; (report no. 8).

Sti82 Stillman RJ. In utero exposure to diethylstilbestrol: adverse effects on the reproductive tract and reproductive performance in male and female offspring. Am J Obstet Gynecol 1982; 142: 905-21.

Suo93 Suominen J, Vierula M. Semen quality of Finnish men. Br Med J 1993; 306: 1579.

SZW93 Ministerie van Sociale Zaken en Werkgelegenheid: Health-based recommended occupational exposure limit for several phthalate esters. Den Haag: Arbeidsinspecties, 1993.

Tom81 Tomczak S, Baumann K, Lehnert G. Occupational exposure to hexachlorocyclohexane. IV Sex hormone alterations in HCH-exposed workers. Int Arch Occup Environ Health 1981; 48: 283-287.

Top96 Toppari J, Larsen JC, Christiansen P, *et al.* Male reproductive health and environmental xenoestrogens. Environ Health Perspect 1996; 104: 741-76.

Ver79 Verdeal K, Ryan DS. Naturally-occurring oestrogens in plant foodstuffs-a review. J Food Protection 1979; 7: 577-83.

Ver96 Verhulst FC. Hoe slecht gaat het met onze kinderen? Ned Tijdschr Geneeskd 1996; 140: 2384-7.

Ver97 Verhulst FC, van der Ende J, Rietbergen A. Ten-year time trends of psychopathology in dutch children and adolescents: no evidence for strong trends. Acta Psychiatrica Scandinavia; 1997, in press.

Ver83 Verloove-Vanhorick SP, Verwey RA. Ernstige vroeggeboorte in Nederland. Ned Tijdschr Geneeskd 1989; 133: 547-550.

Wae96 van Waeleghem K, de Clercq N, Vermeulen L, *et al.* Deterioration of sperm quality in young healthy Begian men. Human Reprod 1996; 11: 325-9.

Wam87 Wams FJ. Diethylhexylphthalate as an environmental contaminant. Science Total Environ 1987; 66: 1-16.

WBC97 WetenschappelijkeBegeleidingsCie Landelijke Neonatologie Registratie.Veranderde incidentie van vroeggeboorte in Nederland. Een verslag van de Landelijke Neonatologie Registratie. In press.

Web96 Weber RFA. Personal communication, 1996.

Wei95 Weisglas-Kuperus N, Sas TJC, Koopman-Esseboom C, *et al.* Immunological effects of background prenatal and postnatal exposure to dioxins and polychlorinated biphenyls in dutch infants. Pediatric Res 1995; 38: 404-10.

WHO89 World Health Organisation. Levels of PCBs, PCDDs and PCDFs in breast milk: results of WHO-coordinated interlaboratory quality control studies and analytical field studies. Copenhagen: WHO, regional Office for Europe, 1989; (EHC 34).

WHO91 World Health Organisation. Congenital malformations worldwide: a report from the international clearinghouse for birth defects monitoring systems. Oxford: Elsevier, 1991: 113-8.

WHO92 World Health Organisation. Diethylhexyl phthalate. Environ Health Crit 1992: 131; 141.

Zob95 Zober A, Hoffmann G, Ott MG, *et al.* Study of morbidity of personnel with potential exposure to vinclozolin. Occup Environ Med 1995; 52: 233-241.

Annexes

Annex **A**

Participants in the workshop on 25 June 1996

The following people were invited to the workshop on 25 June 1996. The names marked with * were interviewed beforehand.

- CJM Arts, medical biologist, TNO Food and Nutrition, Zeist*
- A Brouwer, toxicologist, Wageningen Agricultural University*
- W Bosman, food technologist/dietary specialist, Health Council, Rijswijk
- B van der Burg, developmental biologist, endocrinologist, Hubrecht Laboratory, Utrecht*
- JWW Coebergh, epidemiologist, Erasmus University, Rotterdam and Association of Integrated Cancer Centres, Utrecht*
- JHJ Copius Peereboom-Stegeman, toxicologist, University of Nijmegen*
- E Houthoff, toxicologist, representative of CEFIC-EMSF; AKZO Nobel, Amersfoort*
- HFP Joosten, reproduction toxicologist, Organon, Schaijk*
- professor SWJ Lamberts, clinical endocrinologist, Erasmus University, Rotterdam*
- F van Leeuwen, epidemiologist, Netherlands Cancer Research Institute, Amsterdam*
- FXR van Leeuwen, European Centre for Environment and Health, WHO, Bilthoven
- W Mennes, toxicologist, RIVM, Bilthoven
- professor PWJ Peters, teratologist, European Commission, Luxembourg*
- AH Piersma, reproduction toxicologist, RIVM, Bilthoven*

- N Roeleveld, epidemiologist, University of Nijmegen*
- PT van der Saag, developmental biologist, Hubrecht Laboratory, Utrecht*
- professor JJ Sixma, President of the Health Council of the Netherlands, Rijswijk
- RW Stephany, analytical chemist, RIVM, Bilthoven*
- professor ER te Velde, gynaecologist, Utrecht University Hospital
- N Vermeulen, molecular toxicologist, Free University of Amsterdam
- professor SP Verloove-Vanhorick, paediatrician, TNO Prevention and Health, Leiden*
- RFA Weber, andrologist/endocrinologist, Erasmus University, Rotterdam*
- JH van Wijnen, medical environmental scientist, Municipal Health Service, Amsterdam
- professor JW Wladimiroff, gynaecologist, Rotterdam University Hospital*
- JA van Zorge, advisor on human risks of environmental contaminants, Ministry of Housing, Spatial Planning and Environment, The Hague.

Annex **B**

The Committee

- JH van Wijnen, *chair*
  medical environmental scientist, Municipal Health Service, Amsterdam
- W Bosman, *observer*
  food technologist/dietary specialist, Health Council of the Netherlands, Rijswijk
- A Brouwer
  toxicologist, Wageningen Agricultural University
- JWW Coebergh
  epidemiologist, Erasmus University, Rotterdam and Association of Integrated Cancer Centres, Utrecht
- E Houthoff
  toxicologist, AKZO Nobel, Amersfoort
- N Roeleveld
  epidemiologist, University of Nijmegen
- SP Verloove-Vanhorick
  professor of preventive and curative health care for children, Leiden University and TNO Prevention and Health
- RFA Weber
  andrologist/endocrinologist, Erasmus University Rotterdam
- JA van Zorge, *advisor*
  advisor on human risks of environmental contaminants, Ministry of Housing, Spatial Planning and Environment, The Hague

- S Bosman-Hoefakker, *scientific secretary*
  toxicologist, Health Council of the Netherlands, Rijswijk
- WF Passchier, *scientific secretary from April 1, 1997*
  physical chemist, Health Council of the Netherlands, Rijswijk

The Committee received administrative assistance from E Vandenbussche-Parmeus, C Fortman and D van Bladel.

Annex C

Literature search

The Committee has not collected and appraised all the original literature about the present subject. In the forming of its opinion, it has based its work primarily on recent surveys from the National Institute of Public Health and Environmental (RIVM96), the Miljø-og Energiministeriet Miljøstyrelsen in Denmark (MEE95), the Medical Research Council in the United Kingdom (MRC95) and the Environmental Protection Agency in the United States (Kav96). The members of the Committee contributed scientific articles. The bibliography accompanying this report contains the publications selected by the Committee.

Annex **D**

Links between exposure to endocrine disruptors and effects on reproduction and development in humans and laboratory animals

In this appendix, the Committee provides a summary in table form of the publications about links between endocrine disruptors and effects on reproduction and development in humans and laboratory animals.

Table 1 Links between human and laboratory animal *in utero* exposure to endocrine disruptors and effects on reproduction and development.

suspected effect	species	substance	exposure	reference
development of the reproductive system in males				
sperm concentration and quality (morphology and motility)				
reduction of sperm concentration, motility and morphological abnormalities	man	DES	iatrogenic	Gil78, Pal96
reduction in sperm concentration, no morphological abnormalities	rat	PCBs	food	Bou95
reduction in production of spermatozoa per testis, no effect on morphology or motility	rat	dioxins	food	Mab92
reduction in sperm production	rat	phtalates	food	Sha95
reduction in sperm production	rat, hamster	dioxins	food	Bro95
reduction in sperm concentration and motility	rat/mouse	DES	food	Sti82, Lin88

suspected effect	species	substance	exposure	reference
cryptorchidism				
increase	man	DES	iatrogenic	Gil79, Hen76
increase	man	pesticides	food	Gar96[a]
increase	rat, mouse	DES	food	MEE95
hypospadias/epispadias				
increase	man	DES	iatrogenic	Gil79, Hen76
increase	rat	vinclozolin[b]	food	Gra94
increase	rat, mouse	DES	food	Ara83, New87, Bul88
feminization	rat, mouse, hamster	dioxinen	food	Bro95
testicular cancer				
increase	man	DES	iatrogenic	Pal96
increase	rat, mouse	DES	food	Ara83, New87, Bul88
development of reproductive system in females				
increase in clear-cell carcinoma in vagina/cervix	man	DES	iatrogenic	MRC95
masculinization	rat, mouse, hamster	dioxins	food	Bro95
development of the central nervous system				
neurological, cognitive and (sexual) behavioural disorders				
increase in neurological, cognitive, intellectual and behavioural disorders	man	dioxins, PCBs	food, accident (Yu-Cheng incident)	Rog88, Hsu89 Che92, Che94
increase in neurological and psychomotor development disorders	man	dioxins, PCBs	food (breast milk)	Hui95a,b, Koo94, Wei95, Sau94
poor learning performance and effects on social interactions	monkey	dioxins (TCDD)	food	Bow89a
reduction in head size	man	PCBs	food (fish)	Fei84, Jac85,88, 90a,b

suspected effect	species	substance	exposure	reference
general development				
reduction in duration of pregnancy	man	DES	iatrogenic	MRC95
	man	phtalates	work	Ald75
	man	dioxins, PCBs	food, accident (Yu-Cheng incident)	Luc91, Guo94
	rat	dioxins (TCDD)	food	Mur79
	monkey	dioxins (TCDD)	food	Bow89b
lower birth weight	man	dioxins, PCBs	food, accident (Yu-Cheng incident)	Luc91
	man	PCBs	food (vis)	Fei84, Jac85, 88, 90a,b
	seal	PCBs	food	Reij86
disturbed hormone metabolism	man	DES	iatrogenic	MRC95
	rat, mouse, hamster	dioxins, PCBs	food	Bro95, Pet93
	monkey	PCBs	food	Lio88
retarded growth	man	dioxins, PCBs	food, accident (Yu-Cheng incident)	Guo94
	monkey	PCBs	food	Jon89
change in sex ratio	man	vinclozolin[b]	work	Zob95
	man	mix of fungicides, herbicides and insecticides	work	Coc94
	man	dioxins	food, accident (Seveso incident)	Moc96

[a] ecological study

[b] pesticide

Table 2 Links between exposure of children, adults and laboratory animals to endocrine disruptors and effects on reproduction and development.

suspected effect	species	substance	exposure	reference
functioning of reproductive system from birth onwards in males				
sperm concentration and quality, spermatogenesis				
reduction in motility sperm and morphological abnormalities	man	chlordecon	work	Guz82
reduction in sperm concentration	man	DBCP[a]	work	Egn80
reduction in sperm concentration and morphology	man	DBCP[a]	work	Ols90
reduction in sperm concentration and morphology	man	TCDD[a]	work (US Air Force Vietnam)	Des89
reduction in motility sperm and morphological abnormalities	man	PCBs	food	Bus86
reduction in sperm concentration, no morphological abnormalities	rat	PCBs	food	Bou95
reduction in production of spermatozoa per testis, no effect on morphology and motility	rat	dioxins	food	Mab92
reduction in sperm production	rat	phtalates	food	Sha95
reduction in sperm production	rat, hamster	dioxins	food	Bro95
disturbed hormone levels	man	phtalates	work	Ald75
	man	DBCP[a]	work	Ols90
	man	vinclozolin[a]	work	Zob95
	man	β-hexachloro-cyclohexanes[a]	work	Tom81
	man	TCDD[a]	work	Ege94
	rat, muis, hamster	PCBs, dioxins	food	Bro95, Pet93
	rat	phtalates	food	WHO92
reduction in testis size/weight	man	dioxins	work (S Air Force Vietnam)	Roe91
	hamster	chlordecone[a]	food	Gra82
	rat	DDT[a]	food	Kel95
	rat	APEs	food	Sha95
functioning of reproductive system in females from birth onwards				
problems with breast-feeding (drop in duration of breast-feeding)	man	DDE[a]	work	Rog87
	muis	DDT[a]	food	Smi91

suspected effect	species	substance	exposure	reference
disturbed hormone levels, menstrual cycle or menopausal symptoms	man	phtalates	work	Ald75
	man	DBCP[a]	work	Egn80
	man	DBCP[a]	work	Ols90
	man	vinclozolin[a]	work	Zob95
	man	β-hexachloro-cyclohexanes[a]	work	Tom81
	man	TCDD[a]	work	Ege94
	man	phyto-oestrogens (zearalenone)	food	Ver79, Pri85
	man	isoflavones	food	Cas93,94
	rat	chlorotriazine[a]	food	Eld94
	rat	phtalates	food	Dav94
reproduction				
increase in time to pregnancy	man	pesticides	work	Coc94
hormone-related disorders				
tumours				
increase in breast cancer in females	man	DDT[a], PCBs	food	Key94
increase in endometrial cancer	man	dioxins	food, accident (Seveso incident)	Ber93b

[a] pesticide

Table 3 Links between exposure *in utero* and exposure of children and adults to endocrine disruptors and effects on reproduction and development in the Netherlands.

suspected effect	substance	exposure	reference
effects after in utero exposure			
increase in neurological and psychomotor development disorders	dioxins, PCBs	food (breast milk)	Hui95a,b, Koo94, Wei95, Sau94
change in sex ratio	pesticides	work	Coc94
effects after exposure of children and adults			
increase in time to pregnancy	pesticides	work	Coc94

Annex **E**

Exposure data

Table 4 contains data about exposure to endocrine disruptors in the Netherlands. Table 5 contains information about the consumption of various categories of food in the EU.

Table 4 Data about the intake of endocrine disruptors via food by the population of the Netherlands as a whole.

substance	type of study	average intake	reference
classic PCBs (28, 53, 101, 118, 138, 153, 180)	'market-basket' study 1988/'89	0.5 µg/day	Bru93
	24-hour duplicate study	0.1-0.3 µg/day	RIVM88
planar PCBs with dioxin action	levels in foods/ food consumption survey 1987/88	0.001 ngTEQ/kg/day[a], 14% drop[b]	RIVM91a, RIVM96b
	conversion model RIKILT DLO[c] based on food consumption survey 1987/88	119 pgTEQ/day	RIK96a
	ditto based on food consumption survey 1992	123 pgTEQ/day	RIK96a
dioxins (PCDD, PCDF)	levels in foods/ food consumption survey 1987/88	0.001ngTEQ/kg/day[a], 14% drop[b]	RIVM91a, RIVM96b
	conversion model RIKILT DLO based on food consumption survey 1987/88	78 pgTEQ/day	RIK96a
	ditto based on food consumption survey 1992	76 pgTEQ/day	RIK96a

substance	type of study	average intake	reference
organo-chlorine pesticides			
dieldrin, endosulfan, simazine, atrazine	24-hour duplicate study	< 1 µg/day in food (detection limit) < 3 ng/kg b.w./day in drinking water	RIVM91b, RIVM94
HCH, vinclozolin, mirex, methoxychlor, toxaphene		no intake data available	
DDT	'market-basket' study 1988/'89	1 µg/day	Bru93
	food consumption study based on data from 1985-1990	0.7 µg/day	RIK96b
HCB	'market-basket' study 1988/'89	0.2 µg/day	Bru93
malathion	'market-basket' study 1988/89	1 µg/day	Bru93
PAHs	'market-basket' study 1984-1986 (18 year-old males)	5.4 µg/day	Sch88
	24-hour duplicate study (1976-1978)	10.6 µg/day	RIVM84
phtalates, phenols, phyto-oestrogens		no intake data available	

[a] Intake stated as median

[b] With later fish-oil data

[c] This model reduces foods to their raw materials. For the estimation of the burden, food consumption data is used as collected in the periodical national food consumption surveys in conjunction with data relating to trace substances found in the raw materials (primary products) of the foods in question.

Table 5 Average consumption of foods per capita in 1992 in the European Union on the basis of national food balance sheets[a]; Netherlands = 100 (ECE94).

food	EU	Bel-gium	Den-mar k	France	Ger-many	Greece	Ire-land	Italy	Portu-gal	Spain	UK	min	max
meat	105	119	121	124	119	86	98	98	76	107	88	76	124
- beef & veal	111	122	100	167	122	100	100	144	67	56	89	56	167
- pork	86	105	150	82	136	46	73	68	55	100	55	46	150
- other	111	100	67	133	67	156	144	111	111	144	133	67	156
fish	100	100	400	80	60	60	120	100	240	200	40	40	400
milk & yoghurt	105	87	95	84	84	87	222	89	68	130	157	68	222
butter	100	200	150	200	200	0	150	50	0	0	100	0	200
cheese	100	86	86	157	114	143	43	114	29	43	57	29	157
vegetables & fruit	84	71	62	80	81	102	61	114	68	104	54	54	114
grain	157	134	126	137	134	197	194	217	169	131	160	100	217
potatoes	95	112	73	85	81	100	161	44	129	124	122	44	161

[a] A country's food balance sheet states the quantities of foods (raw materials) which are made available for consumption per person per day. The 'balance sheet method' is used to draw up the balance, *i.e.* consumption = production + import - export. No account is taken of losses which occur as a result of decay, broken packaging etc. during storage, transport, processing and in the home. A food balance sheet therefore actually gives an indication of the food *supply* (=*gross* use) rather than actual consumption (=food *eaten)* but it is at present the only source of data which is generated in the same way in all countries.

Annex **F**

Data about changes in illnesses and health characteristics associated with reproduction and development

Tables 6 and 7 list studies which report changes in time in the incidence of illnesses or disorders relating to reproduction and development. They also include changes in the health characteristics associated with reproduction and development. Tables 8, 9, 10, 11, 12 and 13 state cancer registration data. This data is taken from the Eindhoven Cancer Registry (tables 8 to 12 inclusive) (ECR95) and the Netherlands Cancer Registry (table 13).

Table 6 International reports about effects on human reproduction and development.

illness or health indicator	reference
development of the reproductive system in males	
sperm concentration and sperm quality, spermatogenesis	
reduction in sperm concentration	Car92, Aug95, Irv96
no change in sperm concentration, drop in sperm quality	Wae96
no change in sperm concentration or sperm quality	Mac79, Buj96, Fis96, Pau96
reduction in spermatogenesis	Paj97
cryptorchidism	
increasae	Sco64, MEE95
no change	Ber93a, MEE95

illness or health indicator	reference
hypospadias/epispadias	
increase	Mat85, WHO91
no effect	MRC95
testicular cancer	
increase	MRC95, MEE95, Ber96
development of the central nervous system	
neurological, cognitive and behavioural disorders (including sexual behaviour)	
increase in behavioural disorders and emotional problems	Pro96
general development	
shorter pregnancies	Pow95, Alb94
lower birth weight	Pow95, Alb94
change in sex ratio	Mol96, Pal97, Bro97
hormone-related disorders	
tumours	
increase in breast cancer in women	MRC95, MEE95
increase in breast cancer in men	MRC95, MEE95

Table 7 Dutch reports about effects on human reproduction and development.

disorder and finding	reference
development of the reproductive system in males	
increase in testicular cancer	NCR96, ECR95
development of the central nervous system:	
neurological, cognitive and behavioural disorders (including sexual behaviour)	
no effect	Gun96
no effect	Ver96,97
general development	
shorter pregnancies	WBC97
lower birth weight	WBC97
change in sex ratio	Pal97
hormone-related disorders:	
tumours	
increase in breast cancer in women	ECR95
increase in prostate cancer in young males	ECR95
increase in testicular cancer in young males	ECR95

Table 8 Incidence of breast cancer in the Eindhoven region per 10^5 person-years and according to age, and converted to incidence in the World Standard Population (WSP). N is the number of cases in the stated period.

period	women							men	
		age (years)							
	N	15-	30-	45-	60-	75+	WSP	N	WSP
1958-62[a]	231	1.2	36.3	89	150	180	37.1	3	0.51
1963-67[a]	285	1.1	33.6	104	162	182	39.9	3	0.25
1968-72[a]	656	2.8	52.2	152	173	257	54.3	7	0.55
1973-77	1,475	2.6	60.0	167	239	266	63.4	12	0.53
1978-82	1,776	2.4	61.8	171	245	296	65.4	13	0.54
1983-87	2,068	1.8	62.9	184	251	287	67.7	10	0.42
1988-92	2,288	2.0	66.4	188	262	352	71.2	17	0.54

[a] smaller registration area

Table 9 Incidence of testicular cancer in the Eindhoven region per 10^5 person-years and according to age, and converted to incidence in the World Standard Population (WSP). N is the number of cases in the stated period.

period		age (years)					
	N	15-	30-	45-	60-	75+	WSP
1958-62[a]	16	4.6	2.3	3.1	4.5	-	2.37
1963-67[a]	21	1.5	8.5	2.9	1.8	7.5	2.64
1968-72[a]	33	3.8	6.4	3.5	0.7	-	2.72
1973-77	61	2.9	5.8	3.2	3.4	-	2.63
1978-82	74	4.9	4.1	3.8	2.1	3.5	3.02
1983-87	89	5.3	5.3	4.2	1.3	3.2	3.02
1988-92	106	7.9	6.2	3.5	3.0	-	3.79

[a] smaller registration area

Table 10 Incidence of prostate cancer in the Eindhoven region per 10^5 person-years and according to age, and converted to incidence in the World Standard Population (WSP). N is the number of cases in the stated period.

period		age (years)				
	N	30-	45-	60-	75+	WSP
1958-62[a]	54	-	6.2	52	203	9.8
1963-67[a]	100	-	9.9	105	228	16.0
1968-72[a]	247	-	9.6	126	482	22.8
1973-77	525	-	11.3	141	504	24.0
1978-82	699	-	11.1	178	543	27.8
1983-87	809	0.4	12.7	176	558	28.9
1988-92	1,054	-	21.0	224	637	35.6

[a] smaller registration area

Table 11 Incidence of endometrial cancer in the Eindhoven region per 10^5 person-years and according to age, and converted to incidence in the World Standard Population (WSP). N is the number of cases in the stated period.

period		age (years)					
	N	15-	30-	45-	60-	75+	WSP
1958-62[a]	56	-	2.3	19.0	63.5	32.1	9.4
1963-67[a]	73	-	4.1	29.0	54.6	26.3	10.5
1968-72[a]	129	0.2	2.9	30.7	49.0	41.6	10.5
1973-77	233	-	3.0	31.9	46.0	35.5	10.1
1978-82	293	-	2.4	27.4	54.8	58.5	10.5
1983-87	345	-	2.6	32.3	53.3	55.2	11.2
1988-92	332	0.2	1.3	28.2	54.3	48.6	10.2

[a] smaller registration area

Table 12 Incidence of thyroid cancer in the Eindhoven region per 10^5 person-years and according to age, and converted to incidence in the World Standard Population (WSP). N is the number of cases in the stated period.

periode	men							women						
		age (years)							age (years)					
	N	15-	30-	45-	60-	75+	WSP	N	15-	30-	45-	60-	75+	WSP
1958-62[a]	5	-	0.7	1.0	6.7	-	1.02	5	0.6	-	2.0	-	15.2	0.88
1963-67[a]	2	-	0.6	-	-	7.4	0.24	12	1.1	0.7	2.8	9.7	-	1.66
1968-72[a]	9	1.0	0.3	0.4	0.7	2.7	0.46	25	1.9	4.4	3.4	5.4	2.1	2.25
1973-77	18	-	0.4	1.6	5.1	4.0	0.87	32	0.9	1.8	2.5	4.8	1.7	1.42
1978-82	24	0.9	0.9	1.3	2.5	5.6	0.93	46	1.5	1.6	2.2	8.0	2.6	1.80
1983-87	18	0.1	0.7	1.5	2.7	1.5	0.65	61	1.3	2.8	3.0	6.1	8.6	1.96
1988-92	23	0.5	1.2	2.1	1.3	1.5	0.80	57	2.0	3.1	2.2	4.8	5.7	1.88

[a] smaller registration area

Table 13 Incidence of clear-cell carcinoma in cervix or vagina in the Netherlands, 1989-1993, per 10^5 person-years and according to age, and converted to incidence in the World Standard Population (WSP). N is the number of cases in the stated period.

		age (years)															
	N	15-	20-	25-	30-	35-	40-	45-	50-	55-	60-	65-	70-	75-	80-	85+	WSP
cervix	49	0.8	1.0	1.3	1.0	0.7	-	1.3	1.5	2.2	2.3	2.9	2.1	5.9	2.3	5.9	0.9
vagina	10	-	0.7	0.9	0.3	0.3	0.3	-	0.5	-	-	-	-	-	-	1.5	0.2
total	59	0.8	1.6	2.2	1.3	1.0	0.3	1.3	2.0	2.2	2.3	2.9	2.1	5.9	2.3	7.4	1.1