HEAL
HEALTH AND ENVIRONMENT ALLIANCE

Science report

Chemical pollution and men's health:

A hidden crisis in Europe

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Preface

Environmental pollution is harmful to health – not only for the most vulnerable such as children, older people and pregnant women, but also for men. Having worked for two decades to protect people from the health impacts of pollution and the degradation of our planet, I have never been more concerned about the gap between the mounting evidence of harm and the lack of public policy action.

At HEAL, we have long championed protecting the health of those most vulnerable to chemical pollution and focused on prevention. Showcasing new science to achieve stronger evidence-based policies is at the core of HEAL's mission. Through our participation in the European research project FREIA, we exposed how endocrine disruptors harm female reproductive health. We worked with the International Federation of Gynecology and Obstetrics and the University of California to help pregnant women avoid reducing their exposure to harmful chemicals. We contributed to disseminating groundbreaking research like the EDC-MixRisk project, which revealed how our exposure to a cocktail of chemicals has been systematically underestimated, particularly for children.

Already in 2009, HEAL published evidence on how the decline in male reproductive health may be linked to exposure to chemicals. Today, a robust body of evidence on men's health demands even more urgent public attention and policy action. The trends are alarming:

- prostate cancer rates have climbed steadily over two decades, and now account for over 330,000 cases annually in the EU at a cost exceeding €9 billion in healthcare
- testicular cancer has risen continuously since the 1980s, especially among young men aged 15-44, with a projected 25% increase from 2014 levels
- male infertility affects up to one in 12 couples across Europe, and costs our societies €3-4.5 billion each year

THE COMMON THREAD LINKING THESE PATTERNS? CHEMICAL POLLUTION.

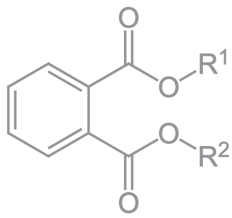
Every day, people across Europe are exposed to a cocktail of harmful substances: endocrine-disrupting chemicals in pesticides and plastics, per- and polyfluoroalkyl substances (PFAS), "forever chemicals" in water and everyday products, heavy metals like cadmium, and lead, microplastics now detected in human reproductive tissue, and industrial pollutants in the air we breathe. The male reproductive system—the testes, prostate, hormones, and sperm production—is particularly vulnerable to these exposures, especially during critical windows of development in the womb and throughout the reproductive years. There is mounting evidence of a transgenerational effect: The chemicals that men are exposed to today will likely harm the health of their future children.

Men's health is not about genetics alone, nor simply lifestyle choices. The impact of chemical pollution on men's health is considerable, and we have the tools to change course. Europe's Beating Cancer Plan can support cancer prevention through advancing health-protecting chemical policies. The European Union's Chemicals Strategy for Sustainability and the ongoing revision of REACH—the EU's flagship chemical regulation—offer a historic opportunity to reverse these trends. The REACH revision must be bold. It needs to reflect the reality that people are exposed to mixtures of chemicals, not one substance at a time. It must phase out the most harmful chemicals more swiftly, regulate substances as groups, and strengthen authorisation and restriction processes.

The scientific evidence is clear. The costs of chemical pollution—human and economic—are mounting. The solutions exist. What we need now is the political will to act.

This report is a call to action. For the health of men today and the generations to come, we cannot afford to wait.

Genon K. Jensen,
Executive Director,
Health and Environment Alliance (HEAL)



Executive summary

Chemical pollution is an escalating and underrecognised threat to human health — and men across Europe are facing unique and often overlooked risks. Mounting scientific evidence links exposure to harmful environmental chemicals—such as endocrine-disrupting chemicals (EDCs), persistent pollutants, and microplastics—to a range of serious male health outcomes, including prostate and testicular cancer, infertility, sexual dysfunction, hormonal imbalances, and impacts on descendants' health.

KEY MESSAGES

Men's health is increasingly compromised: **Prostate cancer has become the third most commonly diagnosed cancer in men in many EU countries, with an estimated 330,000 cases, constituting 12.1% of all cases.** Testicular cancer incidence is rising among younger men, particularly in Northern and Western Europe [age-standardised rate (ASR) of incidence 7.5 and 9.3 cases per 100.000 person-years, respectively]. **Male infertility is widespread, and sperm counts have declined by more than 50% globally in recent decades**—trends mirrored in Europe.

Chemicals are everywhere: People are exposed daily to EDCs and toxic substances through food, drinking water, air, personal care products, and occupational settings. Common culprits include phthalates (found in plastics), PFAS (in waterproof products, and as contaminers in other products, including food and drinking water), bisphenols (in food containers), and pesticides—many of which interfere with hormone systems and reproductive development.

Microplastics—tiny plastic particles from packaging, textiles, cosmetics and industrial processes—have been found in human blood, semen, and testicular tissue. Emerging studies suggest they may impair spermatogenesis, disrupt testosterone production, and induce inflammation and oxidative stress in reproductive organs. Some evidence also indicates that microplastics may cross the blood-brain barrier, raising concerns about potential impacts on brain health.

Health impacts extend to future generations: The consequences of chemical exposure are not limited to the directly exposed individual. Maternal exposure to EDCs has been linked to male reproductive disorders in offspring, including hypospadias, cryptorchidism, testicular cancer, and impaired fertility. Altered sperm epigenetics and high paternal exposure to air pollutants prior to conception—especially during the 15–69 day preconception window—have been associated with reduced birthweight, shorter gestation, and increased risk of fetal growth restriction. These findings highlight the urgent need for preventive measures that protect both prospective parents and their future children.

Europe is affected—and unevenly: Data from France, Germany, Italy, Poland, Sweden, and other countries show rising rates of male reproductive disorders. **Occupational exposures disproportionately impact low-income and industrial workers, while early-life exposures are increasingly linked to male health outcomes later in life.**

The cost is staggering: **The economic burden of male reproductive disorders associated with chemical exposure is estimated in €15 billion each year.** Healthcare costs, lost productivity, and long-term disability place significant pressure on national systems.

Policy reform is urgent and possible: The upcoming REACH revision is a historic opportunity to embed stronger health protections into European chemical regulation. A **health-centered REACH can help reduce exposure to harmful substances, improve health outcomes, and safeguard future generations. This ambition is also aligned with Europe's Beating Cancer Plan (EBCP), which recognises environmental and occupational exposures to harmful chemicals as key modifiable risk factors for cancer.** As the EBCP advances its implementation phase, this must entail full policy alignment between the EBCP, REACH, the EU's Chemicals Strategy for Sustainability, and the Zero Pollution Action Plan to truly deliver on the EU's commitment to reduce cancer incidence and protect health.

CALL TO ACTION

This briefing provides a synthesis of recent scientific findings and European data to support HEAL's contribution to the prevention of health outcomes associated with chemicals exposure, with a focus on men's health.

It calls on EU institutions, national representatives, and regulators to recognise the magnitude of the health impacts of chemical pollution and act decisively.

Protecting health against harmful chemicals requires political will, effective consideration of scientific evidence, stronger regulation, and a commitment to safer chemical policies across Europe.

1

Introduction: Men's health and chemicals

1. **Introduction:** Men's health and chemicals

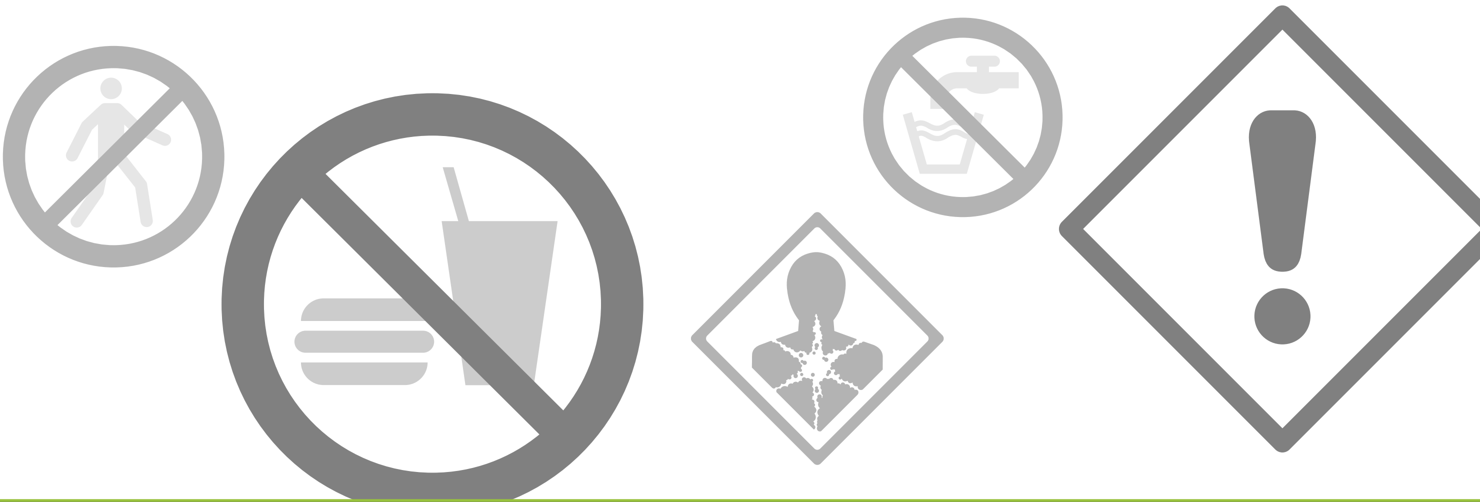
Concerns about the health impacts of chemicals have steadily increased over the past several decades. Men and women may be exposed differently (due to occupation, habits, or physiology), and their bodies may respond differently to chemical exposures[1].

In men, the testes, prostate, endocrine axis (hypothalamus-pituitary-gonadal), and spermatogenesis are uniquely sensitive to chemical insults—especially during early development and reproductive years[2-10]. Conditions like prostate and testicular cancer, infertility, testosterone deficiency, and sexual dysfunction are rising in prevalence. These are not only personal or familial issues—they are public health concerns with broad social, economic, and intergenerational implications.

While genetics and lifestyle factors contribute to health outcomes, a growing body of scientific evidence points to a powerful and often overlooked driver: **exposure to harmful chemicals in the environment.** Chemicals found in everyday consumer products, food packaging, drinking water, air, and occupational settings are linked to a range of male-specific health problems. These include substances that disrupt the endocrine system, damage DNA, impair reproductive function, or act as chronic irritants and inflammatory agents.

In this briefing, "sex" refers to the biological and physiological characteristics of females, males, and intersex individuals, while "gender" refers to socially constructed roles, norms, and behaviors associated with women, men, girls, and boys, which can influence exposure patterns and health outcomes.

Chemicals found in everyday consumer products, food packaging, drinking water, air, and occupational settings are linked to a range of male-specific health problems.



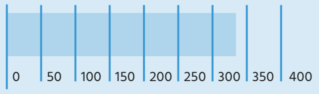
Men's health and chemicals

Prostate cancer[11,122]

3rd

most diagnosed cancer among men in the EU

330,000



Estimated cases annually

Constituting

12.1%

of all cancer cases diagnosed in men

European Commission data in the **European Cancer Information System** (ECIS)

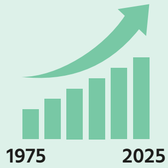
Male fertility[15-17]

Studies show a sharp drop in sperm counts across Europe and globally, with links to environmental exposures.

Sexual dysfunction[18]

Sexual dysfunction and testosterone deficiency (hypogonadism) are increasingly reported, with many cases of unclear etiology.

Testicular cancer[13,14]



Testicular cancer incidence increased significantly in recent decades

Particularly among young men aged

15–44

Health impacts[2-10, 19-24]

Health impacts extend to future generations, as exposures during prenatal development, and even before conception, are associated with reproductive and hormonal disorders in male offspring

Endocrine Disrupting Chemicals (EDCs) can alter the epigenetic profile of sperm cells, including DNA methylation and histone modifications.

These changes may affect the embryonic epigenome at conception, potentially increasing the susceptibility of offspring to a wide range of diseases — even in the absence of direct exposure

Such epigenetic reprogramming has been observed in both animal models and human studies, raising concern that today's chemical exposures may carry consequences not only for current health, but also for the long-term health of future generations

Chemical pollution as a key risk factor

Among the most concerning classes of chemicals are:

Endocrine-disrupting chemicals (EDCs), such as phthalates, bisphenols, and certain pesticides;

Per- and polyfluoroalkyl substances (PFAS), sometimes referred to as "forever chemicals"**;**

Heavy metals, such as cadmium and lead;

Microplastics, which have recently been detected in human reproductive tissue and may carry or leach toxic substances;

Industrial pollutants, including solvents and combustion byproducts.

These chemicals are increasingly found in biological samples—urine, semen, blood, adipose tissue—and accumulate in the body over time. Many are persistent, bioaccumulative, and toxic[25].

This science briefing focuses on the state of the evidence linking environmental chemicals to adverse **male health outcomes**, with an emphasis on **European data**. It is part of HEAL's contribution to increase awareness on the health impacts associated to chemicals exposure and the opportunities for preventing certain health outcomes with urgent improvement of chemicals regulation, including a **health-focused revision of REACH**, the EU's cornerstone chemical regulation.

2

Key chemicals of concern in the EU

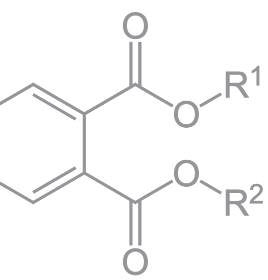
2. **Key chemicals of concern** in the EU

People in Europe are chronically and ubiquitously exposed to a wide array of environmental chemicals that can affect men's health, for example by interfering with hormonal systems, impairing fertility, damaging reproductive organs, and increasing the risk of hormone-dependent cancers[26].

The timing of exposure plays a critical role in the nature and severity of health outcomes[27]:

- **Prenatal exposures,** during critical windows of fetal development, can permanently alter the structure and function of the male reproductive system and contribute to conditions such as cryptorchidism (also known as undescended testicles), hypospadias (a condition related to the location of the urethral opening), and altered testicular function later in life.
- **Early postnatal and childhood exposures** can interfere with hormonal signaling pathways involved in growth, neurodevelopment, and the maturation of the endocrine system.
- **Adult exposures** are associated with reduced semen quality, testosterone disruption, erectile dysfunction (ED), metabolic disorders, and an increased risk of hormone-sensitive cancers such as prostate cancer.

Among the most studied and policy-relevant groups are **endocrine-disrupting chemicals (EDCs), persistent organic pollutants (POPs), per- and polyfluoroalkyl substances (PFAS), heavy metals, and microplastics.**



2.1 ENDOCRINE DISRUPTING CHEMICALS

EDCs interfere with the body's hormonal systems, particularly those regulating reproduction, development, metabolism, and behavior. In men, EDCs are linked to decreased testosterone levels, impaired sperm production, altered sexual development, and increased cancer risk[26].

Phthalates

Phthalates are used as plasticisers in PVC, cosmetics, food packaging, and medical devices. They are anti-androgenic, reducing testosterone synthesis and interfering with male sexual development.

- The EU-funded **DEMOCOPHES** biomonitoring study found phthalate metabolites in the urine of more than 4000 individuals (children and their mothers) across 17 EU countries, with widespread exposure above health-based guidance values[28-32].
- Phthalate exposure during prenatal life, in childhood and in adulthood is associated with **reduced semen quality**[35-38], **DNA fragmentation**[39], and **lower testosterone levels**[9,40-42], as shown in many EU Countries, such as Denmark, Sweden, Germany, Poland. .

Bisphenols (e.g., BPA, BPS, BPF)

Bisphenols are used in food containers, thermal paper, and consumer goods. BPA is an estrogenic compound linked to prostate and testicular dysfunction.

- The **HBM4EU project** (Human Biomonitoring for Europe) found that **up to 100% of participants in some countries had detectable BPA levels**, with many exceeding the EU's new tolerable daily intake[43].
- BPA exposure is associated with **reduced sperm concentration**[35,44], **altered motility, morphology**[45], and **altered testosterone**[9,46,47] levels in multiple EU cohort studies.

Pesticides

Numerous pesticides are known EDCs and reproductive toxicants.

- Adult occupational exposure to pesticides (organophosphate and carbamate insecticides) is linked to declines in sperm concentration, poorer semen quality, and reduced testosterone levels[47,48]. These findings are especially relevant for European agricultural workers, who face chronic low-level exposure through their occupation.
- Commonly used pesticides like **glyphosate** and **organophosphates** have been shown to disrupt the hypothalamic-pituitary-gonadal axis in animal models[50-52].

2.2 PER- AND POLYFLUOROALKYL SUBSTANCES

PFAS, also known as "forever chemicals" since their **extreme environmental persistence**[53], have been used in waterproof coatings, non-stick cookware, firefighting foams and pesticides for decades. Beyond their intended applications, these chemicals are now widely detected in the environment, as well as in food and drinking water. These substances are persistent, bioaccumulative, and toxic to the endocrine and reproductive systems.

- In the **Flemish Human Biomonitoring Campaign**, PFAS were detected in **over 95% of the population**, including children, adolescents, and adults of reproductive age, indicating widespread exposure across all demographic groups in Flanders[54].
- Several line of evidence found that **PFAS exposure was associated with delayed puberty**[55]**, reduced sperm quality and testosterone levels**[56,57] in young men.
- PFAS have also been linked to **altered Sertoli cell function** in animal studies[57]. Since Sertoli cells are essential for supporting and nurturing developing sperm cells, their dysfunction may impair spermatogenesis and ultimately reduce sperm count or quality, with potential long-term consequences for male fertility.

2.3 HEAVY METALS: CADMIUM, LEAD, MERCURY

Heavy metals are reproductive and endocrine toxicants that persist in the environment.

- Lead exposure, especially in occupational settings, is linked to **reduced sperm count, morphology**, and **altered epigenetics**, as confirmed in EU studies (UK, Italy, Spain) of battery and recycling workers[59-61].
- Cadmium accumulates in the testes and is associated with **reduced sperm concentration, total count, motility, morphology**[62,63].
- Mercury exposure, particularly through fish consumption, has been shown to **impair hormonal balance and fertility markers**[64].

2.4 MICROPLASTICS AND NANOPLASTICS

Microplastics (<5 mm) and nanoplastics (<100 nm) are increasingly detected in human tissues, including blood, placenta, lungs, feces[65]—and now, **reproductive organs**[66,67].

- Recent studies in Europe, the US, and China have confirmed the presence of microplastic particles in **100% of human testicular tissue** samples analysed, with findings suggesting a potential association between higher microplastic concentrations and **reduced sperm counts and testicular weight**[68-70].
- *In vitro* studies show that microplastics can **disrupt Sertoli cell function**[71-72] (related to sperm development), cause **oxidative stress**[73], and impair **testosterone synthesis**[74].
- Microplastics may also act as **carriers for EDCs** such as phthalates, bisphenols, and flame retardants, further compounding their toxicity[75-78].

EU-wide human biomonitoring of microplastics is still in its infancy, but pilot studies in Germany[79], the Netherlands[80] and Italy[81-83] have already detected them in human blood, placenta and urine, suggesting widespread systemic exposure.

2.5 COMBINED EXPOSURES AND MIXTURE EFFECTS

Real-world exposure is rarely to one chemical at a time. The **"cocktail effect"** of multiple substances acting simultaneously—even at low doses—can amplify toxicity. This is especially critical for the endocrine and reproductive systems, where additive or synergistic effects may occur.

- The **HBM4EU project**[84] has highlighted the importance of mixture risk assessment and called for stronger regulatory action[85] to account for cumulative exposures.
- Mixtures of phthalates, BPA, and PFAS have been shown to **synergistically reduce sperm production and testosterone**[86] in EU-based *in vitro* and *in vivo* studies[87].

CONCLUSION

People in Europe are exposed to a complex mix of harmful chemicals, many of which have known or suspected effects on male reproductive and hormonal health[86]. Regulatory attention to these substances—particularly in the context of the upcoming REACH revision, implementation of the Chemicals Strategy for Sustainability and review of Europe's Beating Cancer Plan—is both urgent and scientifically justified.

3

Health outcomes in men

3. **Health outcomes** in men

The male reproductive and endocrine systems are vulnerable to chemical insults. The testes, prostate, and hypothalamic-pituitary-gonadal (HPG) axis are highly sensitive to EDCs, and critical periods of development—such as fetal life, puberty, and reproductive age—can determine long-term health outcomes[2].

This section presents the key **male health outcomes** linked to chemical exposure, emphasising European findings and regulatory relevance.

3.1 PROSTATE CANCER

Prostate cancer is the **third most diagnosed cancer in men in the EU**. With an incidence of over 150 cases per 100,000 men and a mortality rate of 40 per 100,000, it accounts for up to 12% of all cancer cases in Europe[11,12]. While age and genetics are key factors, evidence suggests a **growing role for environmental and occupational exposures**, particularly to EDCs and persistent pollutants. Prostate tissue indeed expresses high levels of estrogen and androgen receptors, making it especially vulnerable to EDCs that mimic or block hormonal signaling.

Evidence

- Exposure to **PCBs, cadmium, and BPA** has been associated with increased proliferation of prostate cancer cells in in vitro and in vivo models[88-91].
- Occupational studies in France[91] and Italy[93] have linked pesticide exposure to **elevated prostate cancer risk**, especially among agricultural workers.
- A population-based study in Sweden[94] found that men with higher cumulative exposure to PFAS-contaminated drinking water had a **higher incidence of prostate cancer** compared to unexposed areas.

3.2 TESTICULAR CANCER

Testicular cancer is the most frequent cancer in young men aged 15–44, with the incidence in Europe being significantly higher compared to many other parts of the world[95]. Incidence rates have been rising steadily[96], particularly in Northern and Western Europe [age-standardised rate (ASR) of incidence 7.5 and 9.3 cases per 100.000 person-years, respectively][14].

- Nordic countries report some of the **highest global rates**, with Norway and Denmark showing a ASR of 11.5 and 10.2 cases per 100.000 person-years[97].
- The **Testicular Dysgenesis Syndrome (TDS) hypothesis** proposes that fetal exposure to anti-androgenic chemicals leads to impaired testicular development, increasing risk for testicular cancer, cryptorchidism, hypospadias, and infertility[98].

EU research suggests strong associations between **maternal exposure to phthalates, BPA, and pesticides during pregnancy** and increased risk of testicular abnormalities in sons, including urogenital malformations, cryptorchidism and hypospadias[99-130] (see **Appendix 2** for the full list of the EU studies).

- French data confirmed pesticide exposure in pregnant women[131]. A biomonitoring study condicted in France found that prenatal pesticide exposure significantly **increased the risk of testicular germ cell tumors**[131,132].
- A meta-analysis of 22 studies[133], the majority from EU[134-145], found that maternal exposure to combined EDCs (organochlorine pesticides, organohalogens, phthalates, bisphenol A, per- and polyfluorinated alkyl substance) was associated with a twofold increased risk of **testicular cancer** in male offspring (see **Appendix 3** for the full list of the EU studies).

3.3 MALE INFERTILITY AND SUBFERTILITY

According to the World Health Organization, infertility affects 1 in 6 couples worldwide[146]. In Europe, the prevalence of infertility generally ranges from 6.6% to 16.7%. A 2013 estimation by Fertility Europe and ESHRE indicated that approximately 25 million European citizens were affected by infertility[147], with **male factor infertility responsible in about half** of cases[146]. Chemical exposure is now considered a major contributor[149-150].

Sperm decline

- A 2023 meta-analysis by Levine et al. showed that **global sperm counts declined by 52%** between 1973 and 2018. European countries showed similar or even steeper declines, especially in Western and Southern Europe[15].

- Studies from Spain[151-152], Czech Republic[45] and Denmark[40,44] report significant associations between urinary or seminal levels of phthalate and BPA and both **quantitative and qualitative reductions in sperm parameters**.
- A mixture risk assessment focused on 29 substances (including bisphenols, phthalates, dioxins, paracetamol, and others) was conducted using European exposure data to identify chemicals that impair semen quality, especially after prenatal exposure. Highly exposed individuals had combined chemical exposures that exceeded safe levels by more than 100 times; the median exceedance was 17-fold. BPA was the largest contributor to the overall risk, followed by dioxins, bisphenol S and F, and the phthalate DEHP[5].

Testicular function

- EU studies link exposure to phthalates to **lower testosterone levels**, a key marker of testicular function[153,154].
- Microplastics have been found in **human testicular tissue**[68-70], and pre-clinical studies show that they can reduce **sperm production, disrupts blood-testis barrier integrity**, and impairs Sertoli cell metabolism[71-74] (related to sperm development).

Infertility is not only a quality-of-life issue—it is also an early marker of other chronic diseases, including metabolic syndrome and cardiovascular disease[155].

3.4 HYPOGONADISM (LOW TESTOSTERONE)

Hypogonadism (testosterone deficiency) has an estimated incidence of 12.3 and 11.7 cases per 1,000 people per year[156], and the rate is increasing[157].

- Environmental chemicals that act as **anti-androgens**—including phthalates, PFAS, and certain pesticides—can disrupt Leydig cell function and **suppress testosterone synthesis**[40,153,158].
- The European **HBM4EU study** found significant inverse associations between urinary phthalate metabolites and **serum testosterone levels** in adult men[159].
- BPA and cadmium have also been implicated in **HPG axis dysregulation** (affecting a central endocrine gland system), impairing hormonal feedback loops[38,44].

Symptoms include fatigue, reduced libido, depression, infertility, and increased cardiovascular and metabolic risk[160].

3.5 SEXUAL DYSFUNCTION

Environmental exposure to EDCs is also linked to **erectile dysfunction, reduced libido, and ejaculatory disorders**.

- A study has reported a positive, although statistically insignificant, association between fine particulate matter ($PM_{2.5}$) exposure and odds of incident **erectile dysfunction**[161]. While $PM_{2.5}$ is not formally classified as an EDC, it can carry or contain substances with endocrine activity.
- Gasoline vehicle exhaust (VE), a major source of air pollution containing substances capable of interfering with the endocrine system, and $PM_{2.5}$ have been shown in animal models to impair **nitric oxide signaling and penile blood vessel network**, leading to reduced erectile capacity[162,163].

3.6 INTERGENERATIONAL EFFECTS

Exposure to EDCs may have implications not only for the health of the exposed individual but also for the well-being of their conceived offspring.

- The effects of maternal exposure to EDCs on male reproductive health in offspring — including malformations, hypospadias (location of urethal opening), cryptorchidism (undescended testicles), testicular cancer, and impaired fertility — are discussed in the preceding sections.
- Evidence from animal studies suggest that paternal exposure to EDCs and microplastics can cause **epigenetic alterations** in sperm[19,20], which in turn affect the health of the offspring[21,23,24,164-168]. These intergenerational effects include impaired cognitive function and neuronal aging after cadmium and high-fat diet exposure[21], abnormal neurobehavior following mercury exposure[23], and reproductive and fertility disorders linked to microplastics[24]. Additional studies demonstrate that paternal exposures can alter offspring metabolism, pancreatic function, liver and fat transcriptomes, and epigenetic programming of key developmental genes[164-168].
- In humans, exposure to EDCs alters sperm epigenetics[22,169].
- High paternal exposure to air pollutants before conception—especially during the 15–69 days preconception window—was linked to lower birthweight, shorter gestational age, and greater risk of fetal growth restriction, with $PM_{2.5}$ as the main contributor[170].

Such findings underscore the importance of **early-life protection** and **intergenerational health impacts** in chemical policy design. Preventive measures targeting parental exposures — especially during the preconception window—may have significant transgenerational implications.

CONCLUSION

European men face a spectrum of adverse health outcomes related to chemical exposure, many of which are rising in prevalence. The evidence linking EDCs, PFAS, heavy metals, and microplastics to prostate and testicular cancer, infertility, and hormonal dysfunction is strong and growing. Infertility is not only a quality-of-life issue—it is also an early marker of other chronic diseases, including metabolic syndrome and cardiovascular disease. Public health strategies must address the full spectrum of health harms linked to chemical exposure—including reproductive, cardiovascular, metabolic, neurological, and cancer outcomes—while giving greater attention to male reproductive health as a vulnerable and underrecognised area. Stronger chemical risk reduction measures would align with the EU's Cardiovascular Health vision and broader health policy commitments to prevent chronic disease and protect future generations.

4

European epidemiological data on male reproductive, endocrine, and cancer health

4. European epidemiological data on male reproductive, endocrine, and cancer health

Understanding the geographical distribution, prevalence, and trends of male reproductive and endocrine disorders across Europe is a key step in addressing chemical-related health risks in men.

This section presents available **epidemiological data by country**, indicating **geographical distribution, prevalence, and trends** of male reproductive and endocrine disorders in Europe, emphasizing key outcomes such as prostate and testicular cancer, infertility, hypogonadism, and sperm quality decline.

Where available, it also highlights correlations between regional disease burdens and known chemical exposure hotspots.

4.1 PROSTATE CANCER: HIGH BURDEN AND GROWING INCIDENCE

Prostate cancer is the **leading cancer diagnosis among men in most European countries**, with incidence rates rising over the past two decades[13].

Table 1: Incidence and mortality of prostate cancer in European countries according to the European Cancer Information System[171.]

COUNTRY	INCIDENCE (ASR) (ESTIMATED, 2022)	MORTALITY (ASR) (ESTIMATED, 2022)
Lithuania	265.3 per 100,000	57.2 per 100,000
Sweden	231.6 per 100,000	53.8 per 100,000
Latvia	225.1 per 100,000	76.1 per 100,000
Estonia	218.7 per 100,000	80.4 per 100,000
Ireland	209.2 per 100,000	36.5 per 100,000
Finland	207.9 per 100,000	36.1 per 100,000
Denmark	182.5 per 100,000	54.41 per 100,000
France	179.0 per 100,000	30.7 per 100,000
Slovakia	173.5 per 100,000	60.3 per 100,000
Croatia	172.2 per 100,000	57.3 per 100,000
Slovenia	169.5 per 100,000	57.1 per 100,000
Hungary	164.9 per 100,000	46.5 per 100,000
Czechia	164.8 per 100,000	41.1 per 100,000
Cyprus	156.0 per 100,000	55.8 per 100,000
Germany	154.1 per 100,000	42.7 per 100,000
Poland	150.3 per 100,000	62.8 per 100,000
Spain	147.0 per 100,000	29.8 per 100,000
Portugal	140.0 per 100,000	39.8 per 100,000
Austria	139.9 per 100,000	36.9 per 100,000
Netherlands	136.1 per 100,000	44.4 per 100,000
Romania	134.0 per 100,000	43.5 per 100,000
Greece	131.6 per 100,000	34.7 per 100,000
Malta	119.7 per 100,000	27.1 per 100,000
Italy	119.1 per 100,000	25.7 per 100,000
Norway	254.1 per 100,000	54.0 per 100,000
United Kingdom	175.4 per 100,000	44.0 per 100,000
Switzerland	170.1 per 100,000	39.9 per 100,000
Iceland	149.2 per 100,000	56.8 per 100,000
Serbia	140.8 per 100,000	119.3 per 100,000
Ukraine	83.2 per 100,000	71.4 per 100,000

ASR, Age standardised rate.

4.2 TESTICULAR CANCER: RISING FASTEST IN YOUNG MEN

Testicular cancer shows the **fastest growth in incidence** of any male cancer in the Europe and primarily affects men under 45[13].

Table 2: Incidence and mortality of testicular cancer in European countries according to the European Cancer Information System[171].

COUNTRY	INCIDENCE (ASR) (ESTIMATED, 2022)	MORTALITY (ASR) (ESTIMATED, 2022)
Slovakia	13.5 per 100,000	1.3 per 100,000
Croatia	12.0 per 100,000	0.9 per 100,000
Slovenia	11.7 per 100,000	0.6 per 100,000
Hungary	11.2 per 100,000	1.0 per 100,000
Denmark	10.8 per 100,000	0.3 per 100,000
Germany	10.3 per 100,000	0.4 per 100,000
Czechia	9.5 per 100,000	0.7 per 100,000
Netherlands	9.3 per 100,000	0.2 per 100,000
Austria	8.5 per 100,000	0.4 per 100,000
Poland	8.1 per 100,000	1.0 per 100,000
France	7.6 per 100,000	0.4 per 100,000
Cyprus	7.3 per 100,000	0.0 per 100,000
Sweden	7.4 per 100,000	0.2 per 100,000
Malta	7.1 per 100,000	0.0 per 100,000
Ireland	6.9 per 100,000	0.2 per 100,000
Finland	6.9 per 100,000	0.3 per 100,000
Spain	6.5 per 100,000	0.2 per 100,000
Portugal	6.1 per 100,000	0.5 per 100,000
Estonia	4.3 per 100,000	0.3 per 100,000
Romania	3.8 per 100,000	0.5 per 100,000
Latvia	2.8 per 100,000	0.9 per 100,000
Lithuania	2.3 per 100,000	0.2 per 100,000
Greece	0.9 per 100,000	0.5 per 100,000
Norway	12.2 per 100,000	0.0 per 100,000
Serbia	10.6 per 100,000	1.2 per 100,000
Switzerland	10.6 per 100,000	0.4 per 100,000
United Kingdom	7.1 per 100,000	0.2 per 100,000
Iceland	5.4 per 100,000	0.7 per 100,000
Ukraine	2.2 per 100,000	0.5 per 100,000

ASR, Age standardised rate.

Studies in Denmark and Sweden have linked rising testicular cancer rates to **prenatal and early-life exposure** to EDCs (e.g., phthalates, pesticides) and air pollution[134,135,172].

4.3 SPERM QUALITY AND MALE INFERTILITY: DECLINING IN MULTIPLE REGIONS

Infertility affects an estimated **15% of couples in Europe**, with **male factor infertility present in ~50% of cases**. Several EU studies have shown steep declines in semen quality and sperm counts (**Appendix 1**).

STUDY	LOCATION	KEY FINDINGS
Lassen E, et al., 2024[173]	Denmark	Total motile sperm count and motile sperm concentration dropped by up to 22% (2019–2022)
Levine H, et al., 2023[15]	Multiple EU countries	52% global sperm count decline since 1973; mirrored in Western/Southern Europe
Garcia-Grau E, et al., 2022[174]	Spain	-0.57% for progressively motile sperm and -0.72% for sperm with normal morphology
Sugihara A, et al., 2021[175]	Belgium	A negative trend was found for total sperm count from 2010 onwards
Sengupta P, et al., 2018[176]	Europe	Sperm concentration declined by 32.5 percent over 50 years
Le Moal J, et al., 2014[177]	France	Decrease in sperm concentration between 1989 and 2005
Mendiola J, et al., 2013[178]	Spain	Sperm concentration and total count declined with year of birth; lower values found in Murcia compared to Almeria
Rolland M, et al., 2013[179]	France	From 1989 to 2005, semen concentration decreased by 1.9 percent per year and morphologically normal forms also declined significantly

Geographic variation in sperm quality declines may be linked to differing environmental exposures, industrial pollution, and regulation enforcement. European studies (from Spain, the Czech Republic, and Denmark) have linked urinary and seminal levels of phthalates and BPA to reduced sperm quality and count. A mixture risk assessment of 29 chemicals—including bisphenols, phthalates, dioxins, and paracetamol—revealed that combined exposures, particularly during prenatal development, often exceeded safe levels, with BPA being the top contributor to semen quality impairment[5,40,44,45,151,152].

4.4 REDUCED TESTICLE FUNCTIONING (HYPOGONADISM / LOW TESTOSTERONE): EMERGING CONCERN

Although underdiagnosed, clinical and subclinical testosterone deficiency is increasingly reported across Europe.

- **Sweden:** A cross-sectional population-based Prospective Investigation of the Vasculature in Uppsala Seniors study (PIVUS) links polychlorinated biphenyls (PCBs), monoethyl phthalate (MEP), Ni and Cd levels to lower testosterone levels in old men (>70 years)[158].
- **France:** In a short longitudinal study, increased urinary levels of mono-4-methyl-7-oxo-octyl phthalate (OXO-MINP) were associated with a significant decrease in total serum testosterone concentrations in male workers from six factories in the plastics industry[153].
- **Denmark, Poland:** Levels of di-2-ethylhexyl phthalate (DEHP) and diisononyl phthalate (DiNP) metabolites in serum were associated with reduced testosterone levels[40].
- **Spain:** Increased urinary BPA concentrations were associated with higher serum luteinizing hormone (LH) values - indicating a reduction in Leydig cell capacity – in young men[44].
- The European **HBM4EU** study reported that higher concentrations of urinary phthalate metabolites were significantly associated with lower serum testosterone levels in adult men[159].

There are currently no standardised EU-wide testosterone surveillance systems, but the pattern across studies suggests a **rising burden**, particularly in middle-aged men.

4.5 SEXUAL DYSFUNCTION: UNDERREPORTED BUT INCREASING

Country-specific prevalence of sexual dysfunction has been reported by the European Association of Urology[18,180]. Data on sexual dysfunction (e.g., erectile dysfunction, low libido) are limited due to stigma and inconsistent reporting, but regional studies point to environmental contributors:

- **Italy:** One out of four men seeking medical care for erectile dysfunction was younger than 40 years[181].
- **France (Santé Publique France, 2020):** One man in three suffers from erectile dysfunction[182]. A national strategic roadmap for sexual health has been developed[183].
- A study observed a positive, though not statistically significant, association between exposure to $PM_{2.5}$ and the likelihood of developing **erectile dysfunction**.

4.6 REGIONAL HOTSPOTS AND INEQUITIES

Men in **industrial jobs, rural agricultural areas, or lower socioeconomic groups** are disproportionately affected by the above-mentioned diseases . Epidemiological and cohort studies have shown that occupational and environmental exposures in these populations are associated with higher rates of testicular and prostate cancer, reduced semen quality, and other reproductive disorders.

Certain **geographical clusters** of elevated male reproductive disease rates correlate with **high chemical exposures:**

- **Northern Italy (Po Valley):** Air and water contamination with PFAS, phthalates; elevated kidney/testicular cancer[184-186].
- **France (Gironde, Rhône-Alpes):** Agricultural pesticide exposure linked to prostate and testis cancers[187].
- **Poland (Silesia):** High exposure to cadmium and industrial pollutants; testicular cancer more common[188-190].
- **Sweden (Uppsala, Ronneby):** Documented PFAS contamination linked to prostate cancer[191-193].

CONCLUSION

The epidemiological evidence across Europe reveals consistent and troubling trends: prostate and testicular cancers are increasing, sperm quality is falling, and hormonal disorders are becoming more prevalent. Many of these trends correlate with known or suspected chemical exposures, reinforcing the need for targeted public health measures and policy reforms. As highlighted in EBCP, reducing pollution is also a pathway to reducing health inequalities, since vulnerable and disadvantaged populations are often disproportionately exposed and affected.

5

Economic costs and burden of disease

5. **Economic costs** and burden of disease

Male reproductive and endocrine disorders have significant economic consequences for individuals, families, health systems, and national economies. These include:

- **Direct costs**: medical care, diagnostics, surgery, fertility treatments, hormonal therapies, hospitalizations.
- **Indirect costs**: lost productivity, absenteeism, reduced work capacity, disability, and reduced quality of life.
- **Intangible costs**: psychological distress, relationship breakdown, stigma, and long-term family planning impacts.

Mounting evidence also suggests that these disorders are partly preventable, particularly when environmental and chemical risk factors are addressed.

5.1 INFERTILITY: A COSTLY AND GROWING BURDEN

Infertility is now one of the most common chronic conditions affecting young adults, yet remains underrecognised in economic planning.

- According to ESHRE[194], the **direct cost of infertility treatments in the EU** is estimated at **€6–9 billion annually**, with wide variation by country depending on treatment coverage and utilisation. In France[195], it has been estimated at 70.0 million (IC 95%: 57.6-82.4) € for 10,000 women aged between 18 and 50.
- Male factor infertility accounts for roughly **50% of all cases**, and environmental exposures are estimated to play a major role in the etiology of male infertility cases[196].
- A study commissioned by the Nordic Council estimated that EDCs may contribute substantially to male reproductive disorders and diseases, with nearly **€15 billion annual associated costs** in the EU[197].

The use of **assisted reproductive technologies (ART)** is increasing rapidly in Europe. ART is not only costly, but also emotionally and physically taxing for couples—often with limited success in cases of poor male fertility.

5.2 PROSTATE AND TESTICULAR CANCER: HEALTH SYSTEM COSTS

Prostate cancer

- The **average mean 3-years cost of prostate cancer treatment per patient** with stage I to III disease has been estimated at **€12,023**, with a total survival-adjusted costs until death of **€15,931** in EU.
- **Total EU spending** on prostate cancer care (screening, treatment, follow-up) exceeds **€9 billion per year**, making it one of the costliest male cancers[198,199].

Testicular cancer

- Testicular cancer typically affects younger men and requires intensive treatment (surgery, chemotherapy, radiotherapy).
- Treatment costs, while lower than for prostate cancer, are compounded by **lost productivity during prime working years**.

In both cases, costs extend beyond treatment to include **long-term endocrine monitoring, fertility preservation, and psychological support**.

5.3 HORMONAL DISORDERS AND SEXUAL DYSFUNCTION: UNDERESTIMATED ECONOMIC IMPACT

Testosterone deficiency, sexual dysfunction, and related disorders have a **significant economic footprint**, though they are poorly captured in current burden of disease models.

- **Erectile dysfunction** is associated with cardiovascular and metabolic disease[200], contributing to **long-term co-morbidity costs**.
- A cross sectional study of over 52,000 men across eight countries (Brazil, China, France, Germany, Italy, Spain, UK, USA) found that men with erectile dysfunction experienced significantly greater work impairment: higher rates of absenteeism (7.1% vs 3.2%) and overall work productivity impairment (24.8% vs 11.2%) than men without erectile dysfunction[200].
- European-specific burden (France, Germany, Italy, Spain, UK): In five European countries, erectile dysfunction -related productivity loss was similarly elevated across age cohorts: for men aged 18–39, absenteeism of 11.6% vs 5.0% and overall work productivity impairment of 35.4% vs 18.9%
- **Hypogonadism** is associated with increased risk of type 2 diabetes, osteoporosis, and cardiovascular events—each with high healthcare costs[201,202].

5.4 LOST PRODUCTIVITY AND SOCIAL COSTS

- A UK survey found that **56% of men undergoing infertility treatment experienced work-related performance issues**, with 38% considering quitting or changing jobs[203].
- Chronic reproductive and hormonal conditions can **reduce lifetime earnings, limit career progression**, and affect men's mental health and relationships.

5.5 THE COST OF INACTION

The **cost of inaction**—failing to reduce environmental exposures or reform chemical policy—far outweighs the cost of prevention.

- A 2015 analysis estimated that **EDC-related male reproductive health disorders cost the EU at least €15 billion annually**[197]. This figure includes infertility, testicular dysgenesis, and reduced testosterone levels.
- These figures are likely conservative, as they exclude many newer chemicals (e.g., microplastics) and long-term intergenerational effects.

Investing in **primary prevention through stronger chemical regulation** offers high returns in public health, healthcare cost savings, and productivity.

CONCLUSION

The economic burden of male reproductive and endocrine disorders in Europe is substantial and rising. Infertility treatments, cancer care, and hormone therapies place heavy demands on national health budgets, while lost productivity and quality-of-life impacts affect individuals and society. Strengthening EU chemical policy as presented in the Chemicals Strategy for Sustainability —and including through a health-protective REACH revision—is an urgent and cost-effective strategy to reduce these burdens.

6

Policy implications: Why a comprehensive implementation of the eu chemicals strategy for sustainability is needed

6 **Policy implications:** Why a comprehensive implementation of the eu chemicals strategy for sustainability is needed

The mounting evidence linking chemical exposure to serious men's health outcomes—infertility, cancer, hormonal disorders—demands an urgent policy response. While Europe has made important progress in identifying and regulating hazardous substances, human biomonitoring data and public health trends indicate that the current regulatory mechanisms remain **insufficient to protect male reproductive health**.

Strengthening the EU legal framework on chemicals to address these pressing health concerns, in line with the commitments of the EU Chemicals Strategy for Sustainability is needed, including the protection of consumers, vulnerable groups and workers from the most harmful chemicals such as EDCs or persistent pollutants. A **health-focused revision of the REACH regulation** (Registration, Evaluation, Authorisation and Restriction of Chemicals), in combination with the comprehensive implementation of the new hazard classes in the CLP Regulation (Classification, Labelling and Packaging of substances and mixtures) and coherent approaches to assess and manage chemicals in existing sectorial legislation, offers a crucial and timely opportunity to protect current and future generations of Europeans.

6.1 GAPS IN CURRENT HORIZONTAL CHEMICAL REGULATION

Despite the recent valuable update of the CLP Regulation to include new hazard classes (incl. for endocrine disruptors) and REACH being the most advanced chemicals regulation in the world, several systemic weaknesses persist:

- **Slow identification and restriction of EDCs**: The addition of dedicated EU hazard classes for endocrine disruptors in the CLP Regulation is essential to better identity and classify substances that affect hormone-regulated systems incl. hormonal processes necessary for unimpaired male reproductive health. However, the data available to identify EDCs remains limited for the time being and many known EDCs, including phthalates and bisphenols, are still widely used and insufficiently restricted.
- **Lack of consideration of mixture effects**: People are exposed to multiple chemicals simultaneously, but REACH does not assess risks from combined unintended exposures (the "cocktail effect").
- **Inadequate protection during vulnerable life stages**: Prenatal, pubertal, and early adult exposures critical to reproductive development are not adequately addressed.
- **Limited research and sex-specific assessment**: While many studies have examined the effects of maternal exposure to EDCs on offspring health, research on paternal exposure and effects on offspring remains scarce. Most available evidence comes from recent animal studies, which suggest significant intergenerational impacts through sperm epigenetic alterations. Human data are still limited, underscoring the urgent need to strengthen research on paternal contributions to offspring health outcomes.

6.2 KEY OPPORTUNITIES IN THE REACH REVISION

The ongoing preparation of the REACH revision is a **critical window of opportunity** to strengthen health protections. Several promising policy changes are being considered, but they require strong support from health-focused stakeholders.

HEAL and other public health groups advocate for the following:

- **Full implementation and extension of the Generic Approach to Risk Management (GRA)**: This would ban the use of the most harmful chemicals in consumer products, including known EDCs, without having to rely on lenghthy case-by-case restriction.
- **Group-based chemical bans**: Rather than regulating one substance at a time, entire groups (e.g., all bisphenols, all phthalates) should be restricted together to prevent substitution with equally harmful variants.
- **Mandatory mixture toxicity assessment**: REACH should require chemical risk assessments to account for **combined exposures** to multiple substances.
- **Inclusion of polymers, microplastics and additives in REACH scope**: Polymers requiring registration need to be defined and regulated. REACH risk management must go beyond microplastic size and address **toxicity of associated substances**, many of which are EDCs, across the full lifecycle of materials and products.
- **Increased use of human biomonitoring data**: National and EU-wide studies (e.g., HBM4EU) should be integrated into risk assessment to reflect real exposure levels and population health trends.
- **Improved protections for vulnerable groups**: This includes pre- and peri-conceptional window, fetuses, adolescents, workers in high-exposure sectors, and low-income populations who may be disproportionately exposed.

6.3 COHERENT AND PROTECTIVE APPROACHES IN SECTORIAL LEGISLATION

Complementing a health-focused revision of the REACH regulation, sectorial legislation must be aligned to ensure a high level of protection against the most harmful chemicals at home, at work and in wider environment .

- **Preventative measures**: Restricting the use of hazardous chemicals as intentional additives or unintentional contaminants in products, including food and drinking water, to reduce exposure and health effects. In case of products commonly used by vulnerable groups, such as personal care products used by pregnant women, children or teenagers, addional precautions must be taken.

6.4 CO-BENEFITS OF STRONGER REGULATION

Strengthening chemical regulation in line with the Chemicals Strategy for Sustainability would have **multiple co-benefits**:

- **Decrease healthcare costs and lost productivity** from cancer, infertility, hormonal disease, and associated co-morbidities such as cardiovascular and metabolic disorders.
- **Reduce male reproductive disorders**, support improved fertility rates, and enhance quality of life.
- **Enhance public trust** in EU environmental health policy.
- **Support environmental sustainability** and advance the One Health goal by phasing out persistent and bioaccumulative chemicals, thereby protecting human, animal, and ecosystem health.
- **Promote circular economy and EU resource autonomy** by facilitating clean material cycles.

6.5 A PUBLIC HEALTH APPROACH THAT CONSIDERS CHEMICAL EFFECTS

The health risks from chemical exposure have been largely **overlooked in public health policy**, despite consistent evidence of harm.

- Male reproductive organs and hormonal axes are highly susceptible to disruption by EDCs, particularly during fetal development and puberty.
- The **Testicular Dysgenesis Syndrome** (**TDS**) framework suggests that many adult male disorders originate in early developmental disruptions caused by EDCs.

CONCLUSION

The evidence is clear: men's health is being harmed by daily exposure to toxic chemicals, and actions in line with the EU Chemicals Strategy for Sustainability are needed. The upcoming REACH revision provides a historic opportunity for the EU to act decisively by strengthening its chemical safety framework. A **health-centered REACH** revision would better protect reproductive health, prevent disease, and reduce economic burden. Policymakers must act now—delaying action will only increase human and economic costs.

7

Recommendations

7 Recommendations

To reduce the growing burden of reproductive and endocrine diseases linked to chemical exposure, the EU must take bold and coordinated regulatory action.

The committments of the Chemicals Strategy for Sustainability map actions necessary to **prioritise health protection, prevent disease, and reduce economic costs**. The following recommendations are directed at European Commission officials, Members of the European Parliament (MEPs), national governments, and EU regulatory agencies.

7.1 STRENGTHEN CHEMICAL REGULATION TO PROTECT HUMAN HEALTH

7.1.1 Accelerate the identification and restriction of endocrine-disrupting chemicals (EDCs)

- Require sufficient information during substance registration to allow for the classification of EDCs.
- Prioritise EDCs with known effects on fertility, hormone regulation, and cancer risk (e.g., phthalates, bisphenols, pesticides) for regulatory risk management measures.
- Apply the precautionary principle to restrict (groups of) EDCs based on weight-of-evidence approaches.

7.1.2 Implement group-based restrictions

- Ban harmful chemical groups (e.g., all bisphenols, all ortho-phthalates), not just individual substances.
- Avoid "regrettable substitution" with structurally similar and equally harmful compounds.

7.1.3 Expand horizontal and sectorial regulation to include polymers, microplastics and their additives across their life cycles

- Ensure the transparency on polymers placed on the European market (polymer notification) and the registration of prioritised polymers.
- Include the risk assessment and risk management of **microplastics and associated EDCs across the full lifecycle of products.**
- Prioritise research and monitoring of microplastic effects on human reproductive health.

7.1.4 Mandate mixture toxicity assessment

- Require risk assessments to reflect **combined exposures** to chemicals and their additive or synergistic effects.

7.1.5 Safeguard public health based on a precautionary approach

- Allow for earlier risk management decisions to avoid intended negative health effects by chemicals with indications of concern but incomplete or inconclusive toxicological datasets, incl. for those chemicals with data gaps on sex-specific effects.

7.2 STRENGTHEN PUBLIC HEALTH MONITORING AND PREVENTION

7.2.1 Support EU-wide biomonitoring and surveillance of men's health indicators

- Build on HBM4EU to track biomarkers of exposure (e.g., BPA, phthalates, PFAS) in male populations.
- Include reproductive health outcomes in environmental health surveillance systems.

7.2.2 Strengthen early warning systems and public access to exposure data

- Ensure timely and transparent communication of environmental contamination and human exposure risks.
- Engage with occupational health authorities to identify and monitor male workers in high-risk sectors such as agriculture, manufacturing, and waste management.
- Prioritise upstream risk management measures to reduce harmful exposures, rather than relying solely on end-of-pipe monitoring.

7.2.3 Promote public awareness campaigns

- Develop science-based messaging for men on the risks of chemical exposures and ways to reduce them.
- Integrate men's reproductive health into school curricula, public health education, and fertility awareness programs.

7.3 ALIGN EU POLICY ON CHEMICALS WITH PUBLIC HEALTH GOALS

7.3.1 Implement the chemicals strategy for sustainability

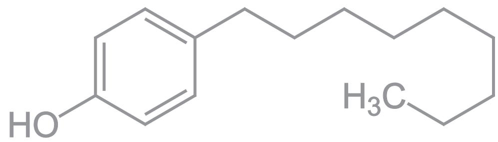
- Use a health-focused REACH revision to **align chemical regulation with Europe's Beating Cancer Plan**, EU Cardiovascular Health Plan, EU Green Deal, and Zero Pollution Strategy.
- Ensure that the protection of reproductive health is clearly stated as a policy objective.
- **Prioritise preventive action when health risks are suspected**. When evidence of harm exists (e.g., declining sperm counts, microplastics in testes), act to reduce exposure—even if full causal mechanisms are not yet understood.
- Shift the burden of proof to industry when it comes to safety claims about EDCs and emerging contaminants.

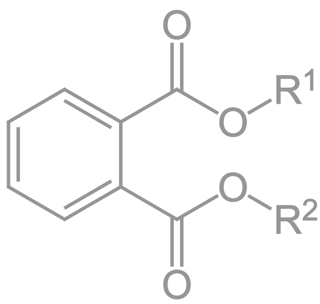
7.4 CALL TO ACTION FOR POLICYMAKERS AND THE MEDIA

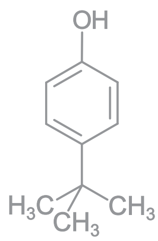
- **EU Commissioners, MEPs, and Member State Representatives**: Acknowledge the growing male health crisis and ensure it is addressed in all forthcoming chemical safety legislation.
- **Journalists and media**: Help elevate this issue by connecting it to broader public concerns about cancer, fertility, male well-being, and intergenerational health.
- **Health professionals**: Advocate for upstream prevention strategies, not just downstream treatment. Promote stronger recognition of environmental risk factors—including chemical pollution—as key determinants of health, and support regulatory actions that protect men's health and future generations.

CONCLUSION

Human health, including the health of men, is a mirror of our chemical environment. Europe's regulatory choices will determine whether the next generation live in a cleaner, healthier world—or face escalating infertility, hormonal disease, and reproductive harm. The evidence is clear, and the time to act is now.







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Appendix 1: ASDR of male infertility and the trends from 1990 to 2021 by country[17].

COUNTRY	ASDR (1/100,000, 95% UI)		
	1990	2021	EAPC (95% CI)
Afghanistan	1.8 (0.6,4.6)	1.7 (0.7,3.7)	-0.4 (-0.7,-0.2)
Albania	2.9 (1.0,6.9)	2.1 (0.8,4.6)	-1.0 (-1.7,-0.3)
Algeria	2.1 (0.8,4.7)	3.1 (1.1,7.1)	1.7 (1.4,1.9)
American Samoa	3.2 (1.1,7.5)	3.2 (1.1,7.5)	-0.0 (-0.0,0.0)
Andorra	2.8 (1.0,7.0)	2.6 (0.9,6.5)	-0.2 (-0.3,-0.2)
Angola	5.1 (1.8,12.3)	4.7 (1.7,11.5)	-0.2 (-0.2,-0.2)
Antigua and Barbuda	4.2 (1.5,10.1)	4.3 (1.5,10.4)	0.1 (0.0,0.2)
Argentina	3.0 (1.0,7.4)	3.0 (1.1,7.4)	-0.0 (-0.1,0.0)
Armenia	2.6 (0.9,6.9)	1.2 (0.5,2.6)	-1.9 (-2.2,-1.6)
Australia	1.7 (0.6,4.3)	1.7 (0.6,4.2)	-0.0 (-0.1,0.0)
Austria	5.0 (1.8,12.3)	5.0 (1.8,12.5)	0.8 (0.5,1.1)
Azerbaijan	3.6 (1.3,9.1)	3.8 (1.4,9.3)	-0.1 (-0.9,0.6)
Bahamas	4.4 (1.6,10.6)	4.3 (1.5,10.6)	-0.1 (-0.1,-0.0)
Bahrain	4.2 (1.5,9.9)	4.4 (1.6,10.4)	0.4 (0.3,0.4)
Bangladesh	1.9 (0.7,4.0)	2.1 (0.8,4.5)	0.5 (0.2,0.8)
Barbados	4.3 (1.6,10.4)	4.3 (1.5,10.6)	-0.0 (-0.0,0.0)
Belarus	4.2 (1.5,10.7)	4.3 (1.5,10.8)	0.0 (0.0,0.1)

COUNTRY	ASDR (1/100,000, 95% UI)		
	1990	2021	EAPC (95% CI)
Belgium	2.9 (1.2,6.5)	4.4 (1.5,10.9)	1.4 (1.0,1.8)
Belize	2.3 (0.9,4.8)	2.8 (1.0,6.5)	0.8 (0.5,1.0)
Benin	4.2 (1.5,10.1)	3.0 (1.2,6.5)	-1.1 (-1.1,-1.0)
Bermuda	4.4 (1.5,10.6)	4.4 (1.6,10.7)	0.0 (0.0,0.0)
Bhutan	2.3 (0.8,5.6)	2.2 (0.8,5.2)	-0.1 (-0.1,-0.1)
Bolivia (Plurinational State of)	1.4 (0.6,2.9)	1.7 (0.6,4.0)	1.4 (0.8,2.1)
Bosnia and Herzegovina	3.1 (1.0,8.1)	3.0 (1.0,7.5)	-0.0 (-0.1,0.0)
Botswana	1.3 (0.5,2.7)	2.2 (0.7,5.3)	0.8 (0.4,1.1)
Brazil	2.4 (0.9,5.9)	3.2 (1.2,7.7)	1.8 (1.4,2.2)
Brunei Darussalam	2.2 (0.8,5.3)	2.1 (0.7,5.2)	-0.1 (-0.3,0.0)
Bulgaria	3.0 (1.0,7.5)	3.0 (1.0,7.7)	0.1 (0.1,0.1)
Burkina Faso	4.2 (1.8,9.1)	4.3 (1.5,10.2)	-0.6 (-1.1,-0.1)
Burundi	1.5 (0.6,3.4)	0.8 (0.3,1.8)	-2.1 (-2.5,-1.7)
Cabo Verde	5.3 (1.9,12.4)	6.4 (2.3,14.9)	0.6 (0.6,0.7)
Cambodia	2.4 (0.8,5.9)	2.7 (0.9,6.4)	-1.1 (-1.7,-0.5)
Cameroon	7.9 (3.2,17.1)	9.3 (3.4,21.9)	-0.3 (-1.1,0.5)
Canada	2.0 (0.7,4.9)	2.0 (0.7,5.0)	-0.0 (-0.1,0.0)
Central African Republic	6.3 (2.5,13.3)	7.6 (2.8,17.8)	0.7 (0.4,0.9)
Chad	5.3 (1.8,12.3)	5.4 (1.9,12.5)	-2.6 (-3.3,-1.9)

COUNTRY	ASDR (1/100,000, 95% UI)		
	1990	2021	EAPC (95% CI)
Chile	3.0 (1.1,7.2)	3.0 (1.1,7.5)	-0.0 (-0.1,0.0)
China	4.2 (1.5,10.4)	4.5 (1.5,10.9)	-0.0 (-0.1,0.0)
Colombia	1.1 (0.5,2.4)	1.2 (0.5,2.6)	0.4 (0.3,0.6)
Comoros	5.0 (1.8,11.7)	5.2 (1.9,12.4)	1.2 (0.7,1.7)
Congo	3.7 (1.3,8.8)	3.7 (1.3,8.9)	-0.6 (-1.1,-0.2)
Cook Islands	3.1 (1.1,7.4)	2.8 (1.0,6.5)	-0.4 (-0.5,-0.4)
Costa Rica	3.0 (1.1,7.3)	2.9 (1.1,6.9)	-0.1 (-0.2,-0.1)
Côte d'Ivoire	5.2 (2,11.2)	7.5 (2.7,17.4)	0.8 (0.4,1.2)
Croatia	3.0 (1.0,7.7)	3.0 (1.0,7.6)	0.0 (0.0,0.0)
Cuba	4.4 (1.6,10.4)	4.5 (1.7,10.8)	0.1 (0.1,0.1)
Cyprus	2.7 (0.9,6.8)	2.6 (0.9,6.4)	-0.2 (-0.2,-0.2)
Czechia	4.0 (1.3,10)	4.0 (1.3,10.1)	1.1 (0.7,1.5)
Democratic People's Republic of Korea	3.0 (1.0,7.1)	3.3 (1.1,8.1)	0.4 (0.4,0.4)
Democratic Republic of the Congo	3.2 (1.1,7.9)	3.4 (1.1,8.2)	-0.6 (-1.4,0.2)
Denmark	1.0 (0.4,2.2)	1.5 (0.5,3.8)	1.4 (1.0,1.9)
Djibouti	5.2 (1.9,12.8)	5.2 (1.9,12.3)	0.2 (-0.2,0.7)
Dominica	4.7 (1.7,11.2)	4.6 (1.6,11.0)	-0.1 (-0.1,-0.1)
Dominican Republic	2.1 (0.8,4.5)	3.8 (1.4,9.2)	1.5 (0.8,2.2)
Ecuador	1.3 (0.5,2.9)	1.8 (0.6,4.3)	2.1 (1.6,2.6)
Egypt	1.8 (0.7,3.6)	2.6 (0.9,6.1)	0.8 (0.4,1.1)
El Salvador	1.4 (0.5,3.0)	1.5 (0.5,3.7)	1.7 (0.9,2.5)
Equatorial Guinea	4.4 (1.6,10.5)	5.2 (1.9,12.4)	0.5 (0.5,0.6)
Eritrea	2.9 (1.1,6)	4.5 (1.6,10.7)	1.9 (1.7,2.1)
Estonia	4.3 (1.5,10.7)	4.4 (1.5,10.9)	0.2 (0.1,0.2)
Eswatini	1.5 (0.5,3.8)	1.6 (0.5,3.9)	-0.1 (-0.8,0.7)

COUNTRY	ASDR (1/100,000, 95% UI)		
	1990	2021	EAPC (95% CI)
Ethiopia	3.4 (1.3,8.1)	2.2 (0.8,5.2)	-1.0 (-1.2,-0.8)
Fiji	4.4 (1.6,10.2)	4.5 (1.6,10.8)	0.1 (0.0,0.1)
Finland	0.9 (0.4,1.8)	1.7 (0.6,4.2)	1.1 (0.6,1.5)
France	2.5 (1,5.3)	3.8 (1.3,9.1)	1.5 (1.0,1.9)
Gabon	6.4 (2.4,15.5)	5.7 (2.1,13.6)	-0.2 (-0.5,0.2)
Gambia	6.1 (2.2,13.9)	6.0 (2.1,13.7)	-0.6 (-0.9,-0.3)
Georgia	2.9 (1.1,6.9)	3.1 (1.1,7.3)	0.1 (0.1,0.2)
Germany	1.1 (0.4,2.5)	1.7 (0.6,4.4)	1.5 (1.1,1.9)
Ghana	4.1 (1.7,8.7)	6.0 (2.1,13.7)	-0.3 (-0.8,0.2)
Greece	2.6 (0.9,6.3)	2.6 (0.9,6.5)	-0.1 (-0.1,-0.0)
Greenland	2.3 (0.8,5.8)	2.1 (0.7,5.4)	-0.3 (-0.3,-0.2)
Grenada	4.5 (1.7,10.9)	4.7 (1.7,11.6)	0.1 (0.1,0.1)
Guam	3.3 (1.2,7.9)	3.2 (1.2,7.6)	-0.1 (-0.2,-0.1)
Guatemala	1.9 (0.7,4.0)	2.5 (0.9,5.8)	-0.4 (-1.0,0.2)
Guinea	6.9 (2.5,16.0)	5.1 (2,11.3)	-0.9 (-1.0,-0.8)
Guinea-Bissau	5.8 (2.1,13.6)	5.9 (2.1,13.5)	0.0 (-0.0,0.0)
Guyana	5.8 (2.2,13.8)	5.7 (2.0,13.2)	-0.4 (-1.0,0.2)
Haiti	3.5 (1.4,7.7)	2.8 (1.1,5.9)	-0.4 (-0.6,-0.3)
Honduras	2.6 (0.9,6.3)	2.5 (0.9,6.0)	0.1 (-0.8,1.1)
Hungary	2.9 (1.0,7.5)	3.0 (1.0,7.6)	0.0 (0.0,0.1)
Iceland	2.7 (0.9,6.5)	2.7 (0.9,6.6)	0.0 (-0.0,0.1)
India	3.0 (1.1,6.8)	4.6 (1.7,10.6)	1.9 (1.4,2.3)
Indonesia	3.8 (1.4,9.2)	5.7 (2.1,14.0)	1.4 (1.0,1.9)
Iran (Islamic Republic of)	4.2 (1.4,9.7)	4.3 (1.4,9.9)	-0.0 (-0.6,0.5)
Iraq	3.5 (1.3,8.0)	3.5 (1.3,7.9)	0.1 (0.0,0.1)

COUNTRY	ASDR (1/100,000, 95% UI)		
	1990	2021	EAPC (95% CI)
Ireland	2.6 (0.9,6.5)	2.5 (0.8,6.0)	-0.1 (-0.1,-0.1)
Israel	3.5 (1.2,8.2)	3.8 (1.3,9.4)	0.2 (0.1,0.3)
Italy	2.8 (1,6.8)	4.1 (1.5,10.0)	1.5 (1.2,1.8)
Jamaica	5.0 (1.8,12)	5.1 (1.9,11.7)	0.1 (0.0,0.1)
Japan	3.1 (1.1,7.7)	3.0 (1.1,7.6)	-0.1 (-0.2,0.0)
Jordan	1.9 (0.7,4.2)	3.2 (1.3,6.9)	1.1 (0.9,1.3)
Kazakhstan	2.3 (0.9,5.0.)	2.9 (1.1,7.1)	1.7 (1.3,2.1)
Kenya	2.0 (0.7,4.7)	2.6 (0.9,6.4)	-2.6 (-3.8,-1.4)
Kiribati	3.0 (1.1,7.0)	2.9 (1.1,6.9)	-0.0 (-0.0,0.0)
Kuwait	4.1 (1.4,9.3)	3.5 (1.2,8.0)	-0.5 (-0.7,-0.4)
Kyrgyzstan	3.6 (1.3,8.4)	3.6 (1.3,8.5)	0.3 (-0.0,0.7)
Lao People's Democratic Republic	2.5 (0.9,5.8)	2.6 (0.9,6.2)	0.2 (0.2,0.2)
Latvia	2.9 (1.2,6.2)	4.4 (1.5,10.9)	1.8 (1.5,2.2)
Lebanon	3.8 (1.4,9.0)	4.1 (1.5,9.9)	1.6 (1.1,2.1)
Lesotho	2.5 (0.9,6.0)	2.9 (1.0,7.1)	-1.7 (-2.7,-0.7)
Liberia	7.3 (2.9,15.4)	7.7 (2.8,18.5)	-0.4 (-0.9,0.0)
Libya	2.5 (1.0,5.3)	3.2 (1.2,7.6)	1.4 (1.1,1.7)
Lithuania	2.9 (1.2,6.1)	4.3 (1.5,10.6)	1.7 (1.4,2.0)
Luxembourg	2.7 (0.9,6.6)	2.6 (0.9,6.8)	-0.1 (-0.1,-0.0)
Madagascar	2.3 (1.0,5.0)	3.0 (1.1,7.1)	0.7 (0.1,1.3)
Malawi	3.2 (1.3,6.6)	0.8 (0.3,1.7)	-4.4 (-4.7,-4.1)
Malaysia	2.2 (0.8,5.2)	2.5 (0.8,6.1)	0.4 (0.3,0.5)
Maldives	5.4 (2,13.3)	6.0 (2.4,12.9)	0.1 (-0.5,0.7)
Mali	6.0 (2.4,12.7)	4.0 (1.5,8.4)	-1.2 (-1.6,-0.8)
Malta	2.6 (0.9,6.7)	2.7 (0.9,6.6)	0.0 (0.0,0.0)

COUNTRY	ASDR (1/100,000, 95% UI)		
	1990	2021	EAPC (95% CI)
Marshall Islands	3.2 (1.1,7.6)	3.2 (1.1,7.8)	0.0 (0.0,0.0)
Mauritania	4.6 (1.8,10.2)	7.4 (2.7,17.7)	1.6 (1.4,1.8)
Mauritius	2.6 (0.9,6.0)	2.5 (0.9,6.1)	-0.1 (-0.1,-0.0)
Mexico	2.2 (0.8,5.3)	3.8 (1.3,8.8)	0.7 (0.3,1.1)
Micronesia (Federated States of)	3.3 (1.2,7.8)	3.2 (1.2,7.7)	0.0 (-0.0,0.1)
Monaco	2.6 (0.9,6.4)	2.5 (0.8,6.2)	-0.1 (-0.2,-0.1)
Mongolia	2.8 (1.0,6.6)	3.0 (1.1,7.1)	0.3 (0.2,0.4)
Montenegro	3.0 (1.0,7.8)	3.0 (1.0,7.5)	-0.1 (-0.1,-0.0)
Morocco	2.5 (1.0,5.5)	4.1 (1.4,9.7)	2.8 (2.0,3.6)
Mozambique	3.8 (1.4,9.3)	3.9 (1.4,9.3)	-1.0 (-1.5,-0.4)
Myanmar	2.6 (0.9,6.6)	1.6 (0.6,3.4)	-2.2 (-2.6,-1.8)
Namibia	1.6 (0.6,3.4)	1.7 (0.6,4.2)	-0.9 (-1.9,0.2)
Nauru	3.1 (1.1,7.6)	3.0 (1.1,7.2)	-0.0 (-0.0,-0.0)
Nepal	2.4 (0.8,5.8)	1.3 (0.5,2.8)	-1.1 (-1.7,-0.6)
Netherlands	2.6 (0.9,6.6)	2.6 (0.9,6.4)	-0.1 (-0.1,-0.0)
New Zealand	1.9 (0.7,4.7)	2.7 (1.0,6.7)	1.5 (1.2,1.7)
Nicaragua	1.8 (0.6,4.3)	1.8 (0.7,4.2)	1.6 (0.9,2.2)
Niger	7.4 (2.9,16.2)	5.9 (2.1,13.8)	-1.3 (-1.8,-0.7)
Nigeria	4.7 (1.7,11.3)	4.1 (1.5,9.8)	-1.3 (-1.6,-1.0)
Niue	3.1 (1.1,7.4)	3.0 (1.1,7.3)	-0.1 (-0.1,0.0)
North Macedonia	3.0 (1.0,7.6)	3.0 (1.1,7.4)	0.1 (0.1,0.1)
Northern Mariana Islands	3.4 (1.2,8.1)	3.3 (1.2,8.1)	0.0 (-0.2,0.2)
Norway	4.2 (1.5,10.5)	4.2 (1.5,10.2)	-0.0 (-0.1,0.0)
Oman	4.5 (1.6,10.4)	4.3 (1.6,10.0)	-0.0 (-0.1,0.1)

COUNTRY	ASDR (1/100,000, 95% UI)		
	1990	2021	EAPC (95% CI)
Pakistan	5.4 (1.5,14.1)	5.4 (1.4,15.5)	-3.5 (-6.4,-0.5)
Palau	3.1 (1.1,7.6)	3.6 (1.3,8.4)	0.4 (0.3,0.5)
Palestine	3.3 (1.2,7.8)	3.4 (1.2,7.8)	-0.0 (-0.1,-0.0)
Panama	3.3 (1.2,7.8)	3.2 (1.2,7.5)	-0.1 (-0.1,-0.0)
Papua New Guinea	2.3 (0.8,5.4)	1.6 (0.6,3.6)	-1.1 (-1.4,-0.8)
Paraguay	2.4 (10.0,5.2)	3.6 (1.3,8.4)	1.5 (1.1,1.9)
Peru	0.9 (0.4,2.0)	1.9 (0.6,4.5)	2.3 (1.9,2.7)
Philippines	4.9 (1.5,12.7)	6.1 (1.8,16.4)	5.3 (3.4,7.4)
Poland	4.4 (1.5,10.9)	5.6 (1.9,14.1)	0.9 (0.7,1.1)
Portugal	2.4 (0.8,6.1)	2.4 (0.8,5.9)	-0.1 (-0.1,-0.0)
Puerto Rico	4.2 (1.5,10.0)	4.3 (1.6,10.5)	0.1 (0.1,0.1)
Qatar	4.9 (1.7,11.3)	5.0 (1.8,11.6)	0.4 (0.2,0.6)
Republic of Korea	2.0 (0.7,5.0)	2.0 (0.7,5)	-0.1 (-0.2,0.0)
Republic of Moldova	4.6 (1.6,11.3)	4.8 (1.8,12.2)	0.9 (0.3,1.6)
Romania	3.0 (1.0,7.5)	3.1 (1.1,7.7)	0.0 (0.0,0.0)
Russian Federation	6.4 (2.2,15.9)	6.4 (2.2,16)	-0.0 (-0.0,0.0)
Rwanda	1.9 (0.8,4.2)	2.2 (0.8,5.6)	-1.3 (-1.9,-0.8)
Saint Kitts and Nevis	4.4 (1.6,10.5)	4.5 (1.7,10.9)	0.1 (0.0,0.1)
Saint Lucia	4.4 (1.6,10.3)	4.5 (1.6,11.2)	0.1 (0.1,0.1)
Saint Vincent and the Grenadines	4.5 (1.7,10.5)	4.6 (1.7,11.2)	-0.1 (-0.1,-0.0)
Samoa	3.2 (1.2,7.6)	3.1 (1.1,7.3)	-0.1 (-0.1,-0.1)
San Marino	2.6 (0.9,6.5)	2.5 (0.9,5.8)	-0.2 (-0.3,-0.1)
Sao Tome and Principe	3.4 (1.2,8.1)	3.6 (1.3,8.5)	0.1 (-0.3,0.5)
Saudi Arabia	4.0 (1.4,9.2)	4.0 (1.4,9.2)	-0.1 (-0.1,-0.0)

COUNTRY	ASDR (1/100,000, 95% UI)		
	1990	2021	EAPC (95% CI)
Senegal	5.5 (2.2,11.7)	4.8 (1.9,10.6)	-0.2 (-0.5,0.1)
Serbia	3.0 (1.0,7.8)	3.1 (1.0,7.6)	0.1 (0.0,0.1)
Seychelles	2.6 (0.9,6.3)	2.8 (1,6.8)	0.4 (0.3,0.5)
Sierra Leone	6.4 (2.3,14.7)	6.6 (2.4,15.3)	-0.7 (-1.1,-0.2)
Singapore	2.0 (0.7,5.0)	2.0 (0.7,5.1)	-0.0 (-0.1,0.0)
Slovakia	3.0 (1.0,7.7)	3.0 (1.0,7.6)	0.0 (0.0,0.0)
Slovenia	1.1 (0.4,2.5)	2.0 (0.7,5.2)	2.7 (2.2,3.2)
Solomon Islands	3.3 (1.2,7.7)	3.1 (1.1,7.5)	-0.1 (-0.2,-0.1)
Somalia	2.8 (1.0,6.6)	2.8 (1.0,6.6)	0.1 (0.1,0.2)
South Africa	3.3 (1.2,8.4)	2.1 (0.7,5.5)	-0.6 (-1.3,0.1)
South Sudan	2.9 (1,6.7)	2.5 (0.9,6.1)	-0.5 (-0.6,-0.4)
Spain	1.1 (0.4,2.4)	1.7 (0.6,4.3)	2.1 (1.7,2.5)
Sri Lanka	1.5 (0.6,3.3)	2.0 (0.7,4.8)	0.3 (0.1,0.6)
Sudan	5.1 (2.1,11.1)	6.8 (2.4,15.6)	1.6 (1.2,2.0)
Suriname	4.5 (1.6,10.5)	4.4 (1.6,10.5)	-0.1 (-0.2,-0.1)
Sweden	4.2 (1.5,10.3)	4.3 (1.5,10.3)	-0.0 (-0.0,0.0)
Switzerland	2.7 (0.9,6.8)	2.6 (0.9,6.6)	-0.1 (-0.1,-0.0)
Syrian Arab Republic	2.2 (0.8,4.7)	2.6 (0.9,5.8)	1.2 (0.7,1.6)
Taiwan (Province of China)	3.2 (1.1,7.9)	3.1 (1.1,7.8)	-0.1 (-0.1,-0.1)
Tajikistan	2.6 (0.9,5.9)	1.7 (0.7,3.7)	-1.5 (-1.8,-1.2)
Thailand	1.7 (0.7,3.8)	2.4 (0.8,5.5)	0.3 (0.1,0.6)
Timor-Leste	2.1 (0.8,5.2)	2.1 (0.7,5.1)	-0.3 (-0.7,0.2)
Togo	3.4 (1.4,7.6)	4.9 (1.8,11.7)	0.3 (-0.1,0.7)
Tokelau	3.0 (1.1,6.9)	3.1 (1.1,7.2)	0.2 (0.1,0.2)
Tonga	2.9 (1,6.7)	2.8 (1.0,6.6)	-0.1 (-0.1,0.0)

COUNTRY	ASDR (1/100,000, 95% UI)		
	1990	2021	EAPC (95% CI)
Trinidad and Tobago	3.8 (1.6,8.6)	5.2 (1.9,12.1)	0.4 (0.2,0.6)
Tunisia	2.5 (1,5.5)	3.3 (1.1,7.7)	1.4 (1.2,1.5)
Turkey	2.1 (0.8,4.6)	3.2 (1.2,7.9)	0.1 (-0.4,0.6)
Turkmenistan	3.0 (1.1,7.1)	3.2 (1.2,7.7)	0.3 (0.3,0.3)
Tuvalu	2.8 (1,6.5)	3.3 (1.2,7.6)	0.6 (0.6,0.7)
Uganda	2.3 (0.9,5)	0.9 (0.4,1.9)	-3.4 (-3.6,-3.1)
Ukraine	6.0 (1.9,15.2)	6.2 (2.1,15.2)	1.3 (0.8,1.8)
United Arab Emirates	4.7 (1.7,10.8)	4.5 (1.6,10.2)	0.0 (-0.1,0.2)
United Kingdom	3.8 (1.4,9.4)	3.8 (1.3,9.2)	-0.0 (-0.1,-0.0)
United Republic of Tanzania	1.5 (0.6,3.2)	0.9 (0.3,2.1)	-1.5 (-1.8,-1.3)
United States of America	2.5 (0.9,6.4)	3.3 (1.1,8.2)	0.8 (0.1,1.5)
United States Virgin Islands	4.2 (1.5,10.2)	4.4 (1.6,10.7)	0.1 (0.0,0.1)
Uruguay	3.0 (1.1,7.4)	2.9 (1.1,7.1)	-0.1 (-0.1,-0.0)
Uzbekistan	2.4 (0.9,5.5)	2.4 (0.9,5.5)	0.7 (0.5,1.0)
Vanuatu	3.1 (1.1,7.4)	3.1 (1.1,7.5)	0.0 (-0.0,0.0)
Venezuela (Bolivarian Republic of)	2.7 (1.0,6.5)	2.6 (0.9,6.2)	-0.0 (-0.1,-0.0)
Viet Nam	1.3 (0.4,3.0)	1.3 (0.5,3.1)	1.7 (1.2,2.2)
Yemen	3.9 (1.4,9.1)	4.5 (1.6,10.8)	0.2 (-0.4,0.9)
Zambia	2.6 (1.1,5.4)	2.2 (0.8,5.3)	-2.5 (-3.2,-1.7)
Zimbabwe	1.4 (0.5,3.0)	1.7 (0.6,4.1)	-0.8 (-1.3,-0.4)

Abbreviations:

DALYs = Disability-Adjusted Life Years;
ASDR = Age-Standardized Disability-Adjusted Life Years Rate;
EAPC = Estimated Annual Percentage Change;
UI = Uncertainty Interval;
CI = Confidence Interval

Appendix 2: Exposure to endocrine disrupting chemicals (EDCs) and testicular abnormalities: summary and baseline characteristics of EU studies[204].

STUDY ID	YEAR OF PUBLICATION	STUDY DESIGN	LOCATION	NUMBER OF HYPOSPADIAS CASES	NUMBER OF CRYPTORCHIDISM CASES	NUMBER OF CONTROLS	EXPOSURE ASSESSMENT	MATERNAL CHARACTERISTICS			MAIN CHEMICALS	CONCLUSIONS
								AGE, MEAN CASES/ CONTROL (IN YEARS)	PREVIOUS PREGNANCY, N CASES/ CONTROL	SMOKING, N CASES/ CONTROL		
García-Rodríguez[109]	1996	Case-control	Spain	131	NA	243	Geographical destination-based	NA	NA	NA	Pesticides	"Our results are compatible with a hypothetical association between exposure to hormone-disruptive chemicals and the induction of cryptorchidism."
Weidner[128]	1998	Case-control	Denmark	1345	6177	23,273	Occupation-based	NA	NA	NA	NR	"The increased risk of cryptorchidism among sons of female gardeners could suggest an association with prenatal exposure to occupationally related chemicals."
Pierik[120]	2004	Case-control	The Netherlands	56	78	313	Survey-based	NA	NA	51/98	EDC Pesticides Solvents	"This study suggests that paternal environmental exposures may increase the risk of cryptorchidism and hypospadias in newborn boys, which may indicate an effect on the paternal germline."
Brouwers[100]	2007	Case-control	The Netherlands	583	NA	251	Survey-based	NA	35/6	133/35	NR	"The associations found in this study support the hypothesis that genetic predisposition, placental insufficiency, and substances that interfere with natural hormones play a role in the etiology of hypospadias."
Carbone[102]	2007	Case-control	Italy	43	48	203	Survey-based	NA	NA	12/9	Pesticides	"The study provides only limited support to the hypothesis of a possible association between the risk of cryptorchidism and hypospadias and the occupational exposure to EDC and agricultural work."

STUDY ID	YEAR OF PUBLICA-TION	STUDY DESIGN	LOCATION	NUMBER OF HYPO-SPADIAS CASES	NUMBER OF CRYPTOR-CHIDISM CASES	NUMBER OF CONTROLS	EXPOSURE ASSESSMENT	MATERNAL CHARACTERISTICS			MAIN CHEMICALS	CONCLUSIONS
								AGE, MEAN CASES/ CONTROL (IN YEARS)	PREVIOUS PREGNANCY, N CASES/ CONTROL	SMOKING, N CASES/ CONTROL		
Fernandez[105]	2007	Case-control	Spain	50		114	Placenta tissue sample	NA	4/6	11/35	DDT Endosulfan I-Lindane-Mirex Heptachlor epox-ide-b-Hexachloro-cyclohexane	"We found an increased risk for male urogenital malformations related to the combined effect of environmental estrogens in the placenta."
Brucker-davis[101]	2008	Case-control	France	NA	78	86	Colostrum sample-based	30/30	41/44	NA	PCB DDE-mBP	"Our results support an association between congenital cryptorchidism and fetal exposure to PCBs and possibly DDE. Higher concentrations in milk could be a marker of higher exposure or for an impaired detoxification pattern in genetically predisposed individuals."
Dugas[104]	2009	Case-control	England	471	NA	490	Survey-based	NA	NA	NA	Biocide Naphthalene Insect repellent Pesticides-POC-ALK-BPC-Heavy metals-Phthalates.	"The authors found an association between the use of insect repellent and total biocide score and risk of hypospadias. In particular, the use of insect repellent warrants further investigation, specifically in relation to type, content, and frequency of use since this information was missing in the current study."
Ormond[119]	2009	Case-control	England	471	NA	490	Survey-based	NA	NA	113/88	Hair spray Cleaning agents Printing ink Exhaust fumes PBDE	"Excess risks of hypospadias associated with occupational exposures to phthalates and hair spray suggest that antiandrogenic EDCs may play a role in hypospadias. Folate supplementation in early pregnancy may be protective."

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								AGE, MEAN CASES/ CONTROL (IN YEARS)	PREVIOUS PREGNANCY, N CASES/ CONTROL	SMOKING, N CASES/ CONTROL		
Giordano[110]	2010	Case-control	Italy	80	NA	80	Serum sample-based	NA	NA	NA	EDC Polychlorinated organic compounds ALK Biphenolic compounds Heavy metals	"This study, although based on a limited number of cases, for the first time provides evidence of an association between maternal exposure to EDCs, in particular elevated plasma hexachlorobenzene concentration, and the development of hypospadias in the offspring."
Gabel[108]	2011	Cohort	Denmark	11	17	477	Survey-based	NA	NA	NA	NR	"The data are compatible with a slightly increased risk of cryptorchidism in sons of women exposed to pesticides by working in horticulture."
Suarez-Varela[124]	2011	Cohort	Spain	262	1002	NA	Survey-based	NA	NA	NA	EDC Pesticides Organochlorine compounds Phthalate esters ALK Heavy metals Bis-phenols	"The study provides some but limited evidence that occupational exposure to possible endocrine disrupting chemicals during pregnancy increases the risk of hypospadias."
Wagner-mahler[126]	2011	Case-control	France	NA	95	188	Survey-based	NA	NA	NA	Phthalates Heavy metals	"Our results suggest that maternal exposure to anti-rust or phthalates could be a risk factor, whereas eating fruits daily seemed somewhat protective. The prevalence of cryptorchidism in our area is on the lower bracket compared with other countries and is associated with familial and environmental risk factors."

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								AGE, MEAN CASES/ CONTROL (IN YEARS)	PREVIOUS PREGNANCY, N CASES/ CONTROL	SMOKING, N CASES/ CONTROL		
Rignell-hydbom[121]	2012	Case-control	Sweden	237	NA	237	Serum sample-based	NA	NA	NA	PCB DDE HCB Halogenated organic monochlorophenoxy acid or ester Organochlorine-Organotin Phosphine-Thiocarbamate	"The present study suggests that fetal exposure to HCB and p,p'-DDE may be a risk factor for hypospadias."
Jørgensen[115]	2013	Cohort	Denmark	33	134	NA	Occupation-based	NA	NA	NA	NR	"Our nationwide cohort study shows that, despite exposure to a complex chemical milieu, hairdressers do not have an increased risk of having boys with cryptorchidism and hypospadias."
Vesterholm Jensen[125]	2014	Case-control	Denmark-Finland	NA	215	108	Cord sample-based	NA	NA	NA	PFOA PFOS	"Our data indicate that women in Denmark and Finland are generally exposed to PFOA and PFOS, but there are differences in exposure levels between countries. We found no statistically significant association between cord blood PFOA and PFOS levels and congenital cryptorchidism; however, our study was small, and larger studies are warranted."
Jørgensen[116]	2014	Cohort	Denmark	NA	229	NA	Occupation-based	NA	NA	NA	NR	"This nationwide cohort study found a slightly increased risk of cryptorchidism in sons of maternal horticultural workers and farmers. However, subgroup analyses indicated similar findings for paternal horticultural workers and no association for women likely working in the first trimester. The main findings should, therefore, be interpreted with caution."
Fernandez[106]	2016	Case-control	Spain	28		51	Placenta tissue sample	29/30	16/4	17/5	Methyl-PB-ethyl-PB Propyl-PB-butyl-PB	"The multivariable regression analyses indicated a statistically significant association between exposure to BPA and propyl-PB and the risk of malformations."

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								AGE, MEAN CASES/ CONTROL (IN YEARS)	PREVIOUS PREGNANCY, N CASES/ CONTROL	SMOKING, N CASES/ CONTROL		
Jensen[114]	2015	Case-control	Denmark	75	270	300	Amniotic fluid sample	NA	NA	NA	Phthalate	"Data on the DEHP metabolite indicate possible interference with human male fetal gonadal function. Considering the DiNP metabolite, we cannot exclude (nor statistically confirm) an association with hypospadias and, less strongly, with cryptorchidism."
Kalfa[117]	2015	Case-control	France	300	NA	302	Survey-based	NA	NA	NA	EDC Pesticides Cosmetics Herbicides Detergents ALK Phthalates Heavy metals	"Our multi-institutional study showed that parental professional, occupational, and environmental exposures to chemical products increase the risk of hypospadias in children."
Koskenniemi[118]	2015	Case-control	Turkey-Denmark-Finland	NA	44	38	Serum sample-based	NA	NA	NA	PCB PBDE	"Prenatal exposure to PCDD/Fs and PCDD/F-like PCBs may be associated with increased risk for cryptorchidism. Our finding does not exclude the possibility of an association between the exposure to PBDEs and cryptorchidism."
Haraux[112]	2016	Case-control	France	57	NA	162	Survey-based	29.7/28.7	NA	NA	EDC Hair cosmetic Insecticides	"Our results suggest that maternal occupational exposure to EDCs is a risk factor for hypospadias and suggests a possible influence of household use of hair cosmetics during early pregnancy on the incidence of hypospadias in the offspring."
Warembourg[127]	2017	Case-control	France	15	14	86	Urine sample-based	NA	NA	19/9	MAA PhAA	"In view of the toxicological plausibility of our results, this study, despite its small sample size, raises concern about the potential developmental toxicity of MAA on the male genital system and calls for thorough identification of current sources of exposure to MAA."

STUDY ID	YEAR OF PUBLICA-TION	STUDY DESIGN	LOCATION	NUMBER OF HYPO-SPADIAS CASES	NUMBER OF CRYPTOR-CHIDISM CASES	NUMBER OF CONTROLS	EXPOSURE ASSESSMENT	MATERNAL CHARACTERISTICS			MAIN CHEMICALS	CONCLUSIONS
								AGE, MEAN CASES/ CONTROL (IN YEARS)	PREVIOUS PREGNANCY, N CASES/ CONTROL	SMOKING, N CASES/ CONTROL		
Haraux[113]	2018	Case-control	France	25	NA	58	Meconium sample-based	29/28.2	NA	21/9	Diazinon Malathion DETP DEP DMP Isoproturon Desmethylisoproturon MCPA	"We conclude that prenatal exposure to these two herbicides (as assessed by meconium analysis) correlated with isolated hypospadias. The results of our case-control study (i) suggest that prenatal exposure to pesticides interferes with the development of the male genitalia, and (ii) emphasize the importance of preventing pregnant women from being exposed to EDCs in general and pesticides in particular."
Cognez[103]	2019	Case-control	France	50	123	8199	Survey-based	NA	NA	30/1679	Pesticides	"Our results suggest a possible increased risk of hypospadias associated with prenatal use of some domestic pesticide products, likely to contain insecticides, and of cryptorchidism with nearby orchard acreage (crops repeatedly sprayed with pesticides). This work is limited by its modest number of cases."
Estors Sastre[129]	2019	Case-control	Spain	210		210	Survey-based	NA	NA	33/29	EDC	"Advanced age, some parental occupational exposure to EDCs, some drug consumption, smoking, and the father's history of urological disorders may increase risk and predict the developments of these malformations. Studies with larger sample sizes are needed to assess associations between individual EDC occupational exposures and drugs and these malformations."
Axelsson[130]	2020	Case-control	Sweden	NA	165	165	Serum sample-based	29/28	NA	15/16	PCB DDE HCB	"We found no evidence of an association between maternal levels of PCB or HCB during the pregnancy and the risk of having cryptorchidism in the sons."

STUDY ID	YEAR OF PUBLICA-TION	STUDY DESIGN	LOCATION	NUMBER OF HYPO-SPADIAS CASES	NUMBER OF CRYPTOR-CHIDISM CASES	NUMBER OF CONTROLS	EXPOSURE ASSESSMENT	MATERNAL CHARACTERISTICS			MAIN CHEMICALS	CONCLUSIONS
								AGE, MEAN CASES/ CONTROL (IN YEARS)	PREVIOUS PREGNANCY, N CASES/ CONTROL	SMOKING, N CASES/ CONTROL		
Fisher[107]	2020	Case-control	UK	NA	30	275	Serum sample-based	32.98/33.54	NA	0/4	Phthalates BPA TCS BP-3	"Our observational findings support experimental evidence that intrauterine exposure to BPA and n-PrP during early gestation may adversely affect male reproductive development. More evidence is required before specific public health recommendations can be made."
Bougneres[205]	2021	Case-control	France	8766	13,105	43,830	Geographical destination-based	NA	NA	NA	NR	"Our study supports that children born to mothers living close to a vineyard have a two-fold increased risk of H. For environmental research, using VC = provides an alternative to a classical case-control technique."
Spinder[123]	2021	Case-control	The Netherlands	364	NA	5602	Survey-based	NA	NA	NA	EDC Pesticides ALK Phthalates Benzophenones parabens-siloxanes Phthalates ALK Heavy metals	"Women, their healthcare providers, and their employers need to be aware that occupational exposure to specific EDCs early in pregnancy may be associated with CAKUT in their offspring. An occupational hygienist should be consulted in order to take exposure to those specific EDCs into consideration when risk assessments are carried out at the workplace."
Rouget[122]	2024	Case-control	France	69	NA	135	Meconium sample-based	NA	35/39	21/36	Nitrophenol-diethyl phosphate-Fenitrothion-Carbofuran	"Our small study provides a robust assessment of fetal exposure. Fenitrothion's established antiandrogenic activities provide biological plausibility for our observations. Further studies are needed to confirm this hypothesis."

Abbreviations:

NA = Not applicable; **NR** = Not Reported; **DDT** = dichlorodiphenyl trichloroethane; **EDC** = Endocrine-disruptors chemicals; **HCB** = Hexachlorobenzene; **PCB** = polychlorinated biphenyls; **ALK** = alkylphenolic compounds; **BPA** = bisphenol; **DETP** = diethyl phosphate; **DDE** = dichloro diphenyl dichloro ethylene; **PHAA** = phenoxy acetic acid; **MAA** = methoxy acetic acid; **DES** = diethylstilbestrol; **PFOS** = perfluorooctanesulfonic acid; **PFOA** = perfluorooctanoic acid; **BP-3** = Benzophenone-3; **TCS** = triclosan; **OR** = Odds ratio.

Appendix 3: Exposure to endocrine disrupting chemicals (EDCs) and testicular cancer: summary and baseline characteristics of EU studies[133].

AUTHOR, YEAR	LOCATION	POPULATION	STUDY DESIGN	EXPOSURE	EXPOSURE CONTRAST	XENOBIOTIC	ALL TGCT			NONSEMINOMA		SEMINOMA	
							NCASES/ CONTROLS	RR/OR	95% CI	RR/OR	95% CI	RR/OR	95% CI
MATERNAL EXPOSURE													
Biospecimens													
Hardell et al[135]	Sweden	Hospital departments in 5 Swedish cities	Case referent	Maternal serum at sons diagnostic	Dichotomized (cutoff median for controls)	Sum PCB	44/45	3.8	1.4-10	4.3	1.3-14	3.1	0.7-14
						HCB		4.4	1.7-12	9.0	2.4-33	2.1	0.6-8.2
						p,p′-DDE		1.3	0.5-3.0	1.4	0.5-4.0	1.0	0.3-3.7
						cis-Heptachlordane		2.1	0.8-5.0	1.8	0.7-4.7	3.2	0.8-13
						cis-Chlordane		2.5	1.0-6.1	2.1	0.7-5.7	4.3	1.1-17
						Oxychlordane		2.6	0.9-7.1	2.5	0.8-7.9	3.3	0.7-16
						MC6		1.3	0.5-3.2	1.3	0.5-3.6	1.3	0.4-5.0
						trans-Nonachlordane		4.1	1.5-11	5.6	1.7-19	1.9	0.5-7.5
						cis-Nonachlordane		3.1	1.2-7.8	2.8	1.0-7.8	4.1	1.0-18
						Sum chlordane		1.9	0.7-5.0	2.4	0.8-7.3	1.2	0.3-4.8

AUTHOR, YEAR	LOCATION	POPULATION	STUDY DESIGN	EXPOSURE	EXPOSURE CONTRAST	XENOBIOTIC	ALL TGCT			NONSEMINOMA		SEMINOMA	
							NCASES/ CONTROLS	RR/OR	95% CI	RR/OR	95% CI	RR/OR	95% CI
Hardell et al[136]	Sweden	Hospital departments in 5 Swedish cities	Case referent	Maternal serum at sons diagnostic	Dichotomized (cutoff median for controls)	PCB 74	44/45	3.0	1.2-7.6	2.8	1.0-7.9	3.3	0.8-14
						PCB 99		2.4	1.0-5.7	2.6	0.9-7.2	1.6	0.5-6.0
						PCB 114		1.7	0.7-4.2	1.7	0.6-4.5	2.0	0.5-7.6
						PCB 105		1.8	0.7-4.3	2.2	0.8-6.1	0.9	0.3-3.3
						PCB 153		2.7	1.1-6.8	3.5	1.2-10	1.4	0.4-5.3
						PCB 138		2.8	1.1-7.1	4.0	1.3-12	1.5	0.4-5.3
						PCB 128/167		3.8	1.5-9.8	3.4	1.2-9.8	5.7	1.1-29
						PCB 156		3.8	1.4-9.9	4.2	1.3-13	3.7	0.9-16
						PCB 178		2.9	1.1-7.7	3.9	1.2-13	1.7	0.4-7.4
						PCB 182/187		2.3	0.9-5.8	2.9	1.0-8.5	1.5	0.4-5.4
						PCB 183		2.5	1.0-6.2	3.1	1.1-8.8	1.7	0.5-5.9
						PCB 174		2.0	0.8-5.0	2.7	0.9-7.5	1.1	0.3-3.9
						PCB 177		2.0	0.8-5.0	3.8	1.2-12	0.7	0.2-2.4
						PCB 180		2.5	1.0-6.3	2.7	0.9-9.6	2.1	0.5-7.9
						PCB 170/190		3.1	1.2-8.2	4.0	1.3-12	1.9	0.5-7.8
						PCB 189		3.3	1.3-8.4	4.7	1.5-14	2.1	0.6-7.6
						PCB 208		3.4	1.3-8.6	2.9	1.0-8.1	5.7	1.2-27
						PCB 207		3.0	1.2-7.5	2.9	1.0-8.1	3.7	0.9-15
						PCB 209		1.4	0.6-3.4	1.5	0.5-4.1	1.4	0.4-5.1
						Estrogenic PCBs	30/20	2.4	1.0-6.0	2.4	0.8-6.8	2.3	0.6-8.9
Hardell et al[134]	Sweden	Hospital departments in 5 Swedish cities	Case referent	Maternal serum at son's diagnostic	Dichotomized (cutoff median for controls)	PBDE (47, 99, 153)	44/45	2.5	1.0-6.0	2.9	1.0-8.2	1.8	0.5-6.5

AUTHOR, YEAR	LOCATION	POPULATION	STUDY DESIGN	EXPOSURE	EXPOSURE CONTRAST	XENOBIOTIC	ALL TGCT			NONSEMINOMA		SEMINOMA	
							NCASES/ CONTROLS	RR/OR	95% CI	RR/OR	95% CI	RR/OR	95% CI
Proxy exposures													
Kristensen et al[139]	Norway	Registry	Cohort	JEM Maternal prenatal exposure	Dichotomous (y/n)	Pesticides	188680 /323359	0.89	0.60-1.32				
						Horticulture		0.79	0.41-1.49				
Le Cornet et al[140,141]	DK, Finland, Sweden, and Norway	NORD-TEST study	Case control (nested in a birth cohort)	JEM prenatal exposure	Dichotomous (y/n)	Pesticides	8443/28752	0.83	0.56-1.23	0.72	0.43-1.21	1.03	0.57-1.88
						ARHC sum	8112/26264	1.23	0.97-1.55				
						Benzene		1.18	0.91-1.52				
						Toulene		1.22	0.88-1.68				
						CHC sum		1.05	0.84-1.31				
						Methylene chloride		1.34	0.97-1.85				
						Perchloroethylene		1.10	0.77-1.57				
						Trichloroethylene		0.92	0.69-1.24				
						1,1,1,-trichloroethane		1.03	0.80-1.32				
Nori et al[142]	Italy	Hospitals in Rome	Case referent	JEM Prenatal exposure	Dichotomous (y/n)	EDC	63/123	0.97	0.23-4.07	1.13	0.19-6.86	0.99	0.16-6.07
						Rural (pesticides)	103/215	1.35	0.49-3.71	1.29	0.34-4.94	1.54	0.44-5.35
Paoli et al[143]	Italy	Hospitals in Rome	Case referent	JEM Prenatal exposure	Dichotomous (y/n)	Pesticide	125/103	1.97	0.36-10.66				
						PVC		1.00	0.57-17.57				
						Phthalates		1.03	0.26-4.11				
						Alkyl phenolic		1.54	0.49-4.80				
POSTNATAL ADULT MALE EXPOSURE													
Biospecimens													
Giannandrea et al[137]	Italy, Rome		Case control	Serum	Dichotomized (cutoff 0.2 ng/mL) (LOD)	p,p´-DDT + HCB	50/48	3.34	1.09-10.19				
						p,p'-DDE		3.21	0.77-13.30				

AUTHOR, YEAR	LOCATION	POPULATION	STUDY DESIGN	EXPOSURE	EXPOSURE CONTRAST	XENOBIOTIC	ALL TGCT			NONSEMINOMA		SEMINOMA	
							NCASES/ CONTROLS	RR/OR	95% CI	RR/OR	95% CI	RR/OR	95% CI
Hardell et al[135]	Sweden		Case-referent	Serum at diagnosis	Dichotomized (cutoff median for controls)	Sum PCB	58/61	1.1	0.5-2.6	1.1	0.4-3.0	1.1	0.4-3.5
						HCB		1.7	0.8-3.6	1.8	0.7-4.4	1.6	0.6-4.5
						p,p'-DDE		1.7	0.8-3.7	1.9	0.8-4.7	1.5	0.5-4.5
						cis-Heptachlordane		1.6	0.8-3.4	2.1	0.9-5.1	1.4	0.5-3.7
						cis-Chlordane		1.2	0.6-2.6	1.9	0.8-4.7	0.7	0.2-1.9
						Oxychlordane		1.4	0.7-2.9	1.9	0.8-4.7	1.0	0.4-2.8
						MC6		1.3	0.6-2.9	1.8	0.7-4.9	0.9	0.3-2.7
						trans-Nonachlordane		1.0	0.4-2.1	1.2	0.4-2.9	0.7	0.2-2.1
						cis-Nonachlordane		2.6	1.2-5.7	2.0	0.8-4.7	4.8	1.4-16
						Sum chlordane		1.3	0.6-2.8	1.8	0.7-4.4	0.8	0.3-2.4
Hardell et al[136]	Hospital-based study of TC cases and healthy controls	Hospital departments in 5 Swedish cities	Case referent	Serum at diagnosis	Dichotomized (cutoff median for controls)	Estrogenic PCBs	29/30	1.3	0.5-3.0	1.5	0.5-4.1	1.0	0.3-3.5
						Enzyme inducing PCBs		1.2	0.5-2.8	1.1	0.4-3.1	1.4	0.5-4.6
						Toxic equivalents		1.4	0.6-3.2	1.6	0.6-4.3	1.1	0.3-3.5

AUTHOR, YEAR	LOCATION	POPULATION	STUDY DESIGN	EXPOSURE	EXPOSURE CONTRAST	XENOBIOTIC	ALL TGCT			NONSEMINOMA		SEMINOMA	
							NCASES/ CONTROLS	RR/OR	95% CI	RR/OR	95% CI	RR/OR	95% CI
Purdue et al[138]	Norway	The Janus Serum Bank (The Cancer Registry of Norway, Oslo, Norway)	Nested case control	Serum	highest tertile vs lowest	o,p'-DDT	34/34	1.4	0.4-4.5			2.2	0.50-8.7
						p,p'-DDT		2.1	0.6-7.2				
						p,p'-DDE		2.2	0.7-6.5				
						HCE		2.4	0.6-9.1				
						Oxychlordane		3.2	0.6-16.8			5.1	0.7-36.8
						t-Nonachlor		2.6	0.7-8.9			1.6	0.4-6.0
						Total chlordane		2.3	0.6-7.2			1.6	0.4-6.6
						β-HCCH		1.8	0.5-6.1				
						α-HCCH		1.1	0.2-5.0				
						Dieldrin		2.1	0.5-9.5				
						HCB		2.9	0.5-15.2				
						Mirex		1.2	0.4-3.0				
						PCB 44		0.6	0.1-3.8			0.2	0.01-2.0
						PCB 49		1.2	0.2-7.6			0.3	0.02-4.7
						PCB52		1.0	0.3-3.5			0.4	0.07-2.3
						PCB 99		2.2	0.8-5.9			4.4	1.0-20.5
						PCB 138		1.8	0.6-5.1			2.1	0.6-7.2
						PCB 153		1.2	0.4-3.4			1.2	0.4-4.3
						PCB 167		4.4	1.0-19.8			6.7	1.1-42.9
						PCB 183		1.3	0.5-3.5			2.9	0.6-13.7
						PCB 195		1.7	0.6-4.6			3	0.8-11.7
						Total PCB		1.3	0.5-3.8			1.2	0.4-4.1
						High degree of PCB chlorination		1.4	0.6-3.3				

AUTHOR, YEAR	LOCATION	POPULATION	STUDY DESIGN	EXPOSURE	EXPOSURE CONTRAST	XENOBIOTIC	ALL TGCT			NONSEMINOMA		SEMINOMA	
							NCASES/ CONTROLS	RR/OR	95% CI	RR/OR	95% CI	RR/OR	95% CI
Proxy exposures													
Giannandrea et al. 2011[137]	Italy, Rome	Hospital cases and controls	Case referent	Survey	Dichotomized (cutoff 0.2 ng/mL) (LOD)	Home use pesticide	50/48	4.8	0.91-25.3				
						Household insecticide		3.21	1.15-9.11				
Hardell et al[144]	Sweden, middle to north	TC patients (registry) and population Registry (controls)	Case control	JEM	None/low-grade and high-grade exposure (days)	PVC (phthalates)	148/315	6.6	1.4-32	-	-	5.6	1.1-196
						Styrene		0.6	0.2-2.0	1	0.2-6.4	0.5	0.2-2.3
						Urethane		1.5	0.4-5.6	3.2	0.3-37	1	0.2-5.5
						Acrylate		3.2	0.3-37	3.2	0.3-37	-	-
						Plastic unspecified		4.3	0.8-24	6	0.6-58	2.5	0.2-40
Helmfrid et al[145]	Sweden	Registry	Case referent	Address	Dichotomous	PCB contaminated site	7/35	2.46	0.99-5.08				

Abbreviations:

ARHC = aromatic hydrocarbon solvents; **BMI** = body mass index; **CHC** = chlorinated hydrocarbon solvents; **CI** = confidence interval; **DDE** = dichlorodiphenyldichloroethylene; **DDT** = dichlorodiphenyltrichloroethane; **HCB** = hexachlorobenzene; **HCCH** = hexachlorocyclohexane; **HCE** = heptachlor epoxide; **IQR** = interquartile range; **JEM** = job-exposure matrix; **LOD** = limit of detection; **OR** = Odds ratio; **PBDE** = polybrominated diphenyl congeners; **PCB** = polychlorinated biphenyl congeners; **PFOA** = perfluorooctanoic acid; **PVC** = polyvinyl chloride; **RR** = risk ratio; **TGCT** = testicular germ cell tumors

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