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Clinical review

How strong is the evidence of a link between environmental chemicals and adverse effects on human reproductive health?

Richard M Sharpe, D Stewart Irvine

Surveys show that the public suspects that synthetic (manmade) chemicals released into the environment, especially pesticides, have adverse effects on human health and cause disease, including cancer. In reality, few scientifically documented examples support this view, especially for effects on the general population.¹ However, the observation that many synthetic chemicals have intrinsic hormonal activity—they are “endocrine disruptors”—has reopened this debate.¹ Pressure groups have called for all synthetic environmental chemicals with the potential to cause harm to be phased out or banned, whereas the chemical industry argues that such action must be based on proof of harm. Vociferous cases have been made on both sides, each lacking definitive data. Yet it is clear that environmental and lifestyle factors are key determinants of human disease—accounting for perhaps 75% of most cancers.² New understanding and emerging results are reshaping our thinking, as is the recognition that establishing cause and effect for environmental chemical exposures is a daunting task.

Methods and scope

Though this article is primarily an overview of the current evidence for reproductive effects resulting from exposure to environmental synthetic chemicals, it is relevant to the debate on wider potential health effects of such exposures. The review was compiled after detailed literature searches and cross referencing and scrutiny of relevant websites on environmental chemicals (see educational resources box). After revising the article in light of reviewers' comments, we sought the opinion of an expert toxicologist in industry to ensure balance in the review.

In this hugely contentious area, polarised opinions predominate (because of the lack of definitive data). There are enormous difficulties in establishing whether exposure to individual chemicals or to chemical mixtures causes harm, as adverse effects may not manifest until many years after exposure (for example, in adulthood after fetal exposure). This difficulty must be factored into any discussion of this topic.

Individuals versus populations, hazard versus risk

Many synthetic chemicals can cause ill health or death if individuals are highly exposed, whether unintentionally^{w1-w3} or by design—for example, from swallowing an undiluted pesticide.³ Clearly, there is not the same health risk to the general population, who may be exposed to the same chemical at levels many thousand times lower, after its release into the environment (such as by spraying on crops). Recognising that a synthetic chemical has the potential to cause harm reveals a “hazard.” The “risk” of this chemical actually inducing a biological effect depends on the properties of that chemical, but will occur only when exposure reaches a particular level, and this can be determined by standard toxicological methods. Risk management is then the process of ensuring that populations and individuals are not exposed to a risk level of the chemical in question, and this always incorporates large (10-fold to 1000-fold) safety margins that allow for differences in susceptibility between individuals and between species (as toxicology testing is primarily in animals). For pesticides, risk assessment is a highly regulated process.

If a chemical can cause harm at very low levels of exposure, or if levels of the chemical can build up in the body (bioaccumulation), it may be decided that risk cannot be safely managed, and in such instances use of the chemical may be banned. For example, use of persistent organochlorine chemicals, of which DDT (dichlorodiphenyltrichloroethane) and PCBs (polychlorinated biphenyls) are prime examples, has been banned or restricted since the 1970s because they bioaccumulate and cause adverse effects.¹ This decision was based primarily on adverse effects on wildlife rather than effects on humans. Indeed, the DDT saga was largely responsible for the introduction of the stringent regulation and surveillance of pesticides that occurs today. Yet despite this reassurance, pesticides dominate the chemical concerns of the public.

It would perhaps be more logical for public concern to be focused on the enormous numbers of

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References w1-w26 and extended explanations of the figures are on bmj.com

(non-pesticide) synthetic chemicals present in the environment, for which toxicity or human exposure levels, or both, are unclear.¹ These chemicals (phthalates, for example) can leach out of plastics, carpets, and fabrics into air, rainwater, and food; are present in many creams, soaps, and perfumes with which we adorn our bodies; or emanate from exhaust, cigarette, and combustion fumes.¹⁻⁴ These are the synthetic chemicals to which we are most highly exposed, yet with a few notable exceptions, we know little about the risk they pose to health.¹ This is so even when a toxicity profile has been established, as is the case for phthalates: arguably their most important potential adverse effect—on sexual differentiation in male fetuses⁵—was discovered only four years ago. It has also become apparent in the past two years that human exposure to phthalates is both higher^{6,7} and more complex^{w4} than had been supposed. This has prompted renewed scrutiny of phthalates.

Endocrine disruptors and reproductive disease or cancers

An endocrine disruptor is a chemical with the potential to alter hormone action within the body.¹ The first endocrine disruptors identified were synthetic chemicals that had weak intrinsic hormonal or anti-hormonal activity, usually oestrogenic or anti-androgenic activity.¹

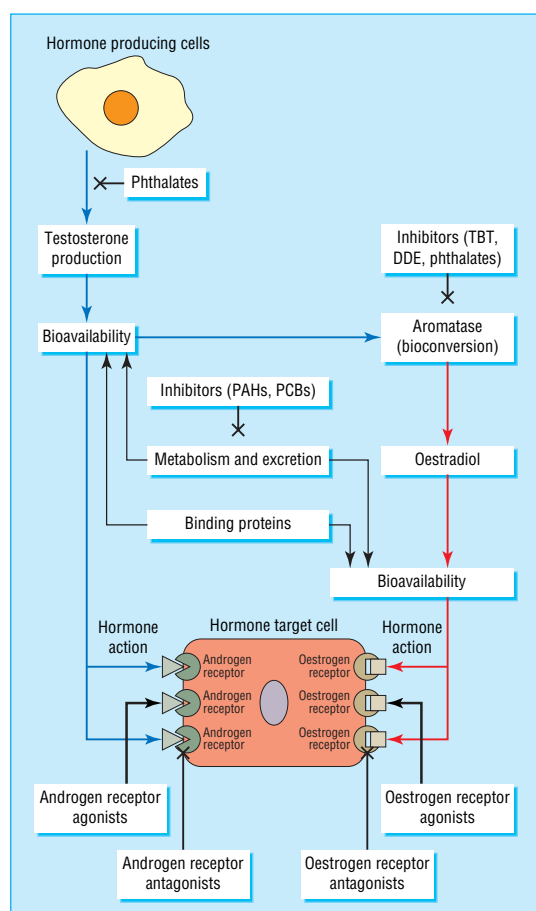


Fig 1 Potential pathways of endocrine disruption by environmental chemicals. DDE=1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene; PAHs=polycyclic aromatic hydrocarbons; PCBs=polychlorinated biphenyls; TBT=tributyltin

Such compounds, when in the body, have the potential to interact with oestrogen or androgen signalling mechanisms (fig 1). Many ubiquitous environmental chemicals, including organochlorine chemicals, and numerous synthetic chemicals prevalent in developed societies (phenolic compounds, for example) are endocrine disruptors.¹⁻⁵ As endocrinology textbooks show, disturbance of hormonal homeostasis can result in clinical problems. However, it remains a topic of heated debate as to whether the potential of endocrine disruptors to disrupt hormone action and cause ill health in humans is a reality or merely a remote, theoretical possibility. What has fuelled this debate has been the increase in incidence of two hormone dependent disorders in humans over the past 70 or more years, namely breast cancer⁸ and testicular dysgenesis syndrome (comprising low sperm counts, testicular cancer, cryptorchidism, and hypospadias) (fig 2).⁸⁻¹⁰

Out of this concern, epidemiological studies were prompted, focusing on exposure to organochlorine chemicals and breast cancer, because many organochlorine chemicals are oestrogenic and, also, they are lipophilic and can accumulate in breast fat. One initial study produced evidence linking organochlorine chemical exposure to increased risk of breast cancer,^{w6} but most subsequent studies have not confirmed this.¹¹ These have included studies in different countries and those that evaluated exposure to organochlorine chemicals many years before breast cancer developed.¹¹ Although these results are reassuring, doubts remain about whether the most important chemicals were measured,¹²⁻¹⁴ whether exposure in the correct age window was evaluated,^{w9} and what effect mixtures of chemicals may have.¹³ Present evidence suggests that exposure, as an adult, to organochlorine chemicals alone is not a major determinant of breast cancer. Indeed, it seems intuitively unlikely that endocrine disruptors with weak intrinsic oestrogenic activity¹⁻¹³ can be as important hormonal players in the aetiology of breast cancer as the woman's own potent endogenous oestrogens.¹⁴

For testicular dysgenesis syndrome in males, the aetiological involvement of endocrine disruptors is mainly theoretical.¹⁰ Testicular dysgenesis syndrome is thought to arise during early pregnancy. Measuring exposure of the human fetus to chemicals and relating this to disorders that may arise decades later (low sperm counts, testis cancer) has major logistical problems. However, a recent study that reported higher levels of organochlorine chemicals in mothers of men with testicular cancer,¹⁵ and new discoveries about phthalates (see below), have reawakened interest in the possible aetiological involvement of environmental chemicals in testicular dysgenesis syndrome.^{w9}

"Trojan horse" environmental chemicals

Phthalates are present everywhere in our environment. In laboratory animals, administering certain phthalates to pregnant females induces a syndrome resembling testicular dysgenesis syndrome in the male offspring.^{5,16} This occurs not because of any intrinsic hormonal activity of phthalates, but because they can suppress endogenous testosterone production by the

fetal testis (fig 1), thus interfering with sexual differentiation. Though recent reports show higher levels of human exposure to phthalates than had been supposed,^{6 7} and although women of reproductive age are identified as a group with notably high exposure,^{4 6} these levels still fall considerably short of those used so far in animal studies.

Arguably the most important lesson from the phthalate studies has been the recognition that environmental chemicals with the potential to alter endogenous hormone production or metabolism may pose a greater risk than do the many weak, receptor mediated endocrine disruptor agents described in the literature.¹ Such biochemical endocrine disruptors seem from screening assays based on hormone receptors to be innocuous—thus they resemble the “Trojan horse.” More and more of these agents are being identified, including common environmental chemicals.¹⁷ For example, polychlorinated biphenyls (PCBs)^{w10} and certain polyhalogenated aromatic hydrocarbons (PAHs),^{w11} which are products of combustion, are potent suppressors of the enzyme oestrogen sulphotransferase-1,¹⁷ which sulphates oestradiol before it is excreted. Such suppression can prolong the action of oestrogen (fig 1), a change relevant to breast cancer.^{w12}

New evidence for reproductive effects of environmental chemicals

Though most concern about effects of environmental chemicals has focussed on fetal effects (for example, in testicular dysgenesis syndrome),^{10 17 w5} recent studies point also to postnatal effects. For example, exposure of boys to endosulfan is associated with delayed puberty, though this could have resulted from prenatal exposure.¹⁸ More dramatically, fertile men in an agricultural area of Missouri have been shown to have sperm counts about 40% lower than men in three urban US areas,^{w13} and to have higher urinary concentrations of three currently used pesticides.¹⁹ Similarly, direct measurement of certain phthalate metabolites is significantly related to reduced semen quality in men,²⁰ endometriosis in women,²¹ and shorter gestation periods in pregnant women.²² Although these new findings are suggestive, for none is the mechanism of the chemical's effect self evident. This leaves doubts as to whether the measured chemicals are the real culprits or are surrogates for other chemical exposures or lifestyle practices.

Warnings from wildlife studies?

Despite these examples, the evidence linking human disease and exposure to environmental chemicals remains sketchy.¹ Whether this reflects absence of such effects or whether it reflects the immense difficulties in demonstrating such effects, especially where these might involve exposure to mixtures of chemicals, remains open to debate. In the absence of definitive data, what should guide our actions? Those who work with wildlife species point to proof of major effects of environmental chemicals, ranging from the effects of DDT on birds to the more recent “feminisation” of male fish by oestrogens.¹ However, the most

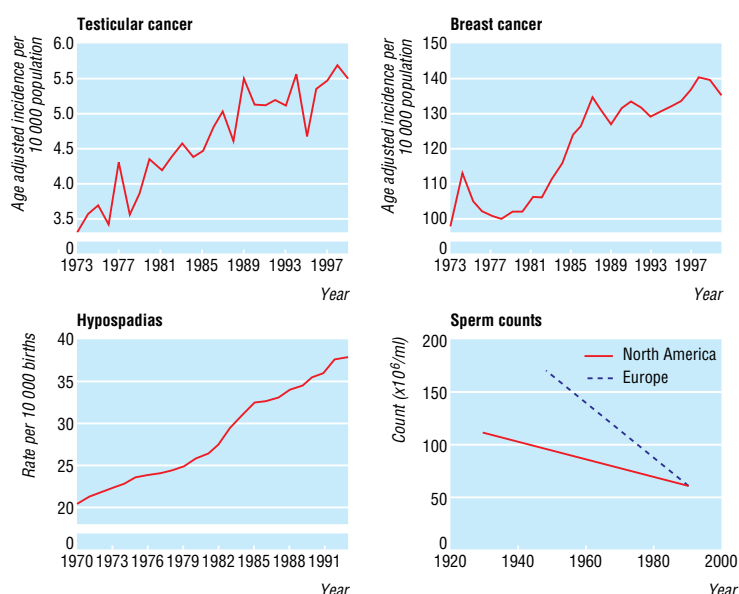


Fig 2 Trends in reproductive health, United States (for data sources see bmj.com)

dramatic example, and the least well known by the public, is the worldwide catastrophic effect of tributyltin (TBT) on certain shellfish.¹ Tributyltin is an antifouling agent painted onto ships' hulls, which then leaches into seawater, where it masculinises female shellfish, preventing reproduction.^{w14} Tributyltin is a “Trojan horse” chemical, suppressing activity of endogenous aromatase, thus preventing oestradiol production (fig 1).¹

As with tributyltin, many examples of the damaging effects of environmental chemicals on wildlife involve aquatic animals.¹ Because they may be exposed continuously to chemicals dissolved in the water, aquatic animals may act as sentinels for potential effects on the fetus, sitting as it does in an aqueous environment for nine months. However, fetal exposure would depend on the mother's level of exposure (fig 3).²³ Recently, fetal

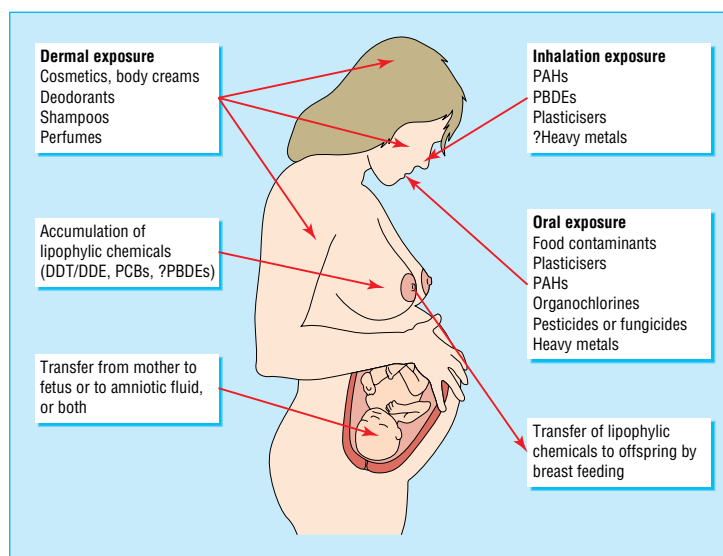


Fig 3 Routes of human exposure to some common environmental chemicals. DDE=1,1-dichloro-2, 2-bis(p-chlorophenyl)ethylene, DDT=dichlorodiphenyltrichloroethane, PAHs=polycyclic aromatic hydrocarbons, PCBs=polychlorinated biphenyls

Key recommendations by the Royal Commission on Environmental Pollution

- *Management:* Government to establish a chemicals safety coordination unit that unites existing organisations dealing with chemicals safety
- *Sorting and safety testing:* All chemicals “of concern” in current use (especially those not safety tested) to be sorted into “categories of concern” according to hazard assessment; the most hazardous to be selected for further investigation
- *Evaluation:* Chemicals found in unexpected environmental compartments or at unexpected concentrations, or associated with unusual biological phenomena, should be selected for further investigation
- *Risk management:* Where synthetic chemicals are found in raised concentrations in biological fluids such as breast milk and in tissues of humans, marine mammals, or top predators, regulatory steps should be taken to remove them from the market immediately
- *Funding (chemicals charge):* Marketed chemicals to be levied with a tax that is scaled according to the “category of concern.” This levy will be used to fund the recommendations and further testing, and will provide a financial incentive for industry to substitute chemicals “of concern” by environmentally safer alternatives
- *Legislation:* New legislation to prohibit marketing of any chemical for which basic environmental safety data is not registered

See www.rcep.org.uk/chreport.html for the full report (Chemicals in Products—Safeguarding the Environment and Human Health)

exposure to organochlorine chemicals has been related to effects on subsequent fertility²⁴ and testicular cancer,¹⁵ and maternal smoking has been related to reduced sperm counts in human offspring.²⁵ As fetal life is increasingly recognised as a time when susceptibility to adult disease may be induced as a result of dietary or lifestyle effects of the mother,^{w15} more effects of chemical exposures seem likely to emerge.^{w16-w20}

Additional educational resources

- Regularly updated information and links on environmental chemicals and research into their effects on wildlife species and humans: www.EnvironmentalHealthNews.org (published daily by Environmental Health Sciences)
<http://ehp.niehs.nih.gov/who> (journal of the National Institute of Environmental Health Sciences)
<http://e.hormone.tulane.edu> (scientific and media information about environmental signalling)
www.OurStolenFuture.org (regularly updated website that followed on from a book by Theo Colborn, Dianne Dumanoski, and John Peterson Myers)
- Exposure data for a wide range of environmental chemicals in a representative US population is available in a recent report: www.cdc.gov/exposurereport (Second National Report on Human Exposure to Environmental Chemicals)
- Overview of the possible relationships between exposure to environmental chemicals and breast cancer: www.breastcancerfund.org/environment_evidence_main.htm
- Data on cancer incidence:
<http://seer.cancer.gov> (USA (Survey, Epidemiology, and End Results), including breast and testicular cancer)
www.enr.com.fr (European data (European Network of Cancer Registries))
www.statistics.gov.uk (UK data)
www.isdscotland.org/isd (Scottish health statistics (Information & Statistics Division))

Summary points

Little definitive data links human reproductive disorders or cancers with exposure to environmental synthetic chemicals; this may reflect difficulties in obtaining such data or the genuine absence of effects

Synthetic chemicals are pervasive in the environment, but understanding of their potential to cause harm is limited

Several recent studies have shown associations between prenatal or postnatal exposure to certain pesticides or phthalates and reproductive disorders in humans

Reproductive effects of environmental chemicals in (aquatic) wildlife are well established; these may provide sentinels for human effects, especially on the fetus

Recent discoveries raise possibilities of effects of common environmental chemicals on endogenous hormones

Conclusion

Human exposure to environmental synthetic chemicals has changed considerably in the past 70 years. This period has witnessed major changes in our diets, lifestyle, and social practices, some of which may be having profound effects on human health. If environmental chemicals are exerting adverse health effects in humans, these are likely to be small in relation to those caused by our dietary and lifestyle changes, although these factors may interact.^{w21 w22} Moreover, proving that environmental chemicals do—or do not—cause health problems in humans against this changing background is challenging. Nowhere is this truer than in evaluating the impact of maternal exposures in pregnancy that may affect health of the fetus in later life. This is unquestionably the greatest concern,¹ and we believe that alternative precautionary strategies must be adopted, which seek to eliminate or minimise unnecessary risks to the fetus, even in the absence of clear proof of harm. Some of these steps can be taken by individuals—for example, lifestyle changes in women seeking to become pregnant (stopping smoking, reduced use of cosmetics and body creams). Reducing exposures by reducing release of chemicals to the environment, however, requires action by industry and government. The proposals by the Royal Commission on Environmental Pollution as to how this may be achieved (box) seem to be a practical and effective path towards such a goal.

Contributors: The authors are both employed and paid by the Medical Research Council (MRC) and each heads a research team, focused on the causes of abnormal male reproductive development and function, within the MRC Human Reproductive Sciences Unit. RMS has a longstanding interest in the area of endocrine disruptors and is currently chairman of the UK Society for Endocrinology Expert Group on this topic.

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Competing interests: RMS and DSI have both received reimbursement of travel expenses for attending meetings sponsored by pharmaceutical companies or the chemical industry.

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Lesson of the week

Bradycardia in acute haemorrhage

Ian Thomas, John Dixon

We describe three patients who all underwent elective surgery and had acute haemorrhage after the operation. All three patients had hypotension but did not develop the typically associated sign of tachycardia. The assumption that occult bleeding is always associated with tachycardia is incorrect and may lead to a delay in diagnosis.

The accepted and traditional cardiovascular signs of acute blood loss are tachycardia, hypotension, and poor peripheral perfusion. In a healthy adult, tachycardia is a heart rate of more than 100 beats/min. The maximum heart rate a person can sustain is generally accepted to be 220 minus the patient's age. Tachycardia occurs in the initial stage of a biphasic cardiovascular response, which attempts to maintain cardiac output in the face of hypovolaemia and a decreased stroke volume. Neural and hormonal mechanisms mediate this tachycardia after arterial baroreceptors are stimulated. In some patients with acute haemorrhage, however, this initial tachycardic response is absent; this may lead to confusion or a delay in diagnosis. The phenomenon has been called relative bradycardia,¹⁻⁴ absence of tachycardic response,¹⁻⁵ or paradoxical bradycardia.⁶ We describe three patients for whom

doctors did not see initial tachycardia during acute haemorrhage.

Case reports

Case 1

A 59 year old woman had an elective total abdominal hysterectomy and bilateral salpingo-oophorectomy. Apart from mild asthma, for which she took a ventolin inhaler, she was otherwise fit and well. She was taking no regular drugs. Her preoperative blood pressure was 145/75 mm Hg, pulse rate was 76 beats/min, and haemoglobin concentration was 147 g/l. Surgery was uneventful. In the recovery room, the woman's blood pressure fell to 70/34, 84/42, and 78/48 mm Hg at 2.5, 4, and 5.5 hours after the operation. At each occasion, doctors prescribed a fluid bolus, which increased systolic blood pressure to greater than 100 mm Hg. Her pulse rate never exceeded 70 beats/min (fig 1). Six hours after the operation, her haemoglobin concentration was 55 g/l. During laparotomy, doctors drained 1500 ml of blood from her peritoneal cavity, securing haemostasis. Subsequent recovery was uneventful.

Patients with acute haemorrhage may not exhibit the typically associated initial tachycardia

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