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Protecting humans and wildlife from harmful chemicals

Men under threat: The decline in male reproductive health and the potential role of exposure to chemicals during in-utero development.

Background to the increasing concerns about male reproductive health

In many industrial countries cancer of the testicle (testicular cancer) is now around twice as common as it was thirty to forty years ago,[1,2] and in addition, the number and quality of sperm that young men produce seem to have deteriorated.[3,4,5,6,7]

Furthermore, cancer of the testicle and low sperm counts are linked with birth defects in baby boys, including un-descended testicles (cryptorchidism) and malformation of the penis (hypospadias), where the hole is not at the end of the penis but somewhere on the underside of the shaft, making urination problematic. Baby boys whose testicles do not descend properly, are known to be at greater risk of low sperm counts and testicular cancer later in life.[8,9]

Testicular Dysgenesis Syndrome

Many scientists now therefore think male genital birth defects, low sperm counts, and testicular cancer (collectively called Testicular Dysgenesis Syndrome or TDS), can all be caused when the baby boy is still in the early stages of development during pregnancy.[10,11,12,13] Testosterone, the male hormone, is needed to make the testicles 'drop' down from inside the abdomen of the baby boy to their final position in the scrotal sac. Therefore, anything that can interfere with the production or action of testosterone at this critical time before birth might be to blame for these birth defects, low sperm counts and testicular cancer,[14] with the mildest manifestation of TDS being impaired sperm production.[15]

The Action of Hormone Disrupting Chemicals and the 'Mixture Effect'

Some man-made chemicals found in consumer products or as food contaminants have the ability to block the action of testosterone and may undermine male reproductive health. Many scientists are particularly concerned because it has been shown that in animals these chemicals can induce many of the symptoms of TDS. Hormone disrupting chemicals, which block the normal functioning of testosterone, can not only cause undescended testicles and hypospadias, but can also lead to a reduced sperm count as the animal reaches adulthood. Recent studies in animals have also shown that many of these hormone disrupting chemicals can act together as a cocktail, and may damage the genitals of the male at dose levels at which each chemical, individually, would not cause effects by itself.[16,17,18,19,20,21,22,23,24,25,26,27,28,29,30] Additionally, feminization and reduced masculinization due to pollutants in the environment have now been reported in many species of wildlife.[31] Both these findings in wildlife and the findings in laboratory studies strengthen the likelihood that sex hormone disrupting chemicals are also playing a role in the reported decline in men's reproductive health.

The Suspected Role of Chemicals in Undermining Male Development

Some men will be more susceptible to the effects of chemicals than others, and not all cases of low sperm counts or birth defects will be due to chemical exposures. However, the rate of increase in testicular cancer is such that it cannot be explained by genetic factors alone, and therefore environmental and/or lifestyle factors must play a part. Other studies corroborate this and, for example, when migrants from a country with a typically low risk of testicular cancer, move to a country such as Denmark, with a higher risk of this cancer, first generation immigrants have the same level of testicular cancer as in their country of origin, whereas the second generation immigrants (i.e. those born in Denmark) have a similar risk as the Danes themselves.[32] Similarly, studies of half brothers, brothers and twins also point to chemical exposures during pregnancy being a possible factor in undescended testicles.[33] There is little doubt that maternal smoking and alcohol consumption can be harmful to the developing testicle,[34] but exposure to mixtures of other chemicals found in our environment probably account for a proportion of these birth defects of baby boy's genitals.[35]

Overall, rates of testicular cancer in the industrialized regions of the world are six times higher than those in less

industrialized countries.[36] Within the European Union (EU) there is also a wide variation in occurrence. For example, Denmark, Germany and Austria have rates of around 10 per 100,000 men, while Lithuania, Estonia, Spain and Latvia have rates of around 2 per 100,000.[37] In the UK, the rate is around 7 per 100,000,[38] and in France there are particularly large regional variations, with rates of between 2 to nearly 8 per 100,000. [39]

Suspect Chemicals - The Difficulty of Proving Direct Cause and Effect

After taking into account all the evidence, many scientists are now suggesting that exposure to sex hormone disrupting chemicals, particularly pollutants that interfere with masculinization, may play a role in some of the adverse effects that are being reported in men.[40,41,42] Chemicals that can block androgen, the male hormone, are currently the most suspect.[43] However, it will be very difficult to prove definitively which chemicals do, or do not, cause these effects in men for a number of reasons. Firstly, because it is, of course, rightly not possible to specifically test such chemicals in a controlled way on pregnant women, and that is why animal experiments often form the basis for regulation. Secondly, it is difficult to find non-exposed mothers, for the necessary comparison, and thirdly, many chemicals may be involved, making analysis exceedingly complicated. Nevertheless, several studies have reported an association between a mother's exposure, or her baby's exposure, to certain chemicals, and negative effects reported in the baby boys, including birth defects of their genitals, reduced testosterone levels, or effects related to reduced testosterone action.[44,45,46,47,48,49,50,51,52,53,54,55,56] In addition, it seems that a mother's exposure to certain pollutants may increase her son's risk of testicular cancer.[57] The chemicals implicated in such studies include some phthalates used in plastics, flame retardant chemicals used in consumer articles, and some pesticides. (Information presented in the Table illustrates how exposure to these chemicals can occur). The difference in exposure to certain hormone disrupting chemicals in a country like Denmark, with high rates of testicular cancer and undescended testicles, as compared to a country like Finland with lower rates, does suggest chemicals may be involved as studies suggest that exposures to several suspected chemicals are typically higher in Denmark.[58]

The Need to Ensure Harmful Chemicals are Phased-Out

Hormone disrupting chemicals are in many consumer products that surround us in the home, and are found as contaminants in the food we eat and in the air we breathe. Everybody living in the modern world is exposed to may worrisome man-made chemicals, and as a result carries them in their bodies. Several such chemicals are also found in the amniotic fluid which surrounds the baby in the womb.

CHEM Trust believes that hormone disrupting chemicals need to be replaced with safer alternatives, which do not interfere with our health and development. It is clearly absurd, but when the risks posed by these chemicals are officially assessed, the total amount of chemicals to which humans are exposed that act by blocking testosterone, is not considered. It is only the risk from a single chemical in isolation that is typically assessed. Therefore, the 'total' risk may be grossly underestimated. This means that regulatory authorities may allow something to be used, when in reality it could be contributing to damage to baby boys, or men's reproductive health.

Don't men deserve better?

Undescended testicles are the most common congenital birth defect in male children,[59] and were generally accepted to affect 2-4% of baby boys, although recent studies in Denmark[60] and the UK[61] suggest the rate may be higher at around nine and six boys (respectively) per hundred boys born. Similarly, malformation of the penis (hypospadia) appears to have increased in recent decades in several European countries,[62] the USA,[63] Australia[64] and China.[65] Testicular cancer is also undoubtedly the most common cancer of young men. Furthermore, studies suggest that young men's sperm counts are much lower than their fathers' with rates declining by perhaps about 2% for each subsequent year in which the young men were born.[66,67] Alarmingly, studies in some European countries show that 1 in 5 young men have a sperm count so low as to impair their fertility.[68,69,70]

Taking Action

Babies in the womb are particularly sensitive to the effects of certain chemicals. Furthermore, the effects caused can be irreversible and may not come to light until after puberty. Therefore, if a woman is planning to get pregnant or is already pregnant she might want to try and avoid exposure to unnecessary chemicals, including certain toiletries that are applied directly to the skin. Eating a healthy varied diet, with plenty of fruit and vegetables, preferably organically grown, may also be beneficial. However, more widespread benefit could result from stricter regulation of chemicals.

The Role of CHEM Trust

CHEM Trust is calling for the phase out of man-made chemicals with hormone disrupting properties, wherever possible. More information and a detailed technical scientific report, commissioned by CHEM Trust, entitled *"Male reproductive health disorders and the potential role of exposure to environmental chemicals"*, written by Professor Richard Sharpe of the Medical Research Council can be found on the CHEM Trust web-site.
See www.chemtrust.org.uk

Examples of chemicals which are reported to disrupt the sex hormones and/or damage the male in animal studies.

Phthalates DBP = di(n)butylphthalate DiBP = di(iso)butylphthalate BBP = benzyl butyl phthalate DEHP = di(2-ethylhexyl)phthalate DPP = dipentyl phthalate DINP = diisononyl phthalate DCHP = dicyclohexyl phthalate	Phthalates are a group of chemicals, produced in high volumes. They are used to impart flexibility to plastic polyvinyl chloride (PVC) products as well as in other applications, including pharmaceuticals, and pesticides. There is widespread human exposure with reported uses in building materials, household furnishings, clothing, cosmetics, dentures, medical tubing and bags, toys, modelling clay, cars, lubricants, waxes and cleaning materials. Exposure may arise via the air, through absorption when used on the skin, and through the diet.[71] Analysis shows that adults, children and new born infants are all exposed to phthalates.[72] Below are some of the main reported uses of the individual phthalates.[73] DBP - adhesives, caulk, industrial solvent, medications. DiBP - adhesives, caulk, industrial solvent. BBP - vinyl flooring, adhesives, sealants, industrial solvent. DEHP - soft plastic including tubing, home products. DINP – soft plastics, replacement for DEHP. DCHP - stabilizer in rubber, in polymers, and as a plasticiser in coatings for cellulose films used in food packaging.[74] In the EU, toys containing the following phthalates can no longer be put on the market. DBP, BBP and DEHP are banned in all toys and childcare articles (at concentrations greater than 0.1%). Similarly, DINP, DIDP and DNOP are banned in toys and childcare articles intended for children under 3 and which can be placed in the mouth. (at concentrations greater than 0.1%).[75] Also in the EU, unless present at low levels as impurities, or due to contact with plastic pipes or containers during production or storage, the following phthalates are banned in cosmetics: DBP, BBP, DEHP. In line with this, DBP, DEHP and BBP have all been found at low levels in perfume (for example, at the mg per kilogram level), as have DiBP, DINP and DCHP[76] As phthalates do not break down very quickly they can be found as contaminants in the food chain. The UK Food Standards Agency is investigating how to identify whether the phthalates in food come from environmental contamination or from the contact of the food with phthalate-containing materials.[77] The use of phthalates are restricted in plastic materials (including lids) coming into contact with foods. For example, BBP, DEHP, DBP, DINP and DIDP can not be used in throw-away packaging for fatty foods, and in tests with food simulants the maximum permitted specific migration limits for BBP, DEHP, DBP, DINP and DIDP are 30mg/kg of food, 1.5mg/kg of food, 0.3mg/kg of food, 9mg/kg of food and 9mg/kg of food (respectively).[78] Only certain phthalates are known testicular toxicants with hormone disrupting properties. For example, DBP, DiBP, BBP and DEHP decrease testicular testosterone production with about the same potency, while DPP is about three times more potent. Furthermore, they can act in an additive way if simultaneous exposure to several of them takes place.[79] In addition, DINP has been reported to have weak feminizing properties,[80] and DCHP has also been reported to have weak feminizing or demasculinzing properties.[81] DEP is not active in this way in animals, but there are some studies suggesting it might be linked to effects in humans.[82]

Paraben	Paraben is the name given to a group of chemicals used as preservatives in cosmetics and body care products, including deodorants, creams and lotions. They are able to penetrate the skin.[83] Studies show that certain paraben can disrupt hormones, with some suggested to be able to disrupt testosterone and/or the female hormone, oestrogen.[84,85]
Triclosan	Triclosan is an anti-bacterial and anti-fungal chemical widely used in personal care products such as some soaps, toothpaste etc.[86] Triclosan has also been added to plastic products such as kitchen chopping boards.[87,88] Research suggests it can interfere with testosterone production.[89,90]
Triclocarban	Triclocarban (TCC or 3,4,4'-trichlorocarbanilide) is also used as an anti-bacterial in personal care products such as soaps. It has sex hormone disrupting properties.[91]
BPA (Bisphenol A)	BPA is the building block of polycarbonate plastic. Some of the plastic bottles stamped with the recycling triangle symbol containing the number 7 are polycarbonate, as are those with the letters PC. BPA leaches from a number of consumer products including babies' bottles, plastic plates and the lining of tin cans. Related compounds are also used in dentistry. BPA has feminizing (oestrogenic) properties,[92] and there is some suggestion of anti-androgenic activity.[93]
Penta-BDE (Penta-brominated diphenyl ether)	There are actually 3 commercial PBDE products, which predominantly contain deca, octa and penta-BDEs, and are therefore called by these names. PBDEs are used as flame retardants to prevent fire taking hold quickly. Penta-BDE is now banned in the EU, but was used in polyurethane foam, for example, in mattresses and car and aeroplane seats. Apart from exposure via dust,[94] and possible hand to mouth transfer, PBDE exposure arises from eating fish and fish-oils.[95] Penta-BDE has been reported to have anti-androgenic properties.[96,97]
PCBs	PCBs were once used in a variety of applications, including electrical applications, dielectric fluids for transformers and capacitors, hydraulic and heat transfer systems, lubricants, gasket sealers, paints, fluorescent lights, plasticizers, adhesives, carbonless copying paper, flame retardants, and brake linings. Although intentional production has been banned in most countries for many years, PCBs may still be found, and can also be accidentally newly generated during certain processes when elevated temperatures are used and chlorine is present. Human exposure also arises due to contamination of the food chain, with fish being a relatively large source. The persistence of PCBs means that they are found as ongoing contaminants in humans. PCBs are reported to have sex hormone disrupting properties.[98]
Dioxins	Dioxins are a group of chemicals which are not intentionally produced, but are emitted during incomplete or relatively low temperature combustion. They can come from industrial or domestic sources, wherever a chlorine source is present. Such sources include, for example, domestic bonfires with PVC plastic, incinerators, certain chemical and metal factories (particularly aluminium recovery sites), paper pulp production using chlorine, and coal burning in power stations and in fire-places in the home. Exposure can arise from inhalation, but mainly comes from contamination of food. In the last decade, the high dioxin levels found in contaminated chicken[99] and pork[100] have received media attention.[101] Dioxin is a sex hormone disruptor, which can affect testicular function.[102,103] A recent study where people suffered high exposures, suggests that it may permanently decrease the amount and quality of sperm in men exposed when young children.[104]
Diesel fuel Exhaust	As diesel is used as a fuel in many cars and lorries, diesel exhaust is widespread. Research suggests that diesel fuel exhaust disrupts androgen action.[105] Prenatal exposure in animals leads to endocrine disruption after birth and suppresses testicular function in male rats.[106]

Cimetidine (Tagamet)	Cimetidine is a prescription drug. It is used for heart-burn, indigestion and peptic ulcers, but can have hormone disrupting properties.[107,108]
Certain sun-screens 4-MBC 3-BC	A few ultraviolet (UV) filters exhibit estrogenic activity and some also show some anti-androgenic activity.[109] They have been found as contaminants in waste water treatment plants and rivers. Some have also been found in humans, with potential exposure during development being suggested. As an example, the UV filter 4-methylbenzylidene camphor (4-MBC) exhibits estrogenic activity, and pre and postnatal exposure of rats to 4-MBC can interfere with male sexual development.[110] Also, 3-benzylidene camphor (3-BC) administered in chow to the parent and to the offspring until adulthood was reported to delay male puberty and affect the reproductive organ weights of adult offspring.[111]
Alkylphenols Nonylphenol Octylphenol	Nonylphenol is the breakdown product of the surface active agent, nonylphenol ethoxylate. Many uses are now banned in the EU, for example, including use in domestic cleaning and industrial and institutional cleaning, and in textiles and leather processing.[112] Octyl phenol is used in the production of phenol/ formaldehyde resins (Bakelite) and in the production of octylphenol ethoxylates, and used in the formulation of printing inks and in tyre manufacture.[113] Both nonyl and octyl phenol have oestrogenic effects and can feminize male fish.[114]
DDT break-down product DDE.	DDT is an insecticide which was used extensively on crops, but is now only used in a few countries against the malaria-bearing mosquito. DDT and DDE last in the soil for a very long time, potentially for hundreds of years.[115] Unfortunately, due to this persistence, it is still found in some produce, such as vegetables, fish and liver.[116] DDE is also found as a persistent contaminant in our bodies. The DDT breakdown product or metabolite, p,p'-DDE, is able to block testosterone.[117,118]
Linuron Diuron	Linuron is a herbicide used to control weeds on hard surfaces,[119] such as, roads, railway tracks, paths, and in crops, and forestry. It has been detected in tap water,[120] and as a residue in vegetables such as carrots, parsnips and spinach[121] Diuron is a similar herbicide, which is also used as a preservative, particularly for masonry,[122] and was previously used as an anti-foulant product.[123] It has also been detected in tap water,[124] and as a residue in produce such as oranges.[125] Linuron is able to block testosterone,[126] and studies suggest that diuron may also block testosterone.[127] In animals, diuron has been found to damage the testes.[128]
Vinclozolin	A fungicide which is no longer used in the EU, but it may be found as a residue in imported fruit and vegetables.[129] Vinclozolin can block testosterone action.[130]
Procymidone	A fungicide which was used, for example, on plums, lettuce and cucumbers. In the EU, some uses were still allowed up to June 2008, but it can still be used elsewhere. In 2008, it was found as a residue in UK-sold beans, breakfast cereals, cucumber and fruit smoothies.[131] Procymidone, like vincolozolin, can block testosterone action.[132]
Iprodione	Iprodione is a fungicide which is used in the EU. It has, for example, been found as a residue in breakfast cereal, Chinese cabbage, cucumber, parsnips, grapes, pears and oranges traded in the UK.[133] Iprodione can reduce testosterone levels.[134]
Prochloraz	A fungicide used on fruits and vegetables. It is to be withdrawn from the EU market by December 2011, but even after this date, produce imported from outside the EU may still be contaminated. In the UK it is approved for use as a fungicide and seed treatment. Prochloraz has anti-androgenic hormone disrupting properties, and is reported to feminize male offspring, such that some scientists have called for its use to be reduced.[135]

Fenarimol	A fungicide which has been use on fruit and vegetables, such as tomatoes, aubergines, peppers, cucumbers and melons.[136] As of the end of June 2009, it will no longer be authorised in the EU,[137] but it may still be used elsewhere. Fenarimol has sex hormone disrupting properties.[138,139]
Fenitrothion	Fenitrothion is an insecticide which is now not permitted in the EU, but which was used, for example, on apples, plums, berries, peas, sweet corn and cereals.[140] It has been found as a contaminant of fruit, such as oranges, imported from outside the EU.[141] It has also been used in small quantities as a licensed animal medicine.[142] Fenitrothion has anti-androgenic activity.[143,144,145]
Chlorpyrifos-methyl	Chlorpyrifos-methyl is an insecticide which is permitted for use in the EU, and is used to protect grain during storage. It is also used, for example, on grape vines. Chlorpyrifos-methyl can block the action of testosterone.[146,147]
Ketoconazole	Ketoconazole is used as an anti-fungal product in pharmaceuticals to treat fungal infections of the skin. It can disrupt hormone function and reduce testosterone.[148] Also, several other azole fungicides, used in agriculture are reported to have endocrine disrupting properties.[149]
Pyrethroid pesticides Permethrin Beta-cyfluthrin Cypermethrin Cyfluthrin Bifenthrin	Some pyrethroid pesticides, such as permethrin, are no longer authorised in the EU, but others including cyfluthrin, beta-cyfluthrin and cypermethrin are still in use, with for example, the latter found as a residue in apples, beans, melons and oranges. Several have anti-androgenic activity, and these are listed in order of suggested increasing potency - permethrin, beta-cyfluthrin, cypermethrin, cyfluthrin, bifenthrin.[150]

(The European Commission's work on identifying lists of endocrine disrupting chemicals can be found at http://ec.europa.eu/environment/endocrine/strategy/substances_en.htm)

A CHEM Trust briefing written by Gwynne Lyons, May 2009

About CHEM Trust

CHEM Trust is a UK charity which aims to protect humans and wildlife from harmful chemicals so that they play no part in causing impaired reproduction, deformities, disease or deficits in neurological function.

CHEM Trust
PO Box 56842
London N21 1YH
United Kingdom
Email: askchemtrust@chemtrust.org.uk
Website: http://www.chemtrust.org.uk/

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