

Endocrine disrupting chemicals and human health: The plausibility of research results on DDT and reproductive health

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Introduction

The publication of Rachel Carson's *Silent Spring* in 1962 brought in an increased awareness on the effects of chemicals in the environment and that human health is inextricably linked to the health of the environment. Since then there has been growing scientific concern, public debate and media attention over the possible effects in humans and wildlife that may result from exposure to chemicals that have the potential to interfere with the endocrine system.

Environmental "Endocrine Disrupting Chemicals" (EDCs) have been described as "exogenous agents that interfere with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behaviour"²

Increasing number of chemical compounds in the environment have been identified as endocrine disruptors using *in vitro* and *in vivo* bioassays. These are most often than not pervasive and widely dispersed in the environment and include pesticides, industrial chemicals, pharmaceuticals and natural hormones acting as ligands for the estrogen-, androgen- or arylhydrocarbon receptor or exerting a combined action (e.g. estrogenic and anti-androgenic activity)³

DICHLORODIPHENYLTRICHLOROETHANE (DDT)

DDT the first of the chlorinated organic insecticides, was originally prepared in 1873;^{4,5} but it was not until 1939 that Paul Muller of Geigy Pharmaceutical in Switzerland discovered the effectiveness of DDT as an insecticide, he was awarded the Nobel Prize in medicine and physiology in 1948 for his discovery.

DDT is a synthetic chemical that does not occur naturally in the environment. As a mixture DDT mainly constitutes of *p,p'*-dichlorodiphenyltrichloroethane (*p,p'*-DDT), (63-77%), *o,p'*-dichlorodiphenyltrichloroethane (*o,p'*-DDT) (8-21%), (*p,p'*-dichlorodiphenyldichloroethylene, (*p,p'*-DDE) (DDE) (0.3-4%). DDT is rapidly transformed to DDE which is the major metabolite of DDT in biological systems.

DDT and DDE have very high octanol-water partition coefficients⁶ and tend to accumulate in lipid compartments⁷ in biological systems. DDE has a very long half-life, which to some extent is of toxicological importance.⁸ The half life of DDT in humans has been estimated to be between 6 and 10 years⁹ such that short-term exposures are also associated with long-term exposures because both elements are slowly released from body fat¹⁰.

Initially, DDT was used in the 1940s to control wartime typhus and agricultural pests, and it then was popular on a worldwide basis as a measure to control malaria vectors, until its deleterious effects on wildlife led to a ban on routine DDT use in many countries in the 1970s.

Today the production and use of DDT is restricted to the control of public health disease vectors such as malaria-transmitting mosquitoes. This was after the Stockholm

Convention on Persistent Organic Pollutants in 1995 which considered banning or restricting the production or use of organic pollutants as a result of their toxicity, resistance to breakdown, bioaccumulation potential and potential to be transported over long distances.

In some Malaria areas, DDT Indoor Residual Spraying (IRS) is used to decrease the incidence and spread of the disease^{11,12} its effects not only kill the mosquitoes but also repel them from interior surfaces, thereby further decreasing the odds of infectivity. Only 8 out of the 44 malarious countries were using DDT for indoor residual spraying by 2007.¹ Studies have also shown the effectiveness of DDT-impregnated bed nets in malaria control.^{14,15}

DDT use is currently under intense debate in several countries for its use in household spraying for malaria control.

DDT and endocrine disruption

Numerous studies and reports indicate that DDT has estrogenic effects.^{16,17,18} Evidence exists that *p,p'*-DDE may interact synergistically with other Endocrine Disrupting Chemicals with prolonged chronic exposure altering sexual steroid hormone homeostasis¹⁹ resulting in induction of expression of hepatic aromatase in adult male rats²⁰ and also impaired sexual development in young male rats following exposure *in-utero*.²¹

One notable study on the endocrine effects of DDE was the discovery of reproductive abnormalities in alligators inhabiting Lake Apopka after a major pesticide spill in 1980. Deformities included small penises abnormal sex hormone levels and ambiguous gonads.¹⁶

In a study by Rhouma et al²² published in 2001 adult male rats were dosed with DDT at levels of 50 and 100 mg/kg bw/day for 10 successive days. Rats exposed to DDT had dose-dependent reductions in both testicular weight and sperm numbers and motility, as well as decreased weights of seminal vesicles, decreased testosterone production, and increased serum levels of Luteinizing Hormone and Follicle Stimulating Hormone.

Similarly Kelce and others in 1997 were able to demonstrate that DDE when dosed at 200 mg/kg/day is able to induce a testosterone-repressed prostatic message TRPM-2 and to repress a testosterone-induced prostatic message C3 mRNA²³ concluding that DDE act as an anti androgen by altering the expression of androgen-dependent genes.

Cannon and Holcomb in 1968 concluded that reproduction in mice can be affected by exposure to 200 and 300 ppm of DDT, resulting in death of females during the gestation period, death of male animals, and/or death of young.²⁴ This was in a study of adult laboratory mice (*Mus musculus*) fed with DDT.

A Mexican cross sectional study between 2000 and 2001 by De Jager et al concluded that non occupational exposure to *p,p'*-DDE / DDT has adverse consequences on male reproductive health brought in by deranged semen parameters in men.¹⁷ Similar results were echoed by another cross sectional study of 311 young men of Limpopo region

South African in 2005 by Aneck Hahn and others.²⁵

Research on DDT and reproductive health

It has always been a norm amongst the scientific world that the intensity of concerns and lack of consensus among scientists can best be ameliorated by an objective evaluation of the available scientific data on the potential adverse effects of chemicals in the environment.

A lot has been written and said in the print and electronic media on the resultant effects of DDT on the environment and health of human beings. The governments of Malawi and Uganda are some of the countries considering bringing back DDT spraying in the wake of the rampant malarial attacks on its citizens.

A number of studies have shown that DDT and its derivatives DDE have damaging effects on the environment and health in humans. It is always good to look at studies that have come up with this conclusion so as to understand the plausibility of the results to the general population and furthermore to the community at hand.

This write-up looks at studies that have presented reproductive health as an endpoint and with DDT or DDE as one of the Endocrine Disrupting Chemicals (EDCs).

A number of studies have come up with the ever-disturbing results of EDCs as culprits in the decline in reproductive potential of men and women in the general population.²⁶ Unfortunately, in most studies, toxicological information is incomplete, endocrine disruptors are almost exclusively tested alone²⁴ or as dimeric mixtures (combinations),²⁷ yet the human population is exposed to multiple disruptors throughout the day.

In most animal testing experiments only one chemical is looked at in evaluating health effects at a time a strategy that fails to provide information about interactive effects, which may occur with exposure to more than one chemical. There certainly appears a need to determine the consequences of exposure to environmentally relevant mixtures (combinations) of endocrine disruptors.

Some studies have further gone to demonstrate the effects of organochlorines in mixtures, DDT included, on sperm parameters and function in vitro. The physiologically-relevant metabolized extracts used by Campagna et al in 2009²⁷ contained organochlorines concentrations 5,000 to 10,000-fold lower than the environmentally relevant mixture that induced marked effects on male reproductive function in vivo in studies published by Bailey in 2002²⁸ and Anas et al in 2005.²⁹ However though the study concluded that exposure to the environmentally-relevant organochlorine mixture altered normal sperm fertility parameters in vitro the concentrations used were far higher than those found in human body fluids.

Furthermore a dose response variation that is crucial in determining effects of substances was found to have no significant variation in the results when the dose is varied amongst the study participants in some studies.³⁰ While in other studies this more important component was explicitly omitted from the study's methodology putting the study's results at risk of a negative plausibility.

Randomized Controlled Trials (RCTs) would have been the best way of determining a true effect of endocrine disruptors in most settings of studies conducted in this field. The only drawback is that they will not be feasible owing to their unethical inclination as to do with effects that are not

with the intent to treat. Most of the studies done in the field of endocrine disruptors on humans have been observational studies¹⁷ with a few case control studies of which a lot of confounding factors that may have influenced the results were not taken into consideration.

Though several other studies have indicated teratogenic effects^{31,32,33,34,35} of endocrine disruptors in their research findings there still remains a gap in the reporting of critical periods of folliculo-genesis or embryo-genesis that increases risk for adverse effects.

Implications of most of the endocrine disruptors on fertility decline has been based on indirect demonstration of chemical elements in observed subjects and clinical applications of infertile couples in reference to retrospective exposure to endocrine disruptors.¹⁷ Sub fertility has also been indirectly associated with clinical conditions resulting from endocrine disruptors all this summed up has a draw back in that the cellular and molecular mechanisms underlying the observed effects of endocrine disruptors have not been thoroughly investigated and presented in a scientific manner in studies conducted on human beings.

It should also be noted that most of the studies have no definite controls and even if they have their case-control methodology (ever exposed versus never exposed) does not always take into account that individuals in the control group may have been exposed to other reproductive toxicants as well.³⁶ This is more evident in most retrospective and some prospective studies in which an effect on the mother is demonstrated on the resultant offspring³ which may be very difficult to control for other confounding factors. Since the bulk of evidence in most chemical associations is derived from animal studies caution is always applied in the scientific plausibility of the results in the human population. This is to say extrapolation from animal data to human populations can be misleading if factors such as species-specific reproductive differences, dose response, and metabolic differences are not considered.

For instance though humans are considered to be non-seasonal mammals, unlike animals that demonstrate a seasonal breeding pattern residual effects of this 'seasonality' may persist. Men, for example, exhibit a consistently lower sperm count in the summer months than in the winter or spring a hypothesis that has been demonstrated in standardized, longitudinal and cross-sectional studies.^{37,38} It may be argued that this phenomenon reflects somehow as an adverse effect of the higher summer temperature on sperm production. In view of this studies looking at environmental and other effects on sperm count in men have to take account of season, in addition to the other factors that have been discussed.

Most of the studies on male sub fecundity concentrate on effects of the endocrine disruptors on sperm parameters such as volume, concentration and motility²⁷ without giving a clear view of the fertilizing potential of the sperm with deranged parameters.^{39,40} The significance of these conflicting reports is unclear, largely because the data are often derived from ecological sources. In addition, many studies do not have adequate exposure information or sample size¹⁷ to make solid conclusions about EDCs and reproductive function.

Conclusions

In considering the potential impact of DDT on reproductive health the following questions are essential:

A. Will exposure in adulthood be compensated for by normal

homeostatic mechanisms and therefore not result in any significant or detectable effect?

B. Because of cross talk between different endocrine systems, will effects occur unpredictably in endocrine systems other than the system predicted to be affected?

C. Will exposure to the same level of DDT at different stages in the life history or in different seasons produce different effects?

D. Will exposure during the period when programming of the endocrine system is in progress result in a permanent change of function or sensitivity to stimulatory / inhibitory signals? In view of this considerable caution should be exercised in extrapolating in vitro measures of hormonal activity to the situation in vivo.

If one looks at the data concerning the effects of environmental exposure, in this case DDT / DDE, more convincing evidence is demonstrated in animals (especially under experimental conditions) than data concerning environmental or occupational exposure in humans.¹⁷ It should be noted that such evidence must be interpreted with caution if extrapolated to the human population.

Furthermore, emphasis should be made that the relationships between exposure and disorder only appears after a sufficient interval of latency time following exposure, and after inclusion of only those persons who have been exposed in a sensitive developmental life stage.^{41,42}

The Weybridge Report⁴³ states that to understand the problem of endocrine-disrupting chemicals, one must study the interactions between combinations of chemicals; one must study these interactions on at least two generations of live animals; one must expose these animals at different moments in their lives (different times prior to birth and after birth). And of course, the animals must be exposed to various concentrations of the chemicals to see if a dose-response relationship becomes evident.

Finally further research studies that takes all the necessary cautions on-board need to be formulated so as to ascertain the deemed reproductive health consequences of exposure to endocrine disrupting DDT. This should be geared to answer the question: Will exposure to endocrine disruptors in complex mixtures result in additive, synergistic, or inhibitory effects on ovarian and testicular function and reproduction as a whole, thereby, influencing the deemed trend in reproductive dysfunction?

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Science Cafe : The truth about epilepsy

Date: 26 August 2010

Time: 5:30pm- 7:30pm

Venue: China de Restaurant (Ginnery Corner)

**Speakers: Dr M. Malewa (MLW)
Action Amos (Country Epilepsy Project Manager)**

