The Reproductive Toxicology of Great Lakes Contaminants

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The Great Lakes basin is characterized as a heavily populated and industrialized region in which a large number of environmental contaminants have been identified. Both the scientific community and the public have voiced concern that contaminants present in the Great Lakes may pose undue risk to human reproduction. Evidence from animal experiments, wildlife studies, and reports of occupational and accidental human exposures indicate that chemical contaminants can adversely affect reproduction. The purpose of this paper is to review the reproductive toxicity of some of the many contaminants known to be present in the Great Lakes. Since the number of chemicals present in the Great Lakes is far too great for each to be adequately reviewed here, discussion will be limited to those contaminants that have been identified in human serum, ovarian follicular fluid, and semen obtained from people residing in the Great Lakes region. It is concluded that a) the data at present is too limited to support the notion that reproduction, in the general population, has been impaired by exposure to chemicals present in the Great Lakes; b) the lack of data in some cases such as for hexachloroethane and 1,2,4-trichlorobenzene does provide reason for concern and underscores the need for further research in this area; and c) the potential for a number of the compounds, including polychlorinated biphenyls (PCBs) and 1,1,1-trichloro-2,2-bis(p-chlorophenyl) ethane (DDT), to disrupt endocrine functions suggests that additive or synergistic effects of these compounds may already be causing adverse effects on reproduction in sensitive individuals, which needs to be explored. — Environ Health Perspect 103(Suppl 9):63-69 (1995)

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Introduction

Waters of the Great Lakes provide a source for drinking water, recreation, and food for many North Americans. The Great Lakes have become contaminated with a vast array of chemical contaminants. The reproductive consequences of human exposure to these contaminants are largely unknown. However, serious effects on reproduction have been shown in epidemiologic studies describing occupational exposure to high concentrations of chemicals (1–6) and also in wildlife populations exposed to environmental pollutants (7). The publication of these data and the media attention given to the potential for human exposure to environmental chemicals have made the public anxious about the potential reproductive hazards posed by these compounds. However, the question of whether contaminants present in the Great Lakes pose undue risk to human reproduction remains unanswered.

This paper addresses the question of whether environmental contaminants in the Great Lakes affect human reproduction. Reproductive hazards will be considered to be any hazard that interferes with production of normal gametes, conception, and in utero development. For the purposes of this review, discussion will be limited to those chemicals that have been identified in the serum, ovarian follicular fluid, or semen of people residing in the Great Lakes basin. Specifically, the reproductive toxicity data of contaminants that are present in a large percentage of the population, such as hexachlorobenzene (HCB), 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT), 1,1-dichloro-2,2-bis(p-chlorophenyl)ethane (DDE), and 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE), or are present in concentrations that are sufficiently high to warrant concern, including polychlorinated biphenyls (PCBs) and chlorinated dibenzo-p-dioxin (CDD), brominated dibenzodioxin (BDD), and chlorinated dibenzo-p-dioxins (CDFs), will be described briefly. The mechanisms of toxicity of these contaminants are beyond the scope of this review and therefore will not be included. Furthermore, the reproductive toxicity of many of these contaminants has been reviewed in detail elsewhere. Consequently, the principal effects of these contaminants on reproduction and the dose or body burden associated with these effects will be briefly discussed.

Contaminants and Residue Levels Identified in Human Serum, Ovarian Follicular Fluid, and Semen

Estimating or, better still, measuring exposure to reproductive toxicants is essential. Without exposure estimation, a predicted dose cannot be calculated, and the risk to a specific reproductive outcome cannot be characterized or given a probabilistic value. There are a number of reports (8–25) from different regions of the world describing trace levels of numerous contaminants found in human serum, breast milk, fat, ovarian follicular fluid, and seminal plasma. The body burdens of a limited number of contaminants from Ontario residents have also been reported (10,17,25). Mean residue levels in the serum, fat, and ovarian follicular fluid of α-chlordane (ALCH), DDE, DDT, heptachlor–epoxide–oxychlordane (OXCH), HCB, total PCBs, and dieldrin for Ontario women (10,25) are summarized in Table 1. In a recent study (25), the body burdens of a number of Great Lakes chemicals in the serum and ovarian follicular fluid of women residing in Hamilton, Ontario were compared with levels found in women from Halifax and Vancouver. Regional differences were observed, with women from Halifax having
the lowest frequency and level of contamination. However, no differences in the rate of oocyte cleavage or time to cleavage of the first egg were found between those with high contaminant levels and those with low levels. In a separate ongoing study, residue levels of 46 PCB congeners and 36 chlorinated contaminants were measured in the serum and ovarian follicular fluid from 25 women undergoing ovulation induction in each of three Ontario fertility clinics (WG Foster, unpublished data). The study design and methods employed were analogous to those of an earlier study (25), with the exception that the male counterpart of the couple was included in one of the centers and more contaminants were included in screening. Briefly, samples were extracted with hexane and analyzed by means of gas chromatography–mass spectrometry. Residue quantification was based on detection of the primary ion for each contaminant of interest. Detection limits varied with the contaminant and ranged from 100 to 300 parts per trillion (ppt) for organochlorine pesticides and from 12.5 to 100 ppt for PCBs. While the majority of contaminants were below the level of detection in the sampled tissues, a few chemicals were found in a high percentage of subjects. The frequency of detection and residue levels of hexachloroethane (HCE), 1,2,4-trichlorobenzene (TCB), DDE, and PCB congeners 153, 138, and 180 are summarized in Table 2.

### Reproductive Toxicity of Contaminants Present in Human Tissues

#### HCB

Hexachlorobenzene was introduced in the 1940s as a seed grain antifungal, and its use in North America was discontinued by mid-1970s. Nevertheless, HCB continues to be produced in large quantities as a byproduct in the manufacture of chlorinated solvents and also exists as an impurity of several pesticides (26). Thus, HCB continues to pose a risk to human health due to its continued entry into the environment, resistance to degradation, and a propensity to bioaccumulate.

Interest in the toxicity of HCB began with an outbreak of cutaneous porphyria in Turkey in 1956 in people who had consumed HCB-tainted wheat (27). Since then, the hepatotoxic and immunotoxic effects of HCB have been well documented. In contrast, the reproductive effects of HCB have received comparatively less attention, and there are no reports of developmental or reproductive effects of HCB in exposed humans.

Data from animal experiments reveal that HCB is both a developmental and reproductive toxicant. HCB has been shown to cross the placenta to the developing conceptus in mice, rats, and rabbits (28–30). Exposure of pregnant rats to doses up to 120 mg/kg/day failed to induce any adverse effects on organogenesis (31). In multigenerational studies, HCB exposure at doses as low as 2 mg/kg/day induced increased liver weights and decreased body weights of pups of both sexes (32,33). Pup viability (33) and lactational index (32) were also decreased at higher doses (8 mg/kg/day). Developmental effects of the skin, bone and nervous system have been described in children accidentally exposed to HCB before attaining puberty (34,35). Unfortunately, there is no exposure data to aid in the dose–response characterization for these effects, and no animal studies have been undertaken to explore the mechanism for these effects.

Data relating to the treatment of adult female animals with HCB suggest that this compound is primarily an ovarian toxicant. This conclusion is supported by the demonstration of altered steroidogenesis in the rhesus monkey in the absence of changes in circulating levels of pituitary gonadotropins (36). Altered ovarian steroidogenesis has also been shown in both the cynomolgus monkey (37) and the rat (38). In a recent study (39), HCB treatment (10 mg/kg/day for 90 days) resulted in depressed ovulatory levels of estradiol and response to ovulation induction in the cynomolgus monkey. Furthermore, degenerative changes in primordial follicles and the ovarian germinal epithelium have been demonstrated in cynomolgus monkeys (40,41) with HCB treatment at levels as low as 0.1 mg/kg/day, which suggests that ovarian function may also be altered at levels lower than previously reported. Ultrastructural changes in the ovary appear to be the most sensitive end point, and these occur with HCB treatment at a dose of 0.1 mg/kg/day for 90 days (41). It is important to note that a no observable adverse effect level (NOAEL) has not yet been established for this compound using this end point. Treatment at this dose level resulted in serum levels of 27±9 parts per billion (ppb) (39) compared to 0.21 ppb for the human population (25). Since a NOAEL has yet to be established and adverse effects occur at levels two orders of magnitude greater than the serum levels measured in the human population, it is suggested that HCB represents a concern to ovarian function.

Morphometric studies in which ovarian follicle numbers have been shown to be significantly reduced following exposure to

### Table 1. The mean ± SD residue concentrations (ppb) of ALCH, DDE, OXCH, HCB, PCB, DDT, and dieldrin in the serum, ovarian follicular fluid, and fat of Ontario women.

| Contaminant | Serum | % ND | Follicular fluid | % ND | Fat | % ND |
|-------------|-------|------|-----------------|------|-----|------|
| ALCH        | 0.29 ± 0.31 | 38   | 0.30 ± 0.30     | 52   |      |      |
| DDE         | 1.04 ± 0.57 | 0    | 0.73 ± 0.40     | 0    |      |      |
| OXCH        | 0.29 ± 0.22 | 48   | 0.27 ± 0.25     | 55   |      |      |
| HCB         | 0.21 ± 0.09 | 10   | 0.14 ± 0.08     | 28   |      |      |
| PCB         | 3.66 ± 4.10 | 38   | 4.06 ± 5.68     | 55   |      |      |
| DDT         | 4.66 ± 3.20 |      | 0.04 ± 0.03     |      |      |      |
| Dieldrin    | 0.22 ± 0.10 |      | 0.22 ± 0.10     |      |      |      |

ND, percentage of samples with residue levels below the level of detection. Data from Jarrell et al. (25) and Frank et al. (17).

### Table 2. The mean ± SD residue concentrations (ppt) of HCE, TCB, DDE, Mirex, and the PCB isomers 153, 138, and 180 in the serum (n=75), ovarian follicular fluid, (n=75), and semen (n=25) of Ontario residents.

| Contaminant | Serum | % ND | Follicular fluid | % ND | Semen | % ND |
|-------------|-------|------|-----------------|------|-------|------|
| HCE         | 80±   | 99.99| 217.86 ± 167.52 | 52   | 80±   | 99.99|
| TCB         | 388.31± 285.25 | 35   | 230.42 ± 162.39 | 0    | 80±   | 99.99|
| DDE         | 3278.9± 1976.36 | 8    | 2289.53 ± 4096.22 | 55   | 392.67 ± 430.23 | 70   |
| Mirex       | 632.23± 1802.59 | 17   | 1474.58 ± 2723.78 | 28   | 100.89 ± 93.86 | 44   |
| PCB-153     | 156.45± 141.38 | 20   | 282.01 ± 290.30 | 55   | 100   | 100  |
| PCB-138     | 133.32± 135.42 | 36   | 124.44 ± 120.77 | 31   | 100   | 100  |
| PCB-180     | 87.46± 83.34  | 40   | 99.05 ± 65.44  | 33   | 100   | 100  |

ND, percentage of samples with residue levels below the level of detection. *Single positive sample only.
reproductive toxins such as 7,12-dimethylbenz[a]anthracene, benzo[a]pyrene, 2,5-hexanedione, and hexachlorobenzene (42–46) suggest that HCB and these agents may induce premature ovarian failure. This hypothesis is supported by the observation of a biexponential decline in ovarian follicle numbers for the human ovary (47). According to this model, ovarian follicles decline at one rate until approximately 37.5 years of age, after which the rate of ovarian aging more than doubles until the follicle population is reduced to about 1000 follicles at the age of around 51 years. Since ovarian failure and menopause are triggered by the number of follicles falling below a threshold level, these data suggest that environmental contaminants such as HCB have the potential of advancing the age of ovarian failure and thus menopause onset.

HCE
Hexachloroethane is a compound that is used as an inhibitor in explosives, in the manufacture of smoke candles and grenades, as a rubber vulcanizing accelerator, and in metal refining. Human exposure is most likely to occur through inhalation or as a result of drinking contaminated water. However, there is virtually no literature describing the developmental or reproductive toxicity of this compound. In a single report (48), Sprague-Dawley rats were treated from day 6 to day 16 of gestation either by inhalation (15, 48, or 260 ppm for 6 hr/day) or gavage (50, 100, and 500 mg/kg/day). At the highest dose, the number of fetal resorptions was increased and the number of live fetuses per litter were decreased. No evidence of structural effects were found. There are no reports of reproductive effects of HCE treatment in adult animals of either sex. Thus, in the absence of data, it is not possible to conclude what risk if any this compound poses to human reproduction. This is a concern since HCE has been identified in the ovarian follicular fluid in 48% of women from three fertility clinics in Ontario (WG Foster, unpublished data). Therefore, there is a need to examine the effect of HCE on follicle selection, growth, differentiation, ovulation and atresia. In addition, the effect of HCE on sperm egg interactions should also be explored.

TCB
1,2,4-Trichlorobenzene has found application as a solvent in chemical manufacturing, dielectric fluid, and synthetic transformer oils and lubricants. It is also used as a heat transfer medium. Human exposure to this compound is likely through drinking contaminated water or consumption of contaminated fish.

Like HCE, there is very little data relating to TCB effects on reproduction. At doses less than 300 mg/kg in the rat, there does not appear to be any effect upon fertility, growth, or viability of the conceptus (49–51). At higher doses of TCB (360 mg/kg/day during days 9–13 of gestation) in the rat, embryonic growth was reduced (51). Interestingly, ip injection of TCB (0, 250, and 500 mg/kg) on 3 consecutive days induced a decrease in the rat uterine weight indicating an antiestrogenic effect (49).

TCB was frequently identified in the serum (65% of all samples) and in all samples of ovarian follicular fluid of women participating in fertility programs in three Ontario cities (Table 2). In contrast, TCB was found in the semen of only one patient in the study. Although levels present in the serum and ovarian follicular fluid are low and the levels at which effects have been seen in the rat are high, it seems unlikely that TCB poses a serious concern to human reproduction. However, the potential antiestrogenic effects of this compound need to be confirmed and the mechanism explored. Furthermore, given the frequency of identification of TCB in the serum and ovarian follicular fluid, the potential for additive and synergistic effects with compounds such as dioxin, dibenzofurans, and PCB congeners needs to be explored.

DDT, DDD, and DDE
DDT is a well-known pesticide formerly widely used to control insects on agricultural crops. It has also been used to control head lice and to kill insects carrying diseases such as typhus and malaria. Both DDD and DDE were present as contaminants in commercial formulations of DDT, and the presence of DDE in the environment is primarily the consequence of the breakdown of DDT. The developmental and reproductive toxicity of these compounds has been well documented, and they are the subject of a recent Agency for Toxic Substances and Disease Registry (ATSDR) update (52). Therefore, the reproductive toxicity of this group of contaminants will not be reviewed in detail here.

There are no studies that establish an association between adverse reproductive outcomes in humans with circulating levels of DDT, DDD, or DDE. In animal experiments these compounds have been shown to be embryotoxic and fetotoxic in the rodent (53), but they are not known to be teratogenic. Effects in the adult are the consequence of high doses while fetal effects are observed at much lower levels. Adverse effects of DDT treatment on fertility have been shown in the rat and in beagle dogs treated with DDT (0.35–39 mg/kg/day) (54,55). A number of lines of evidence suggest that the adverse effects of DDT and related compounds may be mediated through their structural similarity to estrogen and, thus, interaction with the estrogen receptor. In particular, exposed rats have been induced to enter precocious puberty (56); in adult female rats, uterine weight has been increased by treatment with DDT, and RNA or DNA and carbohydrate content was also increased (57–59). In the immature rat uterine glycogen content assay, o,p'-DDT was found to be the most active of this family of environmental pollutants (57). In contrast, DDE was 16 times less active than o,p'-DDT, which was equivalent to phenolphthalein, a compound used in laxative preparations. The relative potency of o,p'-DDT was 1/1.0 × 10^6 compared to estradiol in the MCF-7 cell proliferation assay (60). Although, these contaminants are weak estrogens compared to estradiol they represent a serious concern to human reproduction because they persist in the body at physiologically relevant concentrations, they can interact with the estrogen receptor and induce estrogen responses in sensitive tissues, and, unlike endogenous estrogens, they are not bound to sex hormone binding globulin. Thus, the potential for these compounds to adversely affect human reproduction needs to be carefully investigated.

PCBs
Polychlorinated biphenyls are members of a large family of widely used chemicals that have become ubiquitous environmental contaminants. Commercial production of PCBs commenced in 1929 in the United States, and the resulting products were marketed according to their chlorine content (Aroclor 1221, 1252, and 1260, for example). The last two digits in the PCBs number refers to the percentage of chlorine present in the mixture based on the wet weight. Commercial PCBs are mixtures of a large family of 209 specific congeners. They have been used in a wide variety of applications including plasticizers, pesticide extenders, adhesives, cutting oils, and flame retardants. They are perhaps best known for their use in heat transfer fluids and dielectric
fluids for transformers and capacitors. PCBs are very stable compounds that resist degradation and are lipophilic; thus they bioaccumulate in the food chain. They were first identified as a potential environmental hazard in 1966 by Jensen (61) and were subsequently shown to cause complete reproductive failure in mink (62). Levels of PCBs present in the whole blood of Canadians living in Great Lakes communities range from 6.2 ± 4.2 to 13.0 ± 9.9 ppm (63). The reproductive and developmental effects of PCBs have been well documented and the reader is referred to recent reviews for further details (64–66).

In adult animals (mice, rats, and monkeys) treated with PCBs (Clophen A-60 or Aroclor 1254), there is evidence of increased estrous/menstrual cycle lengths (36,67,68) and evidence of anovulation in the monkeys (36). Effects of PCBs on the estrous cycle, however, have not been found in another study in rats treated with Aroclor 1242 (3.7 or 7.5 mg/kg/day for 36 weeks). Changes in circulating levels of ovarian steroids have been documented (36,55) at PCB treatment levels as low as 7.5 mg/kg/day for 36 weeks. Reduction of the number of fertilized ova that implant has also been reported (67). Moreover, PCB treatment has also shown to induce a reduction in the number of ovarian follicles (67), thus suggesting that prolonged exposure could induced premature ovarian failure in sensitive individuals. In adult males treated with PCB, reduced sperm counts have also been documented. In one study, levels of 32 PCB congeners were measured (69), and 3 were inversely correlated with semen quality in samples with sperm counts below 20 × 10⁶.

It has been proposed that, due to the structural similarities of some of the PCB congeners (the non-ortho substituted congeners: 3,3',4,4'-tetrachlorobiphenyl, 3,3',4,4',5'-pentachlorobiphenyl, and 3,3',4,4',5,5'-hexachlorobiphenyl) with TCDD, a common mechanism is followed. Specifically, it is believed that some PCB congeners interact with the aryl hydrocarbon receptor and are translocated into the cell nucleus and interact with dioxin response elements. However, other PCB congeners such as PCB 153 bear no structural resemblance to TCDD and, indeed, in contrast to TCDD, act like an estrogen rather than an antiestrogen. Lightly chlorinated PCB mixtures with less than 48% chlorine content (Aroclor 1248, 1242, etc.) have been shown to be estrogenic, while the heavily chlorinated PCB mixtures such as Aroclor 1254, 1260, 1262, 1268, and 4465 are inactive in the immature rat uterine glycogen content assay (57). In neonatal rats treated with a PCB mixture containing 21% chlorination (Aroclor 1221), precocious puberty, persistent vaginal estrus, and premature reproductive senescence was induced (70). The role of estrogens in the development of the sexual organs and behavior has been well established. The consequences of exposure to compounds with estrogenic activity can include feminization of the male, developmental abnormalities of the reproductive tract, decreased semen quality, and premature sexual maturation. While estrogenic effects of environmental pollutants have been blamed for developmental abnormalities in wildlife species (7), there have not been any reports of adverse effects following low-level exposure to estrogenic compounds in the human population. However, the majority of these compounds have been shown to be very weak estrogens (60). Information concerning the bioavailability and metabolic fate of estrogenic compounds is sparse. Differences in receptor affinity and the sensitivity of the estrogenic target systems in humans to these compounds need to be evaluated. Thus, at present the link between exposure to estrogenic compounds such as PCBs, DDE, and DDT and adverse reproductive outcomes cannot be established with confidence. Regardless, sufficient evidence exists to suggest that this area should be a priority for future research.

CDD, BDD, and CDF

2,3,7,8-Tetrachlorodibenzop-dioxin (TCDD) is generally considered to be the most toxic isomer of the 75 possible CDD congeners. Moreover, TCDD is also regarded as the most potent of the CDDS, BDDs, and CDFs and thus serves as the model congener for discussion of the development and reproductive toxicity of this chemical class. These compounds occur in the environment at relatively low levels but have been shown to be toxicologically significant environmental contaminants. They are not manufactured commercially but occur through the combustion of industrial and municipal waste, as well as through burning automotive fuels containing chlorinated additives. They are also present as contaminants in some herbicides and fumigicides. An additional route of entry into the environment results from forest fires. Contemporary residue levels of TCDD in human tissues obtained from people residing in the Great Lakes region are sparse and are not different from those of the general population. Patterson et al. (71) have measured TCDD levels in a large number of human adipose and serum samples from the United States. Levels were between 3 and 10 pg/g of lipid. The development and reproductive toxicity of dioxins and related compounds have been reviewed previously (72) and thus will not be covered extensively here.

Postnatal effects in the male have been shown to include altered androgenic status in the male rat (73), which may be responsible for decreases in testis and epididymal weights and decreased number of sperm in the cauda epididymis. Alterations in androgen production reported by Mably et al. (73) have not been reproduced by others using the same protocol in another strain of rat (74,75). The most sensitive end point measured so far is the number of sperm in the cauda epididymis. It is important to note that there is essentially no threshold for this effect, with adverse effects seen as low as 0.016 μg/kg administered once to the dam during gestation. These effects occur in the absence of changes to body weight. Although effects were shown on the number of sperm present in the cauda epididymis, evidence of decreased sperm quality has not been determined. Furthermore, no meaningful changes have been observed in fertility index or gestational index of treated males. The number of sperm in the cauda epididymis is a poor marker of reproductive effects since the number of sperm in the cauda epididymis depends on the time from the last ejaculation. Thus, using this as a sensitive end point will cause problems with interpretation. Moreover, further research will be required to more fully characterize the mechanism of action of TCDD on spermatogenesis.

There are very few data describing the effect of dioxin exposure in the adult female, and the literature to date is equivocal. Effects on female reproduction included reduced fertility, decreased litter size, gonadal effects, and changes in estrous/menstrual cycle characteristics. In the rodent, chronic exposure to TCDD (0.1 μg/kg/day) resulted in altered fertility and was significant at a lower dose (0.01 μg/kg/day) in the F₁ generation than in the F₀ (76). Anovulation and ovarian dysfunction were shown in rats treated with 1 to 2 μg/kg/day TCDD for 13 weeks (77). In contrast to these findings, Kobiba and co-workers (77) were unable to demonstrate any effects on the female reproductive system in a 2-year study using dioxin doses of 0.001 and
TCDD years endometriosis. dentdisease. humanendometriosis Therefore, effects that heinstitute been reviewed in this paper. In general, there is no evidence that, for the compounds reviewed and at the levels present in tissues of people residing in the Great Lakes region, adverse reproductive outcomes have occurred. Nevertheless, on the basis of animal experiments, it is concluded that these compounds possess the potential to affect human development and reproduction, although a link between exposure and adverse effects has yet to be shown. Concern continues to exist due to the lack of data for HCE and TCB, the potential for developmental effects due to TCDD at levels that are relevant to the human population, and the potential for contaminants such as DDT, DDD, DDE, and PCBs to disrupt endocrine function. Consequently, there is a need for studies of the action of these compounds in mixtures. Although the individual estrogenic potencies of DDT, DDD, DDE, and PCBs are relatively low compared to estradiol, the additive and synergistic effects of these compounds need to be explored.

Summary and Conclusion

Residue levels of a number of environmental pollutants present in the Great Lakes have been identified in human tissues, and the reproductive toxicity of some of these were reviewed in this paper. In general, there is no evidence that, for the compounds reviewed and at the levels present in tissues of people residing in the Great Lakes region, adverse reproductive outcomes have occurred. Nevertheless, on the basis of animal experiments, it is concluded that these compounds possess the potential to affect human development and reproduction, although a link between exposure and adverse effects has yet to be shown. Concern continues to exist due to the lack of data for HCE and TCB, the potential for developmental effects due to TCDD at levels that are relevant to the human population, and the potential for contaminants such as DDT, DDD, DDE, and PCBs to disrupt endocrine function. Consequently, there is a need for studies of the action of these compounds in mixtures. Although the individual estrogenic potencies of DDT, DDD, DDE, and PCBs are relatively low compared to estradiol, the additive and synergistic effects of these compounds need to be explored.

The majority of data regarding male reproductive toxicity has been derived from rodent studies. These rodent studies are relatively insensitive to the effects of reproductive toxins on fertility, as rodents have relatively high sperm counts and fecundity and thus a good fertility reserve. Evaluation of spermatogenesis and semen quality in the rodent are much more sensitive end points of reproductive effects of drugs and chemical contaminants. In a number of reports (81-85), it has been demonstrated that it is possible to detect moderate to severe sperm damage in rodents following acute exposure to suspected reproductive toxins. Semen quality and testicular histomorphology with tubular staging can also serve as useful biomarkers.

We conclude that there is no evidence to establish a link between chronic low-level environmental chemical exposure and adverse reproductive effects in the human population in the Great Lakes. However, identification of chemical pollutants in human tissues raises concern but does not constitute an effect on reproduction and the conceptus. It is essential that more sensitive and relevant end points of reproductive toxicity be used to generate a more complete database.

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