CHEMICALS PRIORITIZED FOR CONSIDERATION FOR DEVELOPMENTAL/REPRODUCTIVE TOXICITY EVALUATION
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
September 12, 1996

[Note: These are the data summaries referred to in the September 12, 1997 California Regulatory Notice Register notice, “Availability of Final Data Summaries and Priorities for Chemicals With Respect to Their Potential to Cause Birth Defects or Other Reproductive Harm”].

OEHHA prioritizes chemicals for consideration by the Developmental and Reproductive Toxicant (DART) Identification Committee of OEHHA’s Science Advisory Board using the process described in the document entitled "Procedure for Prioritizing Candidate Chemicals for Consideration Under Proposition 65 by the State's Qualified Experts". The process involves selecting from chemicals proposed for evaluation by the DART Identification Committee and evaluating the potential levels of developmental/reproductive toxicity concern through review of information available from secondary sources. Secondary sources consulted include: databases such as Reprotox™, Reprotext®, Shepard’s Catalog of Teratogenic Agents and RTECS®; publications by bodies such as USEPA, ATSDR, IPCS; and standard texts such as Reproductive Hazards Of Industrial Chemicals, and Chemically Induced Birth Defects. Data summaries, which provide an overview of the data available in secondary sources, were prepared for each of these chemicals, and each chemical was assigned a draft level of developmental/reproductive toxicological concern. The draft data summaries were released for public comment on October 4, 1996. After consideration of all comments received, the priority status of the chemicals in this group have been finalized, with the exception of two chemicals (carbamazepine and progesterone) for which consideration was postponed. These two chemicals are now included as candidates for consideration by the DART Identification Committee in a subsequent group of chemicals. They will go through the same public review and comment procedure as the chemicals listed here.
<table>
<thead>
<tr>
<th>Name of Chemical and Final Level of Developmental/Reproductive Toxicity Concern</th>
<th>Final Level of Exposure Concern</th>
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* Subject to control by the US Food and Drug Administration. Other things being equal, there is less public health benefit listing under Proposition 65 such chemicals which are already subject to stringent controls compared to chemicals for which no such restrictions exist.
ACRYLAMIDE:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Acrylamide (CAS No. 79-06-1) is an organic compound with the formula C₃H₅NO. It is used mostly for polymerization (into polyacrylamide) in water purification, oil drilling, pulp and paper production, mineral processing, and in laboratories. Acrylamide is on the Proposition 65 list as a carcinogen.

Overview of Developmental/Reproductive Toxicity Concern

There is a **HIGH** level of developmental/reproductive toxicity concern. This is due mainly to a large number of reports of male reproductive toxicity in animals, including dominant lethal effects (fertility and pre- and post-implant mortality), testicular damage or atrophy, and reduced sperm count. Little contradictory data was located. There are also both positive and negative reports of developmental toxicity in animals. Effects reported include increased embryonic or fetal loss, and reduced weight, but not malformations. Concern for developmental effects is tempered by use of less relevant routes, and possibly inconsistent results. No studies of reproductive or developmental toxicity in humans were located.

**Developmental toxicity**

There are several reports of adverse developmental effects in animals (mice and rats), including increased embryonic or fetal loss, or reduced litter size. However, one report was by exposure via injection, and one had both male and female exposures (see male reproductive toxicity below). There are three reports, at relatively high doses, which found no effect on these endpoints. There is a single report of malformations in mice by injection, but several studies in mice or rats by an oral route which found no effect on this endpoint. There are several reports of reduced fetal, birth, or postnatal weight, although several other studies did not find these effects. Various other effects have been found in one or two studies each, including reduced dopamine receptors, scattered nerve fiber degeneration, alteration in intestinal enzymes, and extra ribs.

**Female reproductive toxicity**

There are one or two reports of adverse female reproductive effects (fertility or litter size) in rats. However, both males and females were exposed. Several other studies found no effects.

**Male reproductive toxicity**

In animal studies, dominant lethal effects (reduced fertility, pre- and post-implant mortality, reduced litter size), testicular damage or atrophy, reduced sperm count, and increased abnormal sperm have been reported. Effects have been reported in mouse and rat, mainly by oral, and also by injection routes. Dominant lethal effects occur at relatively low doses. The mechanism appears to involve chromosomal damage to male germ line cells. A total of 22 studies showing one or more toxic effects were identified. Only one report showing no effect on chromosomal aberrations was identified.

Overview of Exposure concern

There is a **MEDIUM** level of concern over the extent of exposure. Acrylamide is a reactive monomer used in production of polyacrylamide. Its main uses are in water purification (drinking and sewage). It is also used in oil drilling, pulp and paper production, mineral processing, and in laboratories (gel electrophoresis). Considerable exposure may occur in occupational settings and low level exposures may occur through drinking water. It degrades rapidly (days to weeks) in the environment and does not bioconcentrate.
Data on Developmental and Reproductive Toxicity

NOTE: Unless otherwise indicated, all information, including the citation, is obtained from secondary sources. Full citations of all studies are not provided here.

Developmental toxicity in humans

No studies were identified.

Developmental toxicity in animals

   Mice (female) were treated orally (gavage) at 20 mg/kg/d for gd 7-16. A reduction in dopamine receptors (spiroperidol binding) in striatal membrane of 2 week old, but not 3 week old pups was observed. No effect on litter size or birth weight was observed.

   Rats (female) were treated orally (food) at 50 ppm for 2 weeks plus gestation. No maternal toxicity (death, reduced weight gain or food consumption) was observed. Scattered nerve fiber degeneration in pups was observed. No effects on fertility, “litter and offspring data” (undefined), or “gross postmortem observations” (undefined) were observed.

3. Edwards (1975), as cited in Reprotext®.
   Rats (presumably female) were treated (no details given). Altered intestinal enzymes in pups were observed. No neurological effects in pups were observed. (See also Edwards 1976)

   a. Rats (female) were treated orally (food) at 400 ppm for gd 1-21. Maternal toxicity (ataxia, reduced food consumption) was observed. Reduced fetal body weight but no teratogenicity was observed. Increased extra ribs (a variation) and no reduced fetal weight or teratogenicity (malformations) were observed.
   b. Rats (female) were treated orally (food) at 200 ppm for gd 1-21. Maternal toxicity (abnormal gait) was observed. Altered intestinal enzymes in pups but no effect on postnatal weight gain or neurological effects in pups were observed.
   c. Rats (female) were treated by injection (iv) at 100 mg/kg on gd 9. No gross neurologic defects were observed in the pups.

5. Field et al. (1990), as cited in HSDB, IARCb, Reprotext®, Schardein, Shepard’s Catalog of Teratogenic Agents.
   a. Rats (female) were treated orally (gavage) at 15 mg/kg/d for gd 6-20. Maternal toxicity (reduced weight gain) was observed. Increased extra ribs (a variation) and no reduced fetal weight or teratogenicity (malformations) were observed.
   b. Mice (female) were treated orally by gavage at 45 mg/kg/d for gd 6-17. Maternal toxicity (reduced weight gain, hindlimb splaying) was observed. Reduced fetal weight and increased extra ribs (a variation), but no teratogenicity (malformations) were observed.

   Rats (female) were treated orally (gavage) at 0.3 mg/kg/d from gd 6 until weaning. No adverse effects were observed on body weight of the pups or on other developmental events (eye opening etc.). (Rats fed a low protein diet in addition to acrylamide showed reduced weight and developmental delay.)

   Rats (female) were treated orally (water) at 2 or 5 mg/kg/d for 10 weeks including gestation and lactation. At 5 mg/kg/d, reduced maternal body weight gain and body weight were observed. At 5 mg/kg/d, reduced fertility and increased pre-implantation losses were observed. At 2 mg/kg/d, reduced number of litters was observed. (Also cited in the Female reproductive toxicity in animals section.) (Note: this appears to be a preliminary draft of Union Carbide (1985), although there is a discrepancy in the description of which sexes were treated.)

   Mice (female) were treated by injection (ip) at 75 mg/kg/d for gd 10-12. Reduced litter size, increased malformations (kinked tail), reduced birth weight, hypoplasia of lymphatic tissues, and placental hemorrhages were observed.
   Mice (female) were treated orally (water) at 85 ppm for 4-6 weeks prior to mating. An increase in resorptions, but no effect on fertility was observed.

10. Union Carbide; Bushy Run Research Center (1985), as cited in HSDB.
    a. Rats (male) were treated orally (water) at 2 or 5 mg/kg/d for 10 weeks. Reduced fertility and post-implant loss (dominant lethal effects) were observed at 5 mg/kg/d (NOAEL 2 mg/kg/d).
    b. Rats (male and female) were treated orally (water) at 5 mg/kg/d for 10 weeks (male) and 10 weeks plus gestation plus lactation (female). Paternal and maternal toxicity (reduced body weight gain, sporadic reduced food and water consumption) were observed. Reduced litter size (4.5 pups/litter vs. 9.8 pups/litter for control) was observed. (Same study listed in the Developmental and Male reproductive toxicity in animals sections.) (Note: this appears to be the same study as Nalco Chem. Co. (1985), although there is a discrepancy in the description of which sexes were treated.)

    Rats (female) were treated orally (gavage) at 20 mg/kg/d for gd 6-17. Reduced postnatal weight gain and altered levels of intestinal enzymes in pups were observed.

12. Zenick et al. (1986), as cited in IARCb, Reprotext®, RTECS®.
    Rats (female) were treated orally (water) at 0, 25, 50, or 100 ppm for 2 weeks before mating to 3 weeks after birth. Reduced maternal weight gain was observed at 100 ppm. Reduced birth weight, which persisted until termination of the study on postnatal day 42, and delayed vaginal opening, were observed at 100 ppm. Reduced pup body weight from postnatal day 7 onwards was observed at 50 ppm. No effects on fertility, litter size, or pup survival were observed. (Also cited in the developmental section, and another part of this report cited in the Male reproductive toxicity in animals section.)

**Female reproductive toxicity in humans**

No studies were identified.

**Female reproductive toxicity in animals**

   Rats (female) were treated orally (food) at 50 ppm for 2 weeks plus gestation. No maternal toxicity (death, reduced weight gain or food consumption) was observed. Scattered nerve fiber degeneration in pups was observed. No effects on fertility, “litter and offspring data” (undefined), or “gross postmortem observations” (undefined) were observed.

   Rats (female) were treated orally (gavage) at 0.3 mg/kg/d from gd 6 until weaning. No adverse effects were observed on body weight of the pups or on other developmental events (eye opening etc.). (Rats fed a low protein diet in addition to acrylamide showed reduced weight and developmental delay.)

   Rats (female) were treated orally (water) at 2 or 5 mg/kg/d for 10 weeks including gestation and lactation. At 5 mg/kg/d, reduced maternal body weight gain and body weight were observed. At 5 mg/kg/d, reduced fertility and increased pre-implantation losses were observed. At 2 mg/kg/d, reduced number of litters was observed. (Also cited in the Developmental toxicity in animals section.) (Note: this appears to be a preliminary draft of Union Carbide (1985), although there is a discrepancy in the description of which sexes were treated.)

   Mice (female) were treated orally (water) at 85 ppm for 4-6 weeks prior to mating. An increase in fetal death (resorptions), but no effect on fertility was observed.

5. Union Carbide; Bushy Run Research Center (1985), as cited in HSDB.
   a. Rats (male) were treated orally (water) at 2 or 5 mg/kg/d for 10 weeks. Reduced fertility and post-implant loss (dominant lethal effects) were observed at 5 mg/kg/d (NOAEL 2 mg/kg/d).
   b. Rats (male and female) were treated orally (water) at 5 mg/kg/d for 10 weeks (male) and 10 weeks plus gestation plus lactation (female). Paternal and maternal toxicity (reduced body weight gain, sporadic reduced food and water consumption) were observed. Reduced litter size (4.5 pups/litter vs. 9.8 pups/litter for control)
was observed. (Same study listed under developmental and male reproductive toxicity.) (Note: this appears to be the same study as Nalco Chem. Co. (1985), although there is a discrepancy in the description of which sexes were treated.)

6. Zenick et al. (1986), as cited in IARCb, Reprotext®, RTECS®.
   Rats (female) were treated orally (water) at 0, 25, 50, or 100 ppm for 2 weeks before mating to 3 weeks after birth. Reduced maternal weight gain was observed at 100 ppm. Reduced birth weight, which persisted until termination of the study on post-natal day 42, and delayed vaginal opening, were observed at 100 ppm. Reduced pup body weight from postnatal day 7 onwards was observed at 50 ppm. No effects on fertility, litter size, or pup survival were observed. (Also cited in the Developmental toxicity in animals section, and another part of this report cited in the Male reproductive toxicity in animals section.)

**Male reproductive toxicity in humans**

No studies were identified.

**Male reproductive toxicity in animals**

1. Backer et al. (1989), as cited in HSDB.
   Mice (male) were treated by injection (ip) at 200 mg/kg. Death was observed. No chromosomal aberrations in spermatogonia were observed. No other endpoints were reported.

2. Bishop et al. (1991), as cited in RTECS®.
   Mice (male) were treated orally (water) at 6 mg/kg/d for 20 weeks before mating. Dominant lethal effects were observed.

   Rats (male) were treated orally (water) at 20 mg/kg/d for 90 days. Systemic toxicity (reduced body weight, neurological effects, anemia, atrophy of skeletal muscle) and testicular atrophy were observed.

4. Collins et al. (1992), as cited in Reprotext®.
   Mice (male) were treated (no details given). Increased spermatid micronuclei were observed.

5. Costa et al. (1992), as cited in IARCb, RTECS®.
   Rats (male) were treated by injection (ip) at 50 mg/kg/d for 7 days prior to mating. Reduced vas deferens sperm count was observed. No effect on testicular weight was observed.

6. Dobryzynska et al. (1990), as cited in IARCb.
   Mice (male) were treated by injection (ip) at 125 mg/kg (once). Dominant lethal effects were observed.

   Mice (male) were treated by injection (ip) at 1x 100 mg/kg. Dominant lethal effects were observed.

   Rats (male) were treated by injection at 20 mg/kg/d for 20 days. Reduction of plasma testosterone and prolactin were observed.

   Mice (male) were treated dermally at 25 mg/kg/d for 5 days. Dominant lethal effects were observed.

10. Hashimoto and Tani (1981), as cited in IPCS.
    Mice were treated (no details given). Testicular damage with degeneration of seminiferous tubules was observed. (Note: abstract only).

11. Hashimoto et al. (1981), as cited in HSDB, IARCa, IARCb, RTECS®.
    Mice (male) were treated orally at 35 mg/kg/d, 2d/wk, for 8 weeks before mating. Neurotoxicity, testicular atrophy, and degeneration of epithelial cells were observed.

12. McCollister et al. (1964), as cited in IPCS.
    Rats (male) were treated orally (food) for “short-term” (no dosage given). Marked degeneration of seminiferous tubules was observed.

    Mice (male), prepubertal and adult, were treated orally at 100-150 mg/kg (once). Testicular damage and spermatid death, which reversed in 7-10 days, were observed.
   Mice (male) were treated orally (water) at 85 ppm for 4-6 weeks prior to mating. Reduced sperm count, and increased abnormal sperm morphology, reduced fertility, increased fetal death (resorptions), and reduced litter size were observed. No reduction in birth weight was observed. (Another part of this report cited in the Developmental and Female reproductive toxicity in animals sections.)

15. Shelby et al. (1986), as cited in HSDB, IARCb, RTECS®, Reprotox™.
   Mice (male) were treated by injection (ip) at 125 mg/kg (once) or 50 mg/kg/d for 5 days. Reduced fertility (dominant lethal effect) was observed.

   Mice (male) were treated by injection (ip) at 40-50 mg/kg/d for 5 days. Reduced fertility in F1 males descended from F0 treated males was observed. Indicates production of heritable translocations, resulting in sterility or semi-sterility of male offspring.

   a. Mice (male) were treated orally (food) at 500 ppm for 3 weeks. Chromosome aberrations in spermatogonia (chromatid exchanges, breaks, polyploidy, aneuploidy) were observed.
   b. Mice (male) were treated by injection (ip) at 100 mg/kg (total duration unknown). Testicular atrophy and effects on sperm morphology but no increase in chromatid exchange was observed.

18. Smith et al. (1986), as cited in IARCb, IRIS®.
   Rats (male) were treated orally (water) at 2.8 mg/kg/d for 80 days. Increased post-implantation loss (dominant lethal effect) was observed.

   Rats (male) were treated orally at 15 mg/kg/d for 5 days prior to mating. Effects on fertility were observed. (Note: abstract, probably redundant to Sublet et al. (1989).)

   Rats (male) were treated orally at 5 to 60 mg/kg (/d?) for 5 days and mated for 4-10 weeks after exposure. Reduced fertility and pre- and post-implantation loss were observed in the first 3 weeks after treatment. Decreased entry of sperm to the uterus was observed in week 1, and reduced sperm motility was observed in weeks 2 and 3.

21. Union Carbide; Bushy Run Research Center (1985), as cited in HSDB.
   a. Rats (male) were treated orally (water) at 2 or 5 mg/kg/d for 10 weeks. Reduced fertility and post-implant loss (dominant lethal effects) were observed at 5 mg/kg/d (NOAEL 2 mg/kg/d).
   b. Rats (male and female) were treated orally (water) at 5 mg/kg/d for 10 weeks (male) and 10 weeks plus gestation plus lactation (female). Paternal and maternal toxicity (reduced body weight gain, sporadic reduced food and water consumption) were observed. Reduced litter size (4.5 pups/litter vs. 9.8 pups/litter for control) was observed. (Same study listed under developmental and female reproductive toxicity.) (Note: this appears to be the same study as Nalco Chem. Co. (1985), although there is a discrepancy in the description of which sexes were treated.)

   Rats (male) were treated orally at 30 mg/kg/d for 5 days prior to mating. Effects on male fertility due to pre- and post-implant mortality (dominant lethal) were observed.

23. Zenick et al. (1986), as cited in IARCb, Reprotext®, RTECS®.
   Rats (male) were treated orally (water) at 0, 50, 100, or 200 ppm for 9 weeks prior to mating. Severe toxicity and death were observed in the 200 ppm group; treatment was terminated after 6 weeks. No mortality or weight loss was observed in the other groups. Some hindlimb splaying was observed at 100 ppm on week 8. Reduced sperm count, reduced fertility, and increased post-implantation mortality were observed at 100 ppm (8.6 mg/kg/d). No testicular histopathological changes were observed. (See also other parts of this report in the Developmental and Female reproductive toxicity in animals sections.)

Other relevant data

Acrylamide is cleared quickly from the body (HSDB). It crosses the placenta quickly (Reprotox™, IARC). Many effects appear to be associated with chromosomal damage to male germ line cells. There is also some possibility of neurological effects (a typical acrylamide toxicity) on reproductive function.
Secondary Sources


Reprotext®. Micromedex, Inc. (TOMES APRIL 30, 1995)

Reprotox™. Dr. Anthony M. Scialli. (TOMES APRIL 30, 1995)


Shepard’s Catalog of Teratogenic Agents. Dr. Thomas H. Shepard. (TOMES APRIL 30, 1995)
DDT (1,1,1-TRICHLORO-2,2-BIS(P-CHLOROPHENYL)ETHANE):
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

DDT (1,1,1-Trichloro-2,2-bis(p-chlorophenyl)ethane) (Cas No. 50-29-3) is an organochlorine pesticide with the formula C₁₄H₉Cl₅. DDT and its metabolites/degradation products (DDD and DDE) remain ubiquitous at low levels in the environment from previous use in the U.S. It is used extensively in other countries, and airborne deposition in U.S. occurs. Elevated levels occur in some fish and human milk, compared to other foods. DDT is on the Proposition 65 list as a carcinogen.

Overview of Developmental/Reproductive Toxicity Concern

There is a HIGH level of developmental/reproductive toxicity concern. This is due to reports of developmental and female reproductive toxicity. Studies in humans have found an association of elevated levels of DDT or its metabolites with spontaneous abortion or premature delivery, although the interpretation of this is unclear. Studies in animals have found increased fetal and postnatal death, reduced fertility, and estrogen-like effects.

Developmental Toxicity

In humans, there have been several reports of an association of spontaneous abortion with elevated levels of DDT or its metabolites in maternal blood, cord blood, placenta, or milk. Not all studies found an association, and some of the associations were not statistically significant. In some studies where an association was found, other chlorinated pesticides and polychlorinated biphenyls (PCBs) were also elevated. It is not clear whether the elevated levels of DDT and its metabolites are a cause of spontaneous abortions. Other effects (low birth weight and neurobehavioral; 1 study each) have also been associated with elevated levels of DDT or its metabolites. Other studies have not found an association.

In mice, rabbits, and dogs, there is one report each of increased embryonic or fetal death. Several reports have found no effect on litter size. Several reports in 4 species have found no increase in malformations. Reduced fetal weight has been found in rabbits. Increased constriction rings of the tail was found in 1 study in rats. Postnatal effects of DDT have been studied extensively. Increased postnatal death (during lactation) has been found in mice, rats, and dogs from gestational and/or lactational exposure. Not all studies found this endpoint. A cross-fostering study found that increased postnatal death was observed after gestational treatment, with nursing by untreated mothers. Gestational plus lactational treatment increased the effect by 4-fold. Decreased pup growth and neurobehavioral effects have also been found, although the data are less clear. DDT and its metabolites (especially DDE) are persistent, accumulate in fat, and are secreted in milk. This results in relatively high levels of exposure of the nursing young.

Female reproductive toxicity

In humans, there are several reports of an association between premature delivery and increased levels of DDT or its metabolites in maternal blood or serum, placenta, or milk. Not all studies found an association, and some of the associations were not statistically significant. In some studies where an association was found, other chlorinated pesticides and PCBs were also elevated. It is not clear whether the elevated levels of DDT and its metabolites are a cause of premature delivery.

There are several reports of reduced fertility in mice and rats. Some studies have found no effects on fertility or reproduction, although these were usually at lower doses. There are several reports in mice, rats, or dogs of effects on the developing reproductive system, and of altered estrus cycles. There is 1 report of increased prematurity, but most reports have found no effect on this endpoint. Some isomers of DDT and its metabolites have estrogen-like effects; this may be the cause of some of the observed reproductive effects.
Male reproductive toxicity

In humans, 1 study found no association between semen quality or fertility and DDE levels in semen. Some studies in mice and rats at high doses found reduced fertility, dominant lethal effects, reduced testes weight, or impaired spermatogenesis. However, other studies at comparable or lower doses found no effects on these endpoints.

Overview of Exposure Concern

There is a MEDIUM level of concern over exposure to DDT. DDT was formerly used as broad spectrum insecticide in the U.S. It was banned by U.S. E.P.A. in 1972, except for use in health emergencies against vector-borne diseases. A small amount is manufactured for export. California use was similar to U.S. use. DDT is used extensively in other countries, and airborne deposition in U.S. occurs. DDT and its metabolites/degradation products (DDE, DDD) are ubiquitous in soil and water samples, although usually at low levels. DDT, DDE, and DDD bioconcentrate and biomagnify. The primary route of exposure to humans is via food. Elevated levels occur in some fish and in human milk. A former DDT manufacturing site in Torrance, CA (Montrose Chemical) is now a hazardous waste site. Large amounts were released into Santa Monica Bay between 1947 and 1971.

Data on developmental and reproductive toxicity

NOTE: unless otherwise indicated, all information, including the citation, is obtained from secondary sources. Full citations of all studies are not provided here.

Developmental toxicity in humans

1. Bercovici et al. (1983), as cited in Reprotox™.
Women with spontaneous abortions had higher levels of o,p’-DDT, but not total DDT, than did women with normal pregnancies. (Also cited in the Female reproductive toxicity in humans section.)

2. Gladen and Rogan (1991), as cited in Reprotox™.
In humans, transplacental or lactational exposure to DDT was not found to be associated with persistent neurodevelopmental decrements when compared to controls. (Gladen et al. 1988 also cited.)

In humans, transplacental or lactational exposure to DDT was not found to be associated with persistent neurodevelopmental decrements when compared to controls. (Gladen and Rogan 1991 also cited.)

4. Leoni et al. (1989), as cited in ATSDRb, Reprotox™.
DDT was not increased in maternal blood in cases of miscarriage in humans (n = 120 cases, n = 120 controls). (Also cited in the Female reproductive toxicity in humans section.)

5. O’Leary et al. (1970), as cited in ATSDRb, IARC, IPCS, Shepard’s Catalog of Teratogenic Agents.
A study of 101 spontaneous abortions and 152 normal pregnancies in Florida found an association of DDT or DDE concentrations with spontaneous abortions, but the association was not statistically significant. Other chlorinated pesticides and polychlorinated biphenyls (PCBs) were also elevated. (Also cited in the Female reproductive toxicity in humans section.)

6. Procianoy and Schvartsman (1981), as cited in ATSDRb, IARC.
ATSDR: DDT levels were higher in maternal blood and placental tissue in mothers who gave birth to premature infants or who spontaneously aborted compared to mothers who gave birth to full-term infants. (Saxena et al. 1980, 1981, 1983, Wassermann et al. 1982 also cited.)
IARC: DDT levels in neonates showed no correlation with gestational age at birth (premature delivery). DDT levels in neonates had a significant correlation (p < 0.05) with low birth weight. (Also cited in the Female reproductive toxicity in humans section.)

7. Rogan et al. (1986), as cited in IARC, Reprotox™.
DDE levels in samples from human mother, baby, placenta, and/or milk were associated with neurobehavioral
effects (transient hyporeflexia), but were not correlated with birth weight, head circumference, or hyperbilirubenemia of newborn.

8. Ron et al. (1988), as cited in ATSDRb, Reprotox™.
DDT or related compounds in maternal and cord blood were not found to be associated with premature rupture of fetal membranes in humans. (Also cited in the Female reproductive toxicity in humans section.)

DDT levels were higher in maternal blood and placental tissue in mothers who gave birth to premature infants or who spontaneously aborted compared to mothers who gave birth to full-term infants. (Procianoy and Schvartsman 1981, Saxena et al. 1981, 1983, Wassermann et al. 1982 also cited.) (Also cited in the Female reproductive toxicity in humans section.)

10. Saxena et al. (1981), as cited in ATSDRb
DDT levels were higher in maternal blood and placental tissue in mothers who gave birth to premature infants or who spontaneously aborted compared to mothers who gave birth to full-term infants. (Procianoy and Schvartsman 1981, Saxena et al. 1980, 1983, Wassermann et al. 1982 also cited.) (Also cited in the Female reproductive toxicity in humans section.)

11. Saxena et al. (1983), as cited in ATSDRb, Reprotox™.
ATSDR: DDT levels were higher in maternal blood and placental tissue in mothers who gave birth to premature infants or who spontaneously aborted compared to mothers who gave birth to full-term infants. (Procianoy and Schvartsman 1981, Saxena et al. 1980, 1981, Wassermann et al. 1982 also cited.) However, no “significant” association found. Other chlorinated pesticides and PCBs were also elevated. (O’Leary et al. 1970, Wassermann et al. 1982 also cited.)
Reprotox: Higher concentrations of DDT were found in maternal serum, cord blood, and placenta from stillborn pregnancies than from matched controls. (Also cited in the Female reproductive toxicity in humans section.)

Levels of DDT and its congeners in human milk were associated with preterm birth or miscarriage. (Also cited in the Female reproductive toxicity in humans section.)

13. Wassermann et al. (1982), as cited in ATSDRb, IARC, Reprotox™.
In Israel, DDT levels in maternal serum were elevated in cases of premature births (71.1 ppb, n = 17) compared to controls of term birth (26.5 ppb, n = 10). However, the association was not statistically significant. Other chlorinated pesticides and PCBs were also elevated. (Also cited in the Female reproductive toxicity in humans section.)

**Developmental toxicity in animals**

1. Author not provided (1968), as cited in RTECS®.
Mice (female) were treated by unknown route at 17.5 mg/kg (total) from gd 8-14. Effects on newborn - neurobehavioral were observed.

2. Author not provided (1970), as cited in RTECS®.
Rats (female) were treated by injection (ip) at 21 mg/kg (total) for 21 days after birth. Effects on newborn - weaning or lactation index; Effects on newborn - growth statistics were observed.

3. Author not provided (1975), as cited in RTECS®.
Mice (female) were treated by injection (sc) at 143 mg/kg (total) in for 21 days after birth. Delayed effects - effects on newborn were observed.

4. Author not provided (unknown year), as cited in RTECS®.
Mice (female) were treated by injection (sc) at 418 mg/kg (total) from gd 6-14. Effects on embryo or fetus - extra embryonic structures were observed.

5. Clement and Okey (1974), as cited in ATSDRb, RTECS®.
ATSDR: Rats were treated orally (food) at 1, 10, or 25 mg/kg/d for 7 months. Decreased growth of nursing pups at 10 mg/kg/d (NOAEL 1 mg/kg/d) and pup death by 10 days at 25 mg/kg/d (NOAEL 10 mg/kg/d) was observed.
RTECS®: Rats (female) were treated orally at 430 mg/kg (total)(calculated 10 mg/kg/d) for gd 1-22 and 21 days after birth. Effects on newborn - growth statistics were observed.
6. Craig and Ogilvie (1974), as cited in ATSDRb, RTECS®, Schardein
   a. Mice were treated orally (gavage) at 26 mg/kg/d during gestation; pups were nursed by untreated foster
      mothers. Increased preweaning pup mortality (10%) was observed
   b. Mice were treated orally (gavage) at 26 mg/kg/d during gestation and lactation. Increased preweaning pup
      mortality (39%) and behavioral alterations (impaired learning and memory in maze test) were observed.

7. Dean et al. (1980), as cited in IARC
   Rats (female) were treated by injection (ip) at 40 mg/animal/kg on gd 13. No effect in 2-10 day old male pups
   on circulating testosterone (i.e. no effect on hepatic metabolism of testosterone) or testicular testosterone
   production was observed.
   (Also cited in the Male reproductive toxicity in animals section.)

8. Deichmann and MacDonald (1971), as cited in Schardein
   Not teratogenic (in mouse, rat, dog, rabbit?: Table entry: Ware and Good 1967, Dinerman et al. 1970, Hart et al.
   1971, 1972 also cited)
   (Note: This appears to be redundant to Deichmann et al. 1971.)

9. Deichmann et al. (1971), as cited in ATSDRa, IPCS
   Dogs (female) were treated (oral?) at 12 mg/kg/d for 5d/wk, for 14 months. Dogs (male) were treated orally
   (food) at 60 mg/kg/d plus aldrin at 0.15 mg/kg/d for 14 months, but not during breeding. Increased stillbirths,
   maternal and fetal mortality, delayed estrus, lack of mammary gland development, and reduction in male libido
   was observed. (Also cited in the Female and Male reproductive toxicity in animals sections.) (Note: see also
   Deichmann and MacDonald (1971).)

10. Del Pup et al. (1978), as cited in ATSDRb, IARC
    Mice were treated orally (food) at 1 or 13 mg/kg/d (100 ppm) for 70 weeks (successive generations of a stable
        population of 400 animals). At 13 mg/kg/d, decreased 30-day survival (NOAEL 1 mg/kg/d) was observed. No
        effect on day 4 survival was observed.

11. Dinerman et al. (1970), as cited in Schardein
    Not teratogenic (table: mouse, rat, dog, rabbit? Ware and Good 1967, Hart et al. 1971, 1972, Deichman and
        MacDonald 1971 also cited)

    Rabbits were treated orally at 1 mg (animal/kg/d?) on gd 4-7. Reduction in brain weight of fetuses was observed.

13. Fabro et al. (1984), as cited in ATSDRb, HSDB, IARC.
    Rabbits were treated orally (gavage) at 1 mg/kg/d for gd 4-7. Reduced fetal body, brain and kidney weights
    were observed. No gross abnormalities were observed.

    Rats (male and female) were treated orally (food) at 0.35 mg/kg/d for 60 days. Decreased fertility (P0) was
    observed. F1 pups were completely infertile. Decreased viability of offspring was observed. No effect on litter
    size or teratogenicity was observed. (Also cited in the Female and Male reproductive toxicity in animals
    section.)

15. Hart et al. (1971), as cited in ATSDRb, Reprotox™, RTECS®, Shepard's Catalog of Teratogenic Agents.
    Rabbits were treated with p,p’-DDT orally (gavage) at 10 or 50 mg/kg/d on gd 7-9. Increased resorptions,
    increased prematurity, and decreased fetal size were observed (at both doses). No malformations were
    observed. (Also cited in the Female reproductive toxicity in animals section.)

16. Hart et al. (1972), as cited in ATSDRb, Reprotox™, Schardein.
    a. Rabbits were treated with p,p’-DDT orally (gavage) at 10 or 50 mg/kg/d on gd 7-9. Increased resorptions,
       increased prematurity, and decreased fetal size were observed (at both doses). No teratogenicity was observed.
       (Hart et al. 1971 also cited.)
    b. Rabbits were treated with p,p’-DDT orally (gavage) at 10 or 50 mg/kg/d on gd 21-23. No effect on
       resorptions, teratogenicity, prematurity, or fetal size was observed. (Also cited in the Female reproductive
       toxicity in animals section.)

17. Hayes (1976), as cited in IPCS.
    a. Rats were treated orally at 200 ppm (duration? “focused mainly on DDT in milk”). “Ability of rats to
       reproduce... was demonstrated”.
    b. Rats were treated by injection (ip) up to 100 mg/kg/d (duration? “focused mainly on DDT in milk”). “...ability
of dams... to rear their young was demonstrated”.
(Also cited in the Female reproductive toxicity in animals section.)

18. Keplinger et al. (1970), as cited in ATSDRb, IPCS
Mice were treated orally (food) at 3.2, 13, or 32 mg/kg/d (25, 100, and 250 ppm) for 6 generations, with 2 matings per generation.. At 32 mg/kg/d, frank toxicity was observed: this dose was discontinued after 3 generations. At 13 mg/kg/d for 6 generations, decreased viability and lactation indices (postnatal survival) was observed (NOAEL 3.2 mg/kg/d). At 13 mg/kg/d, no effect on fertility or gestation was observed. (Also cited in the Female reproductive toxicity in animals section.)

19. Kornburst et al. (1986), as cited in ATSDRb, Reprotox™.
Rats were treated with p,p'-DDE orally (gavage) at 10 mg/kg/d for 9 weeks (before mating through gestation and lactation). No effects on reproduction were observed. No effects on milk composition, pup survival, or weight gain were observed. (Also cited in the Female reproductive toxicity in animals section.)

20. Macklin and Bibelin (1971), as cited in IPCS.
No evidence of a relation between DDT and abortion in dairy cattle was found. (Also cited in the Female reproductive toxicity in animals section.)

Mice were treated with p,p'-DDT (unknown route) at 1 mg/kg/d on gd 10, 12, and 17. Altered gonads and decreased fertility of young (especially female), but no teratogenicity was observed. (Also cited in the Female reproductive toxicity in animals section) (Abstract)

a. Rats were treated (unknown route) at 0.02 mg/kg/d during mating. Slower physical development of pups was observed.
b. Rats were treated (unknown route) at 0.02 mg/kg/d for 4 months. An increase in the length of gestation and decrease in the number of fetuses, although not statistically significant, were observed. (Also cited in the Female reproductive toxicity in animals section.)

Rats were treated orally (food) at 1 or 10 mg/kg/d for 2 generations. At 10 mg/kg/d, decreased neonatal survival, and increased constriction rings of the tail, were observed. No adverse effects on reproduction were observed. (Also cited in the Female reproductive toxicity in animals section.)

24. Ottoboni et al. (1977), as cited in ATSDRb, IARC, IPCS, Reprotox™, RTECS®.
Dogs were treated orally (food) at 0, 5 or 10 mg/kg/d for 3 generations. Increased premature puberty (statistically significant only if all generations were combined at 5 or 10 mg/kg/d) was observed. No reproductive effects (length of gestation, fertility, litter size, viability, gestation or lactation indices) were observed. No developmental effects (growth of pups, morbidity, mortality, organ/body weight ratios, or gross histological abnormalities) were observed. (Also cited in the Female reproductive toxicity in animals section.)

25. Shabad et al. (1973), as cited in ATSDRb.
Mice were treated orally (gavage) at 1.3-6.5 mg/kg/d for multiple generations. At 6.5 mg/kg/d, most females died before delivery. At 1.3 mg/kg/d, increased abortions, stillbirths, and pup mortality were observed. (Also cited in the Female reproductive toxicity in animals section.)

26. Schmidt (1973), as cited in IPCS.
Mice were treated (route?) at 25 mg/kg once or 2.5 mg/kg/d “repeated” times “during pregnancy”. It was concluded that DDT “May be embroyotoxic but not teratogenic....”

27. Tarjan and Kemeny (1969), as cited in IARC.
Mice were treated orally (food) at 2.8 - 3.0 ppm for 5 generations. No effect on fertility (number of pregnancies or litters), litter size, or postnatal death was observed. (Also cited in the Female reproductive toxicity in animals section.)

28. Tomatis et al. (1972), as cited in ATSDRb.
Mice were “chronically exposed” to 32.5 mg/g/d. Increased preweaning mortality was observed. (Turusov et al. 1973 also cited.)

29. Treon and Cleveland (1955), as cited in Reprotox™.
Rats. No effects on litter size or postnatal survival were observed. (Duby et al. 1971 cited.) (Also cited in the Female reproductive toxicity in animals section.)
30. Turusov et al. (1973), as cited in ATSDRb
Mice were treated orally (food) at 6.5 or 32.5 mg/kg/d for life. Increased preweaning death was observed. (Tomatov et al. 1972 also cited.) (Also cited in the Female reproductive toxicity in animals section.)

31. Ware and Good (1967), as cited in ATSDRb, RTECS®, Reprotox™, Schardein, Shepard’s Catalog of Teratogenic Agents.
ATSDR: Mice were treated orally (food) at 0.91 mg/kg/d for 110 days. No reproductive effects were observed. RTECS®: Mice were treated orally at 81 mg/kg (total) male 4 weeks prior to mating and female 4 weeks prior to mating through 2 weeks after birth. Effects on fertility - other measures of fertility were observed. Reprotox™: Mice. Not teratogenic. Schardein: Not teratogenic (table: mouse, rat, dog, rabbit? Dinerman et al. 1970, Hart et al. 1971, 1972 and Deichman and MacDonald 1971 also cited) Shepard’s Catalog of Teratogenic Agents: Mice were treated orally (food) at 7 ppm for “long periods of time”. Reduced fertility, but no teratogenicity was observed. (Also cited in the Female reproductive effects in animals section.)

Female reproductive toxicity in humans

1. Bercovici et al. (1983), as cited in Reprotox™.
Women with spontaneous abortions had higher levels of o,p’-DDT, but not total DDT, than did women with normal pregnancies. (Also cited in the Developmental toxicity in humans section.)

2. Leoni et al. (1989), as cited in ATSDRb
DDT was not increased in maternal blood in cases of miscarriage in humans (n = 120 cases, n = 120 controls). (Also cited in the Developmental toxicity in humans section.)

3. O’Leary et al. (1970), as cited in ATSDRb, IARC, IPCS, Shepard’s Catalog of Teratogenic Agents.
A study of 101 spontaneous abortions and 152 normal pregnancies in Florida found an association of DDT or DDE concentrations with spontaneous abortions, but the association was not statistically significant. Other chlorinated pesticides and PCBs were also elevated. (Also cited in the Female reproductive toxicity in humans section.)

4. Procionoy and Schvartsman (1981), as cited in ATSDRb, IARC.
ATSDR: DDT levels were higher in maternal blood and placental tissue in mothers who gave birth to premature infants or who spontaneously aborted compared to mothers who gave birth to full-term infants. (Saxena et al. 1980, 1981, 1983, Wassermann et al. 1982 also cited.) IARC: DDT levels in neonates showed no correlation with gestational age at birth (premature delivery). DDT levels in neonates had a significant correlation (p < 0.05) with low birth weight. (Also cited in the Developmental toxicity in humans section.)

5. Ron et al. (1988), as cited in ATSDRb, Reprotox™.
DDT or related compounds in maternal and cord blood was not found to be associated with premature rupture of fetal membranes in humans. (Also cited in Developmental toxicity in humans section.)

DDT levels were higher in maternal blood and placental tissue in mothers who gave birth to premature infants or who spontaneously aborted compared to mothers who gave birth to full-term infants. (Procionoy and Schvartsman 1981, Saxena et al. 1981, 1983, Wassermann et al. 1982 also cited.) (Also cited in the Developmental toxicity in humans section.)

7. Saxena et al. (1981), as cited in ATSDRb.
DDT levels were higher in maternal blood and placental tissue in mothers who gave birth to premature infants or who spontaneously aborted compared to mothers who gave birth to full-term infants. (Procionoy and Schvartsman 1981, Saxena et al. 1980, 1981, Wassermann et al. 1982 also cited.) (Also cited in the Developmental toxicity in humans section.)

8. Saxena et al. (1983), as cited in ATSDRb, Reprotox™.
ATSDR: DDT levels were higher in maternal blood and placental tissue in mothers who gave birth to premature infants or who spontaneously aborted compared to mothers who gave birth to full-term infants. (Procionoy and Schvartsman 1981, Saxena et al. 1980, 1981, Wassermann et al. 1982 also cited.) However, no “significant” association found. Other chlorinated pesticides and PCBs were also elevated. (O’Leary et al. 1970,
Wassermann et al. 1982 also cited.)

Reprotox: Higher concentrations of DDT were found in maternal serum, cord blood, and placenta from stillborn pregnancies than from matched controls.
(Also cited in the Female reproductive toxicity in humans section.)

Levels of DDT and its congeners in human milk were associated with preterm birth or miscarriage. (Also cited in the Developmental toxicity in humans section.)

10. Wassermann et al. (1982), as cited in ATSDRb, IARC, Reprotox™.
In Israel, DDT levels in maternal serum were elevated in cases of premature births (71.1 ppb, n = 17) compared to controls of term birth (26.5 ppb, n = 10). However, the association was not statistically significant. Other chlorinated pesticides and PCBs were also elevated. (Also cited in the Female reproductive toxicity in humans section.)

Female reproductive toxicity in animals

1. Author not provided (1972), as cited in RTECS®.
   Mice (female) were treated by injection (ip) at 40 mg/kg, 1 day prior to mating. Maternal effects - menstrual cycle [sic] changes or disorders were observed.

2. Author not provided (1973), as cited in RTECS®.
   Mice (female) were treated by injection (ip) in at 40 mg/kg (total) on gd 1-3. Effects on fertility - pre-implantation mortality was observed.

3. Author not provided (1977), as cited in RTECS®.
   Mice (female) were treated by injection (sc) at 40 mg/kg (total) for 3 days prior to mating. Maternal effects - ovaries, fallopian tubes, uterus, cervix, or vagina and menstrual cycle [sic] change or disorders were observed.

   Mice were treated orally (food) at 26 or 39 (conflicting doses on different pages) mg/kg/d for 60-90 days. Reduced fertility was observed.

5. Cannon and Holcomb (1968), as cited in ATSDRb.
   Mice were treated at 13-39 mg/kg/d for 50 days or multiple generations. Effects on fertility were observed. (Bernard and Gaertner (1964) and Keplinger et al. (1970) also cited).

6. Clement and Okey (1972), as cited in ATSDRb.
   Rats (immature) were treated orally (food) at 50 mg/kg (total? /d?) for 7 days (pnd 21-30). o,p',- but not p,p'- DDT produced estrogenic effects (increased uterine weight and glycogen content and premature vaginal opening).

7. Deichmann et al. (1971), as cited in ATSDRb, IPCS.
   Dogs (female) were treated (oral?) at 12 mg/kg/d for 5d/wk, for 14 months. Dogs (male) were treated orally (food) at 60 mg/kg/d plus aldrin at 0.15 mg/kg/d for 14 months, but not during breeding. Increased stillbirths, maternal and fetal mortality, delayed estrus, lack of mammary gland development, and reduction in male libido was observed. (Also cited in the Developmental and Male reproductive toxicity in animals sections.) (Note: see also Deichmann and MacDonald(1971))

8. Duby et al. (1971), as cited in ATSDRb, Reprotox™, RTECS®.
   ATSDR: Rats were treated orally (food) at 0.75 mg/kg/d (tech DDT) or 0.6 mg/kg/d (p,p'-DDT) or 0.15 mg/kg/d (o,p'-DDT) for 2 generations. No effects on reproduction were observed.
   Reprotox™: Rats. No effects on litter size or postnatal survival were observed. (Treon and Cleveland 1955 also cited.)
   RTECS®: Rats (female) were treated by injection (ip) at 60 mg/kg (total) 3 days prior to mating. Effects on uterus, cervix, or vagina were observed.

   Rats were treated with p,p'-DDT (dose not given) by injection on postnatal days 3-4. Altered maturation of the reproductive system was observed.

10. Gellert and Heinrichs (1975), as cited in ATSDRb, RTECS®.
   ATSDR: Rats were treated with p,p'-, o,p'-DDT, o,p'-DDE, or o,p'-DDD orally (gavage) at 28 mg/kg/d from gd 15-19. “No significant effects on the development of the reproductive system in the offspring were noted”.

-15-
RTECS®: Rat were treated orally at 250 mg/kg (total) (calculated 10 mg/kg/d) from gd 15-19. Specific developmental abnormalities - urogenital system were observed.

11. Green (1969), as cited in ATSDRb, Reprotox™. Rats (male and female) were treated orally (food) at 0.35 mg/kg/d for 60 days. Decreased fertility (P0) was observed. F1 pups were completely infertile. Decreased viability of offspring was observed. No effect on litter size or teratogenicity was observed. (Also cited in the Developmental and Male reproductive toxicity in animals section.)

12. Hart et al. (1971), as cited in ATSDRb, Reprotox™, RTECS®, Shepard’s Catalog of Teratogenic Agents. Rabbits were treated with p,p'-DDT orally (gavage) at 10 or 50 mg/kg/d on gd 7-9. Increased resorptions, increased prematurity, and decreased fetal size were observed (at both doses). No malformations were observed. (Also cited in the Developmental toxicity in animals section.)

13. Hart et al. (1972), as cited in ATSDRb, Reprotox™, Schardein. a. Rabbits were treated with p,p'-DDT orally (gavage) at 10 or 50 mg/kg/d on gd 7-9. Increased resorptions, increased prematurity, and decreased fetal size were observed (at both doses). No teratogenicity was observed. (Hart et al. 1971 also cited.) b. Rabbits were treated with p,p'-DDT orally (gavage) at 10 or 50 mg/kg/d on gd 21-23. No effect on resorptions, teratogenicity, prematurity, or fetal size was observed. (Also cited in the Developmental toxicity in animals section.)

14. Hayes (1976), as cited in IPCS. a. Rats were treated orally at 200 ppm (duration? “focused mainly on DDT in milk”). “Ability of rats to reproduce... was demonstrated”. b. Rats were treated by injection (ip) up to 100 mg/kg/d (duration? “focused mainly on DDT in milk”), “...ability of dams... to rear their young was demonstrated”. (Also cited in the Developmental toxicity in animals section.)

15. Heinrichs et al. (1971), as cited in IPCS, Shepard’s Catalog of Teratogenic Agents. Rats were treated with o,p'-DDT by injection (sc) at 1 mg/animal/d (about 83.3 mg/kg/d) on postnatal days 2-4. Persistent vaginal estrus after a period of normal estrus and “other reproductive abnormalities” were observed.

16. Jonsson et al. (1976), as cited in ATSDRb, RTECS®. Rats (female) were treated orally (food) at 3.75 or 7.5 mg/kg/d for 36 weeks. Sterility and decreased serum progesterone at 7.5 mg/kg/d (NOAEL 3.75 mg/kg/d) were observed.

17. Keplinger et al. (1970), as cited in ATSDRb, IPCS, Reprotox™. Mice were treated orally (food) at 3.2, 13, or 32 mg/kg/d (25, 100, and 250 ppm) for 6 generations, with 2 matings per generation. At 32 mg/kg/d, frank toxicity was observed: this dose was discontinued after 3 generations. At 13 mg/kg/d for 6 generations, decreased viability and lactation indices (postnatal survival) was observed (NOAEL 3.2 mg/kg/d). At 13 mg/kg/d, no effect on fertility or gestation was observed. (Also cited in the Developmental toxicity in animals section.)

18. Kornburst et al. (1986), as cited in ATSDRb, Reprotox™. Rats were treated with p,p'-DDE orally (gavage) at 10 mg/kg/d for 9 weeks (before mating through gestation and lactation). No effects on reproduction were observed. No effects on milk composition, pup survival, or weight gain were observed. (Also cited in the Developmental toxicity in animals section.)

19. Ledoux et al. (1977), as cited in ATSDRb. Mice were treated orally (food) at 2.6 mg/kg/d for 86 days. No reproductive effects were observed.

20. Lundberg (1973), as cited in ATSDRb, RTECS®. a. Mice were treated orally at 124 mg/kg (total) (calculated 2.0 mg/kg/d) for 62 days prior to mating. Persistent estrus were observed. b. Mice were treated orally at 148 mg/kg (total) (calculated 2.0 mg/kg/d) for 66 days prior to mating and gd 1-8. Decreased implanted ova was observed.

21. Lundberg and Kihlstrom (1973), as cited in Reprotox. Mice were treated with “high doses.” Inhibition of implantation was observed.

22. Lundberg (1974), as cited in ATSDRb. Mice were treated with p,p'-DDT orally (gavage) at 1.67 mg/kg/d for 28 days. Decreased corpora lutea and implants were observed.

23. Macklin and Bibelin (1971), as cited in IPCS. No evidence of a relation between DDT and abortion in dairy cattle was found. (Also cited in the Developmental toxicity in animals section.)
24. McLachlan and Dixon (1972), as cited in IPCS, Reprotox™, RTECS®, Schardein. Mice were treated with p,p'-DDT (unknown route) at 1 mg/kg/d on gd 10, 12, and 17. Altered gonads and decreased fertility of young (especially female), but no teratogenicity was observed. (Also cited in the Developmental toxicity in animals section) (Abstract)

25. Naishtein and Leibovich (1971), as cited in ATSDR®. Rats were treated (unknown route) at 0.02 mg/kg/d during mating. Slower physical development of pups was observed.

26. Ottoboni (1969), as cited in ATSDR®, IARC, IPCS, Shepard’s Catalog of Teratogenic Agents. Rats were treated orally (food) at 1 or 10 mg/kg/d for 2 generations. At 10 mg/kg/d, decreased neonatal survival, and increased constriction rings of the tail, were observed. No adverse effects on reproduction were observed. (Also cited in the Developmental toxicity in animals section.)

27. Ottoboni (1972), as cited in ATSDR®, IPCS. Rats were treated orally (food) at 1 mg/kg/d (20 ppm) for 11 generations. A significant increase in reproductive lifespan (14.55 months vs. 8.91 months controls), number of females becoming pregnant after the age of 17 months, and number of successful pregnancies after the age of 17 months was observed.

28. Ottoboni et al. (1977), as cited in ATSDR®, IARC, IPCS, Reprotox™, RTECS®. Dogs were treated orally (food) at 0, 5, or 10 mg/kg/d for 3 generations. Increased premature puberty (statistically significant only if all generations were combined at 5 or 10 mg/kg/d) was observed. No reproductive effects (length of gestation, fertility, litter size, viability, gestation or lactation indices) were observed. No developmental effects (growth of pups, morbidity, mortality, organ/body weight rations, or gross histological abnormalities) were observed. (Also cited in the Developmental toxicity in animals section.)

29. Shabad et al. (1973), as cited in ATSDR®. Mice were treated orally (gavage) at 1.3-6.5 mg/kg/d for multiple generations. At 6.5 mg/kg/d, most females died before delivery. At 1.3 mg/kg/d, increased abortions, stillbirths, and pup mortality were observed. (Also cited in the Developmental toxicity in animals section.)

30. Tarjan and Kemeny (1969), as cited in IARC. Mice were treated orally (food) at 2.8 - 3.0 ppm for 5 generations. No effect on fertility (number of pregnancies or litters), litter size, or postnatal death was observed. (Also cited in the Developmental toxicity in animals section.)

31. Treon et al. (1954), as cited in ATSDR®. Rats were treated orally (food) at 1.25 mg/kg/d for 2 generations. No effects on reproduction (including litter size) were observed.

32. Treon and Cleveland (1955), as cited in Reprotox™. Rats. No effects on litter size or postnatal survival were observed. (Duby et al. 1971 cited.) (Also cited in the Developmental toxicity in animals section.)

33. Turusov et al. (1973), as cited in ATSDR®. Mice were treated orally (food) at 6.5 or 32.5 mg/kg/d for life. Increased preweaning death was observed. (Tomatov et al. 1972 also cited.) (Also cited in the Developmental toxicity in animals section.)

34. Uphouse and Williams (1989), as cited in Schardein. Rats (no route etc. given). Decreased sexual behavior in females.

35. Ware and Good (1967), as cited in ATSDR®, RTECS®, Reprotox™, Schardein, Shepard’s Catalog of Teratogenic Agents. ATSDR: Mice were treated orally (food) at 0.91 mg/kg/d for 110 days. No reproductive effects were observed. RTECS®: Mice were treated orally at 81 mg/kg (total) male 4 weeks prior to mating and female 4 weeks prior to mating through 2 weeks after birth. Effects on fertility - other measures of fertility were observed. Reprotox™: Mice. Not teratogenic. Schardein: Not teratogenic (table: mouse, rat, dog, rabbit? Dinerman et al. 1970, Hart et al. 1971, 1972 and Deichman and MacDonald 1971 also cited) Shepard’s Catalog of Teratogenic Agents: Mice were treated orally (food) at 7 ppm for “long periods of time”. Reduced fertility, but no teratogenicity was observed.
(Also cited in the Developmental effects in animals section.)
[Note: Contradiction in reports of effects on fertility.)

36. Wolfe et al. (1979), as cited in ATSDRb.
Mice were treated orally (food) at 2.4 mg/kg/d for 15 months. No reproductive effects were observed.

37. Wrenn et al. (1971a), as cited in ATSDRb, IPCS.
Rats (female) were treated with o,p'-DDT orally (food) at 2.0 mg/kg/d (40 ppm) for 20 weeks (2 pregnancies).
No effects on reproduction, litter size, birth weight, postnatal survival or weaning weight were observed.

38. Wrenn et al. (1971b), as cited in IPCS.
Sheep (female: ewes) were exposed to o,p'-DDT at 10 ppm for 2-9 months. No effect on reproduction was observed.

Male reproductive toxicity in humans

1. Bush et al. (1986), as cited in Reprotox™.
In human males, the concentration of DDE in semen samples did not appear to be related to semen quality or a history of infertility.

Male reproductive toxicity in animals

1. Author not provided (1978), as cited in RTECS®.
Rat (male) were treated orally at 112 mg/kg (total) 56 days prior to mating. Paternal effects - spermatogenesis, testes, epididymus, or sperm duct were observed.

2. Author not provided (1979), as cited in RTECS®.
   a. Mice were treated orally at 100 mg/kg (total), duration unknown (once?). Dominant lethal effects were observed.
   b. Mice were treated (by unknown route) at 200 mg/kg (total) for 10W-I (10 weeks to intercourse?). Dominant lethal effects were observed.

   a. Mice (male) were treated at 150 mg/kg/d for 2 days. When mated to untreated females, increased dead implants and chromosome damage in sperm were observed.
   b. Mice (male) were treated at 100 mg/kg/d for 2d/wk, for 10 wks. When mated to untreated females, increased dead implants were observed. Reductions in testes weight, sperm viability, and spermatogenesis were observed.

4. Dean et al. (1980), as cited in IARC
   Rats (female) were treated by injection (ip) at 40 mg/animal?/d? on gd 13. No effect in 2-10 day old male pups on circulating testosterone production (i.e. no effect on hepatic metabolism of testosterone) or testicular testosterone was observed.
   (Also cited in the Developmental toxicity in animals section.)

5. Deichmann et al. (1971), as cited in ATSDRa, IPCS.
   Dogs (female) were treated (oral?) at 12 mg/kg/d for 5d/wk, for 14 months. Dogs (male) were treated orally (food) at 60 mg/kg/d plus aldrin at 0.15 mg/kg/d for 14 months, but not during breeding. Increased stillbirths, maternal and fetal mortality, delayed estrus, lack of mammary gland development, and reduction in male libido was observed. (Also cited in the Developmental and Female reproductive toxicity in animals sections.) (Note: see also Deichmann and MacDonald (1971))

6. Epstein and Shafner (1968), as cited in IPCS.
   Mice were treated at 105 mg/kg (route etc. not given). No dominant lethal effects were observed.

   Rats (male and female) were treated orally (food) at 0.35 mg/kg/d for 60 days. Decreased fertility (P0) was observed. F1 pups were completely infertile. Decreased viability of offspring was observed. No effect on litter size or teratogenicity was observed. (Also cited in the Developmental and Female reproductive toxicity in animals section.)

8. Krause et al. (1975), as cited in ATSDRb, IARC, RTECS®.
   Rats (male) were treated orally (gavage) at 200 mg/kg/d on pnd 4-23 or at 500 mg/kg/d on pnd 4-5. Decreased fertility and testes weight, and impaired spermatogenesis, were observed at both dosages.
9. Krause (1977), as cited in ATSDRb  
Rats (adult male) were treated orally (gavage) at 200 mg/kg/d for 2 days/wk for 2 weeks or 3 days/week for 3 weeks. Decreased testosterone was observed. No histological effects on spermatogenesis were observed.

10. Linder et al. (1992), as cited in ATSDRb  
Rats were treated orally (gavage) at 100 mg/kg (1 day) or 50 mg/kg/d (5 days). No spermatotoxic effects were observed.

Mice (male) were treated orally (gavage) at 8.33 mg/kg/d for 28 days. No reproductive effects (including testes weight) were observed.

12. Palmer et al. (1973), as cited in ATSDRb, RTECS®.  
Rats (male) were treated orally (gavage), at 50 or 100 mg/kg/d for 1 day. At 100 mg/kg, increased dead implants (dominant lethal effects) were observed (NOAEL 50 mg/kg/k/d).

13. Seiler (1977), as cited in ATSDRb  
Mice (male) were treated orally at 50 mg/kg once. No inhibition of testicular DNA synthesis was observed.

Other relevant data

DDT and its metabolites, DDD and DDE, are persistent in the environment, are lipophilic, and are excreted slowly. They bioconcentrate and bioaccumulate. DDT and its metabolites are secreted in milk (ATSDRb, Reprotox). DDT and its metabolites (especially the o,p'- isomers) have been shown to be estrogenic in several systems in vivo and in vitro, although the potency is much lower than naturally occurring estrogens (ATSDRb, IPCS, Reprotox). Low doses of DDT administered to mice on pnd 10 have been shown to produce neurobehavioral effects much later in life (ATSDRb).

Secondary Sources


ATSDRb. (1994) Agency for Toxic Substances and Disease Registry. Toxicological Profile for DDT, DDE, and DDD


Reprotox™. Dr. Anthony M. Scialli. (TOMES APRIL 30, 1995)


Shepard’s Catalog of Teratogenic Agents. Dr. Thomas H. Shepard. (TOMES APRIL 30, 1995)
FORMALDEHYDE:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Formaldehyde (formula HCHO, CAS No. 50-00-0) exposures result from car exhaust, sterilants, preservatives, resins, tobacco smoke, and cosmetics. Formaldehyde (gas) is on the Proposition 65 list as a carcinogen.

Overview of Developmental/Reproductive Toxicity Concern

There is a MEDIUM-HIGH level of developmental/reproductive toxicity concern over formaldehyde due to recent (1994) reports of spontaneous abortions in cosmetologists and laboratory workers. These human studies are consistent with animal studies reporting resorptions in animals (rats, mice, hamsters) exposed by the inhalation, oral or dermal route. Potential confounding in the human studies and incomplete reporting of maternal toxicity data in the animal studies make interpretation difficult at this level of review. More complete evaluations of endpoints, doses, routes and general toxicity are needed to integrate this diverse set of studies, many of which were published in non-English journals.

Developmental toxicity

While older studies by the inhalation route in Russian language journals reported developmental toxicity in animals, two more fully reported recent studies were essentially negative. Animal studies by the inhalation, oral and dermal routes have reported increased resorptions, but others at apparently higher doses reported no effects. Maternal toxicity data was mentioned for some of these studies, but not others. Malformations were reported only in an abstract of a study using i.p. injection. More complete evaluations of endpoints, doses, routes and general toxicity are needed to integrate this diverse set of studies, many of which were published in non-English journals.

Female reproductive toxicity

Associations were found between formaldehyde exposure and spontaneous abortion in two recent studies of cosmetologists, and of pathology and histology laboratory workers. However earlier studies in hospitalization sterilization workers did not demonstrate this association. Studies in rats, mice and hamsters by the inhalation and dermal routes have reported increased resorptions.

Male reproductive toxicity

No adverse effects have been reported in studies with exposures in male animals, with the exception of effects after i.p. injection. The irritant effects of formaldehyde complicate interpretation of injection studies.

Overview of Exposure Concern

There is a HIGH level of concern over exposure to formaldehyde. The general population is exposed via car exhaust, sterilants, preservatives, resins, tobacco smoke, cosmetics, and offgassing from pressed wood, insulation, carpets and upholstery (HSDB, 1995). Indoor air in mobile homes averages 0.1 ppm from offgassing (IARC, 1995). The 1994 TRI reports releases from industrial sources of 571,631 lbs in California, of which 439,271 lbs were released to air. Cars contribute 54% of all emissions, refineries 13%. The 1987 annual release in California reports motor vehicle emissions of 11,000 tons. The photolysis half life of formaldehyde in air is about 4 hours (ARB, 1992). In occupational settings, exposures up to 30.5 ppm occur in manufacture of formaldehyde and formaldehyde based resins. Other occupational exposures are from wood product, paper, textile, and metal product manufacture, medical laboratories and construction.

Data on developmental and reproductive toxicity
NOTE: Unless otherwise indicated, all information, including the citation, is obtained from secondary sources. Full citations of all studies are not provided here.

Developmental toxicity in humans

No human studies examining endpoints other than spontaneous abortion were located. Studies of spontaneous abortion are described under *Female reproductive toxicity in humans.*

Developmental toxicity in animals

1. Bektemirova and Merkur’eva (1990), as cited in RTECS®.
   Rats were given formaldehyde orally at a dose of 168 mg/kg/day during pregnancy. Biochemical and metabolic effects in offspring were reported.
2. Gofmekler and Bonashevkaya (1969), as cited in Barlow and Sullivan, IPCS.
   In a study with relatively low doses, rats were given 0, 0.012, or 1.0 mg/m³ formaldehyde 24 hr/day before and during gestation and no effects were reported.
3. Hurni and Ohder (1973), as cited in IRIS®, Reprotox™, Barlow and Sullivan, Schardein, TERIS, IPCS.
   Dogs were fed formaldehyde in diet at a dose of 3 and 9 mg/kg/day from 4 days after mating to gd 56. No effects were reported on pregnancy rate, litter size, defects, or stillbirths. Behavior, mobility and appearance of all dogs were normal up to 9 months postnatal.
   A Russian language report was described in which rats were given 168 mg/kg (total dose) formaldehyde orally during pregnancy and effects on hepatobiliary systems of offspring were identified.
5. Lane and Alarie (1977), as cited in Reprotox®.
   A rat inhalation study reported shortened gestational time and increased fetal resorptions. No further experimental details were given.
   When mice were given 74, 148 or 185 mg/kg formaldehyde by the oral route on gd 8-12, no malformations or effects on fetal weight were reported but there were increased resorptions and decreased litter size at the 185 mg/kg dose, which also produced >50% maternal mortality.
7. Martin (1990), as cited in TERIS, Reprotox™.
   Rats were exposed by inhalation at concentrations up to 40 ppm. No embryolethal or teratogenic effects were reported.
8. Overman (1985), as cited in IPCS.
   Hamsters were exposed by the dermal route to 0.5 ml of 37% formaldehyde on gd 8, 9, 10 or 11. Increased resorptions were reported but no effects on fetal weight or length or on malformations.
   This early study in the Russian language literature reported changes in ascorbic and nucleic acid content of embryos after formaldehyde exposure at concentrations of 0.012 or 1 mg/m³ 10 to 20 days before gestation. Little information was provided in the secondary sources.
    Rats were given formaldehyde by inhalation at concentrations of 0, 5, 10, 20 or 40 ppm 6 hr/day, on gd 6-20. Decreased fetal weights were reported at the 40 ppm dose accompanied by reduced maternal weights and weight gain.
11. Sheveleva (1971), as cited in RTECS®, Shepard’s Catalog of Teratogenic Agents, Barlow and Sullivan and IPCS.
    Rats were exposed to 0.4 or 4 ppm formaldehyde by inhalation 4 hr/day throughout gestation. Decreases in activity and in length were noted in female offspring at one month postnatal. Also, an increased number of preimplantation deaths occurred.
    Using the Kavlock screen for developmental toxicity, mice were given 540 mg/kg/day formaldehyde by gavage on gd 8-12. There were no statistically significant effects on any parameter examined.
13. Yasamura et al. (1983), as cited in RTECS®, IPCS. 
Mice were injected i.p. with formaldehyde at doses of 0, 30, 40, or 50 mg/kg/day on gd 7-14. Fetotoxicity and craniofacial and musculoskeletal abnormalities were reported. Mean body weight of treated fetuses was lower than that of controls. The major malformations were cleft palate and malformations of the extremities. (Abstract only).

Mice were injected i.p. with formaldehyde at 160 or 240 mg/kg (total dose) on gd 7-14. Fetal death and other (unspecified) developmental abnormalities were reported. (Abstract only).

Female reproductive toxicity in humans

No relation between formaldehyde exposure and spontaneous abortion was found in an occupational study of hospital sterilization workers.

2. John et al. (1994), as cited in Reprotext®, TERIS. 
Formaldehyde was found to be a risk factor for spontaneous abortion in cosmetologists.

3. Shumilina (1975), as cited in Reprotox™, Barlow and Sullivan, IARC. 
A Russian language study reported menstrual disturbances, primarily dysmenorrhea, and problems with pregnancy in 446 women workers using urea-formaldehyde resins. 130 workers were exposed to 1.4-4.3 mg/m³ and 316 were exposed to .0005-0.67 mg/m³. There were no differences in fertility, but anemia, toxemia and low birthweight were more frequent in the more highly exposed group. There was no evaluation of confounding factors.

4. Taskinen et al. (1994), as cited in TERIS. 
A significant association between spontaneous abortion and exposure to formalin >=3 days a week was reported in women working in pathology or histology labs.

Female reproductive toxicity in animals

1. Chaterjee (1965), as cited in Reprotext®. 
Formaldehyde administered by injection disturbed the estrous cycles of rats. This was attributed to stress. No further information was given.

2. Gofmekler et al. (1968), as cited in IPCS. 
Rats were given formaldehyde by inhalation at concentrations of 0, 0.012, or 1.0 mg/m³, 24 h/day, 10-15 days before mating through gestation. Increased gestation length was reported. No other information concerning pregnancy rate or litter size was provided in this Russian language study.

3. Hagino (1968), as cited in Barlow and Sullivan. 
Rats were given formaldehyde by inhalation for 4 min, 4 times/day for 26 days. Estrus abnormalities but no fertility effects were reported.

4. Lane and Alarie (1977), as cited in Reprotox®. 
A rat inhalation study reported shortened gestational time and increased fetal resorptions. No further experimental details were given.

5. Marks et al. (1980), as cited in IRIS®. 
When mice were given 74, 148 or 185 mg/kg formaldehyde by the oral route on gd 8-12, no malformations or effects on fetal weight were reported but there were increased resorptions and decreased litter size at the 185 mg/kg dose, which also produced >50% maternal mortality.

6. Maronpot et al. (1986), as cited in Reprotext®. 
Mice given formaldehyde at a "close to lethal" dose of 40 ppm had some degenerative changes in the uterus and ovaries. No further information was given.

7. Overman (1985), as cited in IPCS. 
Hamsters were exposed by the dermal route to 0.5 ml of 37% formaldehyde on gd 8, 9, 10 or 11. Increased resorptions were reported but no effects on fetal weight or length or on malformations were identified.

Male reproductive toxicity in humans
Male reproductive toxicity in animals

1. Epstein (1972), as cited in Barlow and Sullivan, IPCS.
   In a dominant lethal study, mice were injected i.p. with 16, 20, 32 or 40 mg/kg formaldehyde (1 injection).
   No fertility effects were observed.
2. Fontignie-Houbrechts (1981), as cited in RTECS®, Reprotox™, IPCS.
   In a dominant lethal study, mice were injected with 50 mg/kg i.p. They were mated for 3 or 8 weeks. No effect was observed on the number of pregnant females, but increased pre-implantation death was reported in the 3rd wk. This was variously described as a weak, or no, dominant lethal effect by different secondary sources.
3. Freeman and Coffery (1973), as cited in RTECS®.
   Rats were given intratesticular injections of formaldehyde at a dose of 400 mg/kg, 1 day prior to mating. An effect was reported on the male fertility index.
4. Gofmekler and Bonashevskaya (1969), as cited in Barlow and Sullivan, IPCS.
   In a study with relatively low doses, rats were given 0, 0.012, or 1.0 mg/m³ formaldehyde 24 hr/day for 10 days. No effects on testes were reported.
5. Guseva (1972), as cited in IPCS, RTECS®.
   Male rats were given combination inhalation and ingestion exposures to formaldehyde (0.005 mg/L and 0.12 mg/m³; 0.1 mg/L and 0.25 mg/m³; 0.1 mg/L and 0.5 mg/m³) for 6 months. The formaldehyde was given in the drinking water and during 4/h exposure periods 5 times/wk. No adverse effects on reproduction were reported, but there was a decrease in the amount of nucleic acid in the testes. No information was given concerning the offspring.
   Rats were given i.p. formaldehyde at 80 mg/kg (total dose) for 10 days. Effects on testes, epididymis, sperm duct, prostate, seminal vesicle, Cowper’s gland, accessory glands were reported.
7. Shell Oil (no date given), as cited in HSDB.
   Male rats were given a single dose of 100 or 200 mg/kg formaldehyde by gavage. Abnormal sperm heads but no testes histopathology was reported.
8. Ward et al. (1984), as cited in IPCS.
   Male mice were intubated with 100 mg/kg formaldehyde for 5 days. No effects were found on 500 sperm examined.

Other relevant data

1. Natvig et al. (1971), as cited in TERIS; Della Porta et al. (1970) as cited in IPCS.
   Formaldehyde is unlikely to reach the fetus intact, it is rapidly metabolized to formate. Hexamethylphosphoramide, an agent that releases formaldehyde during metabolism, did not demonstrate reproductive or developmental toxicity when administered in drinking water in a single generation study.

Secondary Sources


Reprotox™. Dr. Anthony M. Scialli. (TOMES JULY 31, 1995)

Reprotext®. Micromedex, Inc. (TOMES JULY 31, 1995)


Shepard’s Catalog of Teratogenic Agents. Dr. Thomas H. Shepard. (TOMES JULY 31, 1995)

Trichloroethylene (TCE) (formula C₂HCl₃, CAS No. 79-01-6) is a solvent used for metal degreasing, adhesives and vinyl chloride polymer manufacturing. TCE is on the Proposition 65 list as a carcinogen.

Overview of Developmental/Reproductive Toxicity Concern

There is a MEDIUM-HIGH level of developmental/reproductive toxicity concern over TCE due to recent studies in human populations and animal models that suggest the potential for intrauterine exposure to produce cardiac and eye defects. Spontaneous abortion has been reported in some human epidemiological studies in worker populations, but another study has reported decreased risks of abortion. Exposure levels by inhalation in animals are limited by anesthetic properties; maternal toxicity was not usually achieved in inhalation studies. No effect studies were generally at lower doses than studies showing effects, indicating consistency in dose response.

Developmental toxicity

Epidemiological studies in Arizona have described an increased rate of cardiac defects in a population exposed to TCE contaminated drinking water. Recent studies by the same group have reported increases in cardiac defects in rats after oral exposure to TCE. Previous large scale developmental toxicity studies in laboratory animals were confined to inhalation routes of exposure and did not identify developmental toxicity effects. Issues of confounding in the human studies, and design and dose levels in the animal studies make interpretation difficult at this level of review. Cardiac defects have also been seen in chick embryos and in other nonmammalian models. Trichloroacetic acid, a metabolite of TCE, produces cardiac malformations and micro/anophthalmia in animal models.

Female reproductive toxicity

Increases in spontaneous abortion rates have been reported in operating room nurses and in other workers exposed to TCE in the workplace. However, a decreased risk of abortion has also been reported in a worker population, and no adverse reproductive effects were seen in a population exposed to TCE as a drinking water contaminant. Animal multigeneration studies have been generally negative, but a continuous breeding study described reduction in fertility and live pups/litter.

Male reproductive toxicity

A single study of 15 male workers found no effect on sperm. Two animal studies have reported effects on sperm (motility and morphology). No dominant lethal effects, or fertility effects in multigeneration studies, have been identified.

Overview of Exposure Concern

There is a HIGH level of concern over exposure to TCE. TCE is mainly used as a metal cleaning solvent. (This accounts for 91% of its use). It is also used as a solvent in adhesives and in vinyl chloride polymer manufacturing. 1,023 tons were used in California in 1987. According to the TRI, 14,562 lbs were released to air in California in 1994. TCE is present in nearly all rural air (mean US concentration 0.2 µg/m³) urban air (2.5 µg/m³) and industrial areas (64 µg/m³) (IARC, 1995). The 1995 statewide California average in ambient air was 1.18 µg/m³ (ARB, 1995). A 1986 survey reported 6.7% of groundwater wells sampled in California were contaminated with TCE (CDHS, 1986).
Data on developmental and reproductive toxicity

NOTE: Unless otherwise indicated, all information, including the citation, is obtained from secondary sources. Full citations of all studies are not provided here.

Developmental toxicity in humans

   Increased miscarriages were reported in operating room nurses exposed to TCE from anesthesia.
2. Freni and Bloomer (1988), as cited in ATSDR.
   No effect on congenital defects was reported in three Michigan communities exposed to drinking water contaminated with chlorinated solvents including TCE.
3. Goldberg (1990), as cited in ATSDR, Reprotox™, Reprotext®, TERIS.
   Increased congenital heart disease was reported in Tucson, AZ where drinking water was contaminated with TCE, as well as other contaminants.
4. Lagakos (1986a), as cited in ATSDR, Reprotext®.
   Increased incidence of specific groups of birth anomalies (combination of eye and ear anomalies, combination of CNS, chromosomal and oral cleft anomalies) was reported in Woburn, MA where drinking water was contaminated with solvents including 267 ppb TCE. The study was criticized in ATSDR for the use of groupings. No effect on childhood leukemia was reported.
5. Tola et al. (1980), as cited in ATSDR, USEPA HAD, IPCS.
   No increase in malformed babies was reported in offspring of 2,000 mothers and fathers exposed in the workplace.
   In a case-control study, an increased risk of spontaneous abortion was reported in women exposed at home and in the workplace to TCE.

Developmental toxicity in animals

1. Beliles et al. (1980), as cited in ATSDR, USEPA HAD, IPCS.
   Rats and rabbits were exposed via inhalation to 500 ppm TCE for 7 h/day, 5day/wk, for 3 wks premating and on gd 1-18 (rats) or gd 1-21 (rabbits). No teratogenic effect was found. Embryotoxicity or maternal toxicity were mentioned in some secondary sources but not others. Results were not reported separately by species. The study was also reported in Hardin et al. (1981).
2. Bell (1977), as cited in USEPA HAD, IPCS.
   Rats were exposed via inhalation to 300 ppm TCE, 6h/d, gd 6-15. Embryotoxicity and maternal toxicity were mentioned in some secondary sources, but no teratogenic effects were reported.
3. Cosby and Dukelow (1992), as cited in Reprotext®, Shepard’s Catalog of Teratogenic Agents, TERIS.
   Mice were given TCE by gavage at doses up to 0.1 LD50, 24-240 mg/kg/day, various days before implantation and during organogenesis. No adverse reproductive effect and no teratogenic effect were identified.
4. Dawson et al. (1989), as cited in Reprotox™.
   Rats were exposed prenatally. An increase in cardiac malformations was reported. (Abstract only).
5. Dawson et al. (1990), as cited in TERIS.
   Intrauterine infusion of TCE in rats resulted in an increased frequency of heart malformations. (Abstract only).
6. Dorfmueller et al. (1979), as cited in ATSDR, HSDB, IRIS®, Reprotext®, Reprotox™, Shepard’s Catalog of Teratogenic Agents.
   a. Rats were exposed via inhalation to 1800 ppm TCE, 6h/day, on gd 1-20. Developmental delay, reduced sternebral ossification, reduced body weight, and effects on the urogenital system were reported.
   b. Rats were also exposed via inhalation to 1800 ppm TCE 2 wk, 6h/day, 5d/wk, and premating 2 wk + gd 1-21. No behavioral effects were found in this study.
7. Healy (1982), also reported in Healy et al. (1978) and Healy et al. (1981), as cited in ATSDR, RTECS, Reprotext®, Barlow and Sullivan, TERIS.
   Rats were exposed by inhalation. Musculoskeletal defects were reported. (Abstracts only)
Rats were given drinking water containing 1140 mg/kg (total dose) 14 days prior to mating through pnd 21.
Decreases in myelinated fibers were reported in the dorsal hippocampus.
Rats were given TCE by gavage 2 weeks prior to mating and throughout mating and pregnancy. The high dose
was maternally toxic and was associated with decreased neonatal survival.
10. Schwetz et al. (1975), as cited in ASTDR, Reprotox™, Shepard’s Catalog of Teratogenic Agents, Barlow and
Sullivan, TERIS, IARC, USEPA HAD, IPCS.
Mice and rats were exposed via inhalation to 300 ppm, 7 h/day on gd 6-15. Embryotoxicity and maternal
toxicity were reported in some secondary sources, but no teratogenic effects were noted. This study was also
reported in Leong et al. (1985) as cited in Reprotox™, Schardein, USEPA HAD, IPCS. This may also be the
same study as Bell et al., described above.
11. Taylor et al. (1985), as cited in HSDB.
Rats were given 312, 625, or 1250 mg/L in drinking water 14 days prior to breeding through pnd 21. Increased
exploratory activity was reported on pnd 60 and 90 but not pnd 28; feeding, drinking and wheel-running on pnd
55-60 were not affected.

Female reproductive toxicity in humans

1. Byers et al. (1988), and Lagakos et al. (1986a), as cited in ATSDR.
No adverse reproductive effects were reported in a human population in Massachusetts exposed to TCE in
drinking water.
Increased miscarriages were reported in operating room nurses exposed to TCE from anesthesia.
3. Lindbohm et al. (1990), as cited in Reprotex®,
Reduced risk of abortion (OR=.6) was reported in female workers exposed to TCE.
4. Sugawa et al. (1973), as cited in Reprotex®.
In a case report, a 20 year old female had amenorrhea for several months after exposure to TCE that resulted
in a 2 hr unconscious period.
5. Windham et al. (1991), as cited in Reprotex®.
In a case-control study, an increased risk of spontaneous abortion was reported in women exposed at home
and in the workplace to TCE.

Female reproductive toxicity in animals

1. George et al. (1990), as cited in Reprotex®.
Both rats and mice were studied in a continuous breeding protocol. Doses were not stated. Decreases in live
litters/mating pair and in live pups/litter were reported "in some groups".
2. NTP (1986b), as cited in ATSDR.
Rats were given TCE in diet at doses 0, 75, 150, 300 mg/kg/day, 7 days prior to mating through birth of F2
generation. No effect on fertility was found.
3. NTP (1985), as cited in ATSDR.
No effect on reproduction were found in a 2 generation fertility study in which mice were given TCE in diet at
doses up to 750 mg/kg/day.
4. Coberly et al. (1992), as cited in Reprotex, Shepard’s Catalog of Teratogenic Agents.
Mice were treated with up to 483 mg/kg TCE (no further details given). No effect on ova were reported.
Male reproductive toxicity in humans

1. Rasmussen et al. (1988), as cited in Reprotext®.
   No sperm defects were found in 15 male workers exposed to TCE compared to controls.
2. Saihan et al. (1978), as cited in Reprotext®.
   In a case report, impotence and gynecomastia were described in a male exposed to TCE vapor.

Male reproductive toxicity in animals

1. NTP (1985), as cited in ATSDR.
   Mice were exposed to TCE in diet at doses up to 750 mg/kg/day in a 2 generation fertility study. Sperm motility was reduced 45% in F0 males and 18% in F1 males.
   Mice were exposed to TCE at a concentration of 2,000 ppm via inhalation, 4 hr/day for 5 days. An increase in abnormal sperm morphology was reported 28 days later.
3. NTP (1986b), as cited in ATSDR.
   Rats were given TCE in diet at dose of 0, 75, 150, 300 mg/kg/day, 7 days prior to mating through birth of the F2 generation. Some changes in ratios of weights of reproductive organs attributed to general toxicity were reported. There were no effects on fertility.
4. Slacik-Erben et al. (1980), as cited in HSDB, Reprotox™, Reprotext®, Barlow and Sullivan, IPCS.
   Mice were exposed via inhalation at concentrations of 50, 202, or 450 ppm for 24 hours. No dominant lethal effect (pregnancy rate, pre and post implantation loss) was found.
   Male rats were given TCE by gavage at doses of 0, 10, 100 or 1000 mg/kg, 5 days/wk for 6 wks. A reversible (5 wk) reduction in ejaculation latency was reported.

Other relevant data

1. Loeber (1988) and Goldberg (1992), as cited in ATSDR.
   Cardiac defects were reported after TCE injection in chicken eggs.
   A physiologically based pharmacokinetic model for TCE distribution and metabolism during pregnancy is available.

Secondary Sources


Reprotox™. Dr. Anthony M. Scialli. (TOMES APRIL 30, 1995).


Shepard’s Catalog of Teratogenic Agents. Dr. Thomas H. Shepard. (TOMES APRIL 30, 1995).


CHLORDANE:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Chlordane (Cas No. 57-74-9, formula C_{10}H_{6}Cl_{8}) is an organochlorine pesticide. It was used extensively until 1983, when all uses (except for use on termites), were banned. All uses were banned in 1988. Chlordane is on the Proposition 65 list as a carcinogen.

Overview of Developmental/Reproductive Toxicity Concern

There is a MEDIUM-HIGH level of developmental/reproductive toxicity concern. This is due to reports of developmental toxicity in animal models, including postnatal death, behavioral effects, and changes in prenatal and postnatal immune parameters. Chlordane is accumulated in fat, and secreted in milk, which may be partly or wholly responsible for the observed postnatal effects.

Developmental Toxicity

In humans, there are two case reports of prenatal exposure in children with neuroblastoma.

In animals, there is one report of malformations from exposure to chlordane by an unknown route at doses stated to be toxic to maternal animals. However, there are several reports by the oral route which found no increase in malformations, no reduction in litter size, no increase in fetal death, and/or no reduced fetal or birth weight. Effects on immune parameters have been reported. These include reduction of granulocyte-macrophage and splenic cell colony forming units in fetal liver, but no changes in liver cell numbers. The significance of these immune effects is not clear.

There are several reports in animals of postnatal effects resulting from prenatal and/or postnatal maternal exposure. There are published reports of postnatal death during lactation in mice, and an unpublished report in rats. There are reports of behavioral effects, including changes in excitability and learning. There are numerous studies of effects on immune parameters. Reduction of granulocyte-macrophage and splenic cell colony forming units of postnatal bone marrow, but no changes in bone marrow cell numbers, have been reported. Delayed hypersensitivity was reduced. Survival of young offspring against influenza virus infection was enhanced. A possibly related effect was a sporadic increase in plasma corticosterone. The significance of these immune effects is not clear.

Chlordane and/or its metabolites are accumulated in fat and secreted in the mother’s milk, even if chlordane is only administered prenatally. The relative contribution of prenatal and lactational exposure to postnatal effects is not clear. One cross-fostering study found behavioral effects in the offspring of treated mothers if the offspring were nursed by treated mothers, but no effects when the offspring were nursed by untreated mothers.

Female reproductive toxicity

In humans, a study found an increased incidence of unspecified ovarian and uterine disease in women whose homes had been treated for termites with chlordane.

A study in rats with males and females treated orally from weaning through mating and lactation found reduced mating and fertility. A study in mice treated orally for multiple generations found decreased viability (although details were not specified). Several reports have found no adverse histopathological changes in female reproductive organs. As described in the developmental section above, there are several postnatal effects in offspring which may be linked to secretion of chlordane or its metabolites in milk.

Male reproductive toxicity

-30-
Dominant lethal studies in mice revealed no effects on fertility, pre- or post-implantation mortality, or litter size. However, a study in which male and female rats were treated orally found reduced matings and fertility. A study in mice found degeneration of spermatogenic epithelium and reduction in size of seminiferous tubules. However, other studies in mouse, rat, and hamster have found no histopathological effects in testes or other reproductive organs.

**Overview of Exposure Concern**

There is a LOW level of concern over the extent of exposure. Chlordane was used extensively as a pesticide until 1983, when all uses (except for use on termites) were banned. All uses were banned in 1988. The only U.S. production facility is in Memphis, Tennessee (production is for export only). It is no longer used or produced in California. However, approximately 50 million people in the US are exposed to low levels of chlordane in their indoor air from its previous use in subterranean termite control. Chlordane is persistent in the environment, and widely distributed. In general, chlordane and its metabolites bioaccumulate and biomagnify, although the pattern of metabolites changes among different trophic levels and species. Chlordane and its metabolites have been detected in numerous foods, including human milk.

**Data on developmental and reproductive toxicity**

**Developmental toxicity in humans**

1. Infante *et al.* (1978), as cited in TERIS
   A history of prenatal exposure was recorded in 2 children with neuroblastoma.

**Developmental toxicity in animals**

1. Al-Hachim and Al-Baker (1973), as cited in ATSDR, RTECS®, TERIS.
   Mice were treated orally (gavage) with 1 or 2.5 mg/kg/d for gd 15-21. Depressed acquisition of avoidance response, increased exploratory activity, and increased electroshock seizure threshold were observed in offspring at both dosages. ATSDR notes that exposure could also have occurred via nursing, because the pups were allowed to nurse to the treated dams.

2. Ambrose *et al.* (1953), as cited in ATSDR, IARCa, IARCb, Reprotext®, IPCS.
   Rats (male and female) were treated orally (food) at 320 ppm (16 mg/kg/d) from weaning through mating, gestation, and lactation. Decreased rates of mating, fertility (decreased number of females delivering litters) and survivability (none of the litters survived to weaning) were observed. No histopathological lesions were found in reproductive organs. (Also cited in Female and Male reproductive toxicity in animals sections.)

3. Author not provided (1980), as cited in RTECS®.
   Mice were treated by unreported route at 8 mg/kg/d, for gd 1-21. Effects on newborn - delayed effects. (Abstract. Probably from Cranmer *et al.*)

   Mice were treated orally (food) at 4 or 8 mg/kg/d for gd 1-18. In offspring, reduced delayed-type hypersensitivity response and enhanced survival against influenza A virus infection was observed. (ATSDR comments that it is likely that nursing pups were exposed through milk.)

5. Barnett *et al.* (1985b), as cited in ATSDR, Reprotox™, TERIS.
   Mice were treated orally (food) at 4 mg/kg/d for gd 1-19. In offspring, reduced delayed-type hypersensitivity response and mixed lymphocyte reactivity was observed. (ATSDR comments that it is likely that nursing pups were exposed through milk.)

6. Barnett *et al.* (1990a), as cited in ATSDR, IARCb, TERIS.
   Mice were treated orally (food) with 4 mg/kg/d for gd 1-18. In offspring, decreased myeloid cell colony forming capacity (granulocyte-macrophage and spleen-forming stem cells in the bone marrow) at 100 and 200 days of age was observed. The number of bone marrow cells was unchanged at 100 days of age.
7. Barnett et al. (1990b), as cited in ATSDR, HSDB, TERIS. Mice were treated orally (food) with 8 mg/kg/d for gd 1-18. In the fetus, decreased liver cell-colony forming capacity (granulocyte-macrophage and spleen-forming stem cells in the liver) was observed. No change in liver cellularity was observed.

8. Barnett et al. (1990c), as cited in HSDB. Mice were treated (route not given) at 0, 4, or 8 mg/kg/d for 18 days of pregnancy. At gd 18, reduced fetal liver granulocyte macrophage colony forming units and spleen colony forming units were observed. No effect on liver cellularity was observed. (Abstract: redundant to Barnett et al. 1990b)

9. Blaylock et al. (1990a), as cited in ATSDR, HSDB, IARCh. Mice were treated (route, dose, period not given, but probably the same as Barnett et al. 1990a). In 100 day old offspring, natural killer cell activity was increased among females, but not males. In 200 day old offspring, natural killer cell activity had declined among males and females. (See also Blaylock et al. 1990b)

10. Blaylock et al. (1990b), as cited in HSDB. Mice were treated at 8 mg/kg prenatally (no details provided). No effect on cytotoxic T-lymphocyte response was observed. Natural killer cell response was increased in female, but not male mice at 100 days of age. By 200 days, no increase was detectable, but male mice showed a decrease. At 100 days of age, chlordane exposed mice were equally susceptible to influenza virus infection as were controls. Serum anti-influenza IgM antibody titers were increased in male, but not female, mice. Primary anti-influenza IgG titers were identical in exposed and control. (Note this may be an abstract, and partially redundant to Blaylock et al. 1990a.)

11. Chernoff and Kavlock (1982), as cited in ATSDR, IARCb, TERIS. Mice were treated orally (gavage) at 50 mg/kg/d for gd 8-12. No effect on number of live pups or pup weight on postnatal days 1 or 3 was observed.

12. Cranmer et al. (1978), as cited by Reprotext®, RTECS®. Mice were treated orally at 0.16 mg/kg/d for gd 1-21. In offspring, complex effects on steroid metabolism were observed.

13. Cranmer et al. (1979), as cited in Reprotox™, RTECS®, Shepard’s Catalog of Teratogenic Agents. Mice were treated (by undescribed route) at 8.0 mg/kg/d for gd 1-21. A defect in the cell-mediated immune response was observed. (Abstract)

14. Cranmer et al. (1984), as cited in ATSDR, HSDB, IARCh, Reprotox®, RTECS®. Mice were treated orally (food) at 0, 0.16, or 8.0 mg/kg/d through gestation. No effect on live litter size, gross malformations, or birth weight was observed. At 8.0 mg/kg/d, postnatal death (55%) in the first week of nursing was observed. ATSDR speculates that death resulted from high levels of chlordane and/or its metabolites in the dam’s milk. No effect on postweaning survival was observed. In offspring, plasma corticosterone at 400 days of age was elevated in males at both dosages and in females at 0.16, but not 8.0. No effect on plasma corticosterone was observed at 800 days of age, although not enough high dose males survived for evaluation. (Note study continued from Spyker-Cranmer et al. 1982.)

15. Deichman and Keplinger (1966), as cited in IARCa. Mice were treated orally (food) at 100 ppm for 4 months. Decreased viability of offspring was observed. (Abstract)

16. Deichman (1972), as cited in Reprotext®. Mice were treated orally (food) at 25 ppm for 6 generations. No effect on reproduction was observed. (Also cited in the Female reproductive toxicity in animals section.)

17. Ingle (1952), as cited in Reprotox™, Schardein, Shepard’s Catalog of Teratogenic Agents. Rats were treated orally (food) at 150 to 300 ppm during and after gestation. They gave birth to “normal offspring.” No teratogenicity was observed. If maintained with their lactating mothers, excitability and tremors were observed. If cross-fostered to untreated mothers, development was normal.

18. Ingle (1967), as cited in IPCS. [Note: unpublished study, described in detail.] Rats (male and female) were treated orally (food) at 0, 0.3, 3, 15, 30, and 60 ppm for 3 generations. Two or more litters of each generation were studied. Up to 30 ppm, no effects on fertility, number of offspring, or weight, growth, or mortality rate of young to weaning age, or gross or microscopic changes, were observed. At 60 ppm, increased mortality during the latter part of nursing in the 2nd and 3rd F3 generation litters was observed. A group of dams removed from the 60 ppm diet 30 days prior to remating had no increased mortality.
in the 3rd F3 generation. No teratogenicity was observed. (Also cited in the Female reproductive toxicity in animals section.)

19. IRDC (Velsicol) (1972), as cited in IPCS.
   Rabbits were treated orally at 0, 1.0, 5.0, or 15 mg/kg/d for gd 6-18. No effects on maternal behavior, appearance, or body weight were observed. Miscarriages were observed, but did not display a dose-response relationship (3 at 1.0 mg/kg/d, 0 at 5.0 mg/kg/d, and 1 at 15 mg/kg/d). No effects on “maternal or fetal parameters” or teratogenicity were observed.

20. Keplinger et al. (1968), as cited in IPCS.
   Mice were treated orally (food) at 25-100 ppm for 6 generations. At 100 ppm, decreased viability was observed in the 1st and 2nd generations, and no offspring were produced in the 3rd generation. At 50 ppm, viability was reduced in the 4th and 5th generations. At 25 ppm, no statistically significant effects were observed after 6 generations. (Also cited in the Female reproductive toxicity in animals section)

21. Lau et al. (1990), as cited in HSDB
   Mice were treated at 8 mg/kg prenatally (no details given). In females, a reduced macrophage cytotoxicity to tumor cells was observed. Reduced RNA for granulocyte macrophage colony stimulating factor in peritoneal macrophages was observed. (Abstract)

22. Menna et al. (1985), as cited in ATSDR, IARCb.
   Mice were treated orally at 0.16, 2.0, 4.0, or 8.0 mg/kg/d for gd 1-19. At 38 days of age, mice were challenged with influenza virus at 3 different rates. In offspring of chlordane treated animals, survival was enhanced, and anti-viral titers were higher.

23. Nemec et al. (1990), as cited in Reprotox™.
   Rats were exposed (no details were provided). Increased craniofacial defects at maternally toxic doses were observed.

24. Spyker-Crammer et al. (1982), as cited in ATSDR, IARCb, Reprotext®, RTECS®.
   Mice were treated orally (food) at 0.16 or 8.0 mg/kg/d from mating to parturition on gd 22. At 8.0 mg/kg, in the first week, 55% of offspring died. At 101 days of age, no effect on plasma or adrenal corticosterone or adrenal weight was observed in females. In male offspring of 0.16 mg/kg treated dams, increased levels of plasma corticosterone and increased adrenal weight were observed. Reduced contact hypersensitivity to oxazolone (implying cell-mediated immunity) at 101 days old was observed. No effect on humoral immune response was observed. (Note: study continued in Crammer et al. (1984).) (ATSDR comments that it is likely that nursing pups were exposed through milk.)

25. Theus et al. (1992a), as cited in TERIS.
   Mice were treated at 4-16 mg/kg/d during pregnancy. In offspring, various alterations of granulocyte and macrophage function were observed. (Barnett et al. 1985b, 1990a, 1990b, Theus et al. 1992b also cited.)

26. Theus et al. (1992b), as cited in ATSDR, TERIS.
   Mice were treated orally (gavage) at 8.0 mg/kg/d for gd 1-18. Decreased 5'-nucleotidase activity in macrophages, and activation of macrophages to inflammatory state was observed.

27. Usami et al. (1986), as cited in ATSDR, Shepard’s Catalog of Teratogenic Agents, TERIS.
   Rats were treated orally (gavage) at 0, 20, 40, or 80 mg/kg/d for gd 7-17. At 80 mg/kg/d, death was observed in 4/8 dams. A developmental NOAEL at 80 mg/kg/d was observed. (No evidence of fetotoxicity, including fetal death, malformations, or retarded skeletal development.)

   Mice were treated (no details given). No teratogenicity was observed.

Female reproductive toxicity in humans

1. Menconi et al. (1988), as cited in ATSDR.
   In humans, chronic exposure in homes treated with chlordane for termites was associated with an increased incidence of unspecified ovarian and uterine disease, compared with a reference population.
Female reproductive toxicity in animals

1. Ambrose et al. (1953), as cited in ATSDR, IARCa, IARCh, Reprotext®, IPCS.
   Rats (male and female) were treated orally (food) at 320 ppm (16 mg/kg/d) from weaning through mating, gestation, and lactation. Decreased rates of mating, fertility (decreased number of females delivering litters) and survivability (none of the litters survived to weaning) were observed. No histopathological lesions were found in reproductive organs. (Also cited in Developmental and Male reproductive toxicity in animals sections.)

2. Deichman (1972), as cited in Reprotext®.
   Mice were treated orally (food) at 25 ppm for 6 generations. No effect on reproduction was observed. (Also cited in the Developmental toxicity in animals section.)

3. Ingle (1967), as cited in IPCS.
   [Note: unpublished study, described in detail.]
   Rats (male and female) were treated orally (food) at 0, 0.3, 3, 15, 30, and 60 ppm for 3 generations. Two or more litters of each generation were studied. Up to 30 ppm, no effects on fertility, number of offspring, or weight, growth, or mortality rate of young to weaning age, or gross or microscopic changes, were observed. At 60 ppm, increased mortality during the latter part of nursing in the 2nd and 3rd F3 generation of litters was observed. A group of dams removed from the 60 ppm diet 30 days prior to remating had no increased mortality in the 3rd F3 generation. No teratogenicity was observed. (Also cited in the Developmental toxicity in animals section.)

4. Keplinger et al. (1968), as cited in IPCS.
   Mice were treated orally (food) at 25-100 ppm for 6 generations. At 100 ppm, decreased viability was observed in the 1st and 2nd generations, and no offspring were produced in the 3rd generation. At 50 ppm, viability was reduced in the 4th and 5th generations. At 25 ppm, no statistically significant effects were observed after 6 generations. (Also cited in the Developmental toxicity in animals section.)

5. Khasawinah et al. (1989), as cited in ATSDR.
   a. Rats were treated by inhalation at 28.2 mg/m3, 8 hr/d, 5 d/wk, for 28 days. No histopathological effects on reproductive organs were observed. (Velsicol Chem. Co. 1984 also cited).
   b. Rats or monkeys were treated by inhalation at 10 mg/m3, 8 hr/d, 5 d/wk, for 90 days. No histopathological effects on reproductive organs were observed. (Velsicol Chem. Co. 1984 also cited). (Also cited in the Male reproductive toxicity in animals section.)

6. Khasawinah and Grutch (1989a), as cited in ATSDR.
   Rats (male) were treated orally (food) at 1.175 mg/kg/d (male) or 1.409 mg/kg/d (female) for 30 months. No histopathological lesions of the reproductive tract were observed. (Velsicol Chemical Co. 1983a also cited.) (Also cited in the Male reproductive toxicity in animals section.)

7. Khasawinah and Grutch (1989b), as cited in ATSDR.
   Mice were treated orally (food) with 1.21 mg/kg/d for 24 months. No histopathological lesions (of reproductive organs implied) were observed. (Velsicol Chemical Co. 1983b also cited.) (Also cited in the Male reproductive toxicity in animals section.)

8. NCI (National Cancer Institute) (1977), as cited in ATSDR.
   a. Rats (male) were treated orally (food) at 20.4 mg/kg/d for 80 weeks. No histopathological lesions of the reproductive tract were observed.
   b. Rats (female) were treated orally (food) at 12.1 mg/kg/d for 80 weeks. No histopathological lesions of the reproductive tract were observed.
   c. Mice (male) were treated orally (food) at 7.3 mg/kg/d for 80 weeks (analytical grade cis and trans isomers). No histopathological lesions of the reproductive tract were observed.
   d. Mice (female) were treated orally (food) at 8.3 mg/kg/d for 80 weeks (analytical grade cis and trans isomers). No histopathological lesions of the reproductive tract were observed. (Also cited in the Male reproductive toxicity in animals section.)

   Rats were treated orally (food) at 0, 1, 5, or 25 ppm for 130 weeks. Daily dose levels of 0.045, 0.229, or 1.175 mg/kg/d for males were calculated. Daily dose levels of 0.055, 0.273, or 1.409 mg/kg/d for females were calculated. No histopathological lesions of the reproductive tract were observed. (Khasawinah and Grutch 1989a also cited in ATSDR.) (Also cited in the Male reproductive toxicity in animals section.)
10. Velsicol Chemical Co. (1983b), as cited in ATSDR.
   ATSDR: Mice were treated orally (food) with 1.21 mg/kg/d for 24 months. No histopathological lesions (of reproductive organs implied) were observed. (Khasawinah and Grutch (1989b) also cited.) (Also cited in the Male reproductive toxicity in animals section.)

   a. Rats were treated by inhalation at 28.2 mg/m3, 8 hr/d, 5 d/wk, for 28 days. No histopathological effects on reproductive organs were observed. (Khasawinah et al. (1989) also cited).
   b. Rats or monkeys were treated by inhalation at 10 mg/m3, 8 hr/d, 5 d/wk, for 90 days. No histopathological effects on reproductive organs were observed. (Khasawinah et al. (1989) also cited.) (Also cited in the Male reproductive toxicity in animals section.)

Male reproductive toxicity in humans

No studies were identified.

Male reproductive toxicity in animals

1. Ambrose et al. (1953), as cited in ATSDR, IARCa, IARCb, Reprotext®, IPCS.
   Rats (male and female) were treated orally (food) at 320 ppm (16 mg/kg/d) from weaning through mating, gestation, and lactation. Decreased rates of mating, fertility (decreased number of females delivering litters) and survivability (none of the litters survived to weaning) were observed. No histopathological lesions were found in reproductive organs. (Also cited in Developmental and Female reproductive toxicity in animals sections.)

2. Arnold et al. (1977), as cited in IARCb, IPCS, Reprotox™.
   a. Mice were treated orally (gavage) at 100 mg/kg once. No dominant lethal effect was observed.
   b. Mice were treated by injection (ip) at 100 mg/kg once. No dominant lethal effect was observed.

3. Balash et al. (1987), as cited in ATSDR.
   Mice (male) were treated orally (gavage) at 100 or 300 mg/kg/d for 30 days. Reduced size of seminiferous tubules, and degeneration of spermatogenic epithelium were observed.

4. Epstein et al. (1972) as cited in IARCb, IPCS, Reprotox™.
   a. Mice (male) were treated with α-chlordane by injection (ip) at 42, 58, or 290 mg/kg, once. No significant dominant lethal effect was observed.
   b. Mice (male) were treated with α-chlordane orally at 75 mg/kg/d for 5 days. No significant dominant lethal effect was observed.
   c. Mice (male) were treated with γ-chlordane orally at 50 mg/kg/d for 5 days. No significant dominant lethal effect was observed.

5. Khasawinah et al. (1989), as cited in ATSDR.
   a. Rats were treated by inhalation at 28.2 mg/m3, 8 hr/d, 5 d/wk, for 28 days. No histopathological effects on reproductive organs were observed. (Velsicol Chem. Co. 1984 also cited).
   b. Rats or monkeys were treated by inhalation at 10 mg/m3, 8 hr/d, 5 d/wk, for 90 days. No histopathological effects on reproductive organs were observed. (Velsicol Chem. Co. 1984 also cited).
   (Also cited in the Female reproductive toxicity in animals section.)

6. Khasawinah and Grutch (1989a), as cited in ATSDR.
   Rats (male) were treated orally (food) at 1.175 mg/kg/d (male) or 1.409 mg/kg/d (female) for 30 months. No histopathological lesions of the reproductive tract were observed. (Velsicol Chemical Co. 1983a also cited.) (Also cited in the Female reproductive toxicity in animals section.)

7. Khasawinah and Grutch (1989b), as cited in ATSDR.
   Mice were treated orally (food) with 1.21 mg/kg/d for 24 months. No histopathological lesions (of reproductive organs implied) were observed. (Velsicol Chemical Co. 1983b also cited.) (Also cited in the Female reproductive toxicity in animals section.)

8. NCI (National Cancer Institute) (1977), as cited in ATSDR.
   a. Rats (male) were treated orally (food) at 20.4 mg/kg/d for 80 weeks. No histopathological lesions of the reproductive tract were observed.
   b. Rats (female) were treated orally (food) at 12.1 mg/kg/d for 80 weeks. No histopathological lesions of the
reproductive tract were observed.
c. Mice (male) were treated orally (food) at 7.3 mg/kg/d for 80 weeks (analytical grade cis and trans isomers).
No histopathological lesions of the reproductive tract were observed.
d. Mice (female) were treated orally (food) at 8.3 mg/kg/d for 80 weeks (analytical grade cis and trans isomers).
No histopathological lesions of the reproductive tract were observed.
(Also cited in the Female reproductive toxicity in animals section.)

9. Shain et al. (1977), as cited in ATSDR.
   Rats (male) were treated orally (food) at 19.5 mg/kg/d for 90 days. A 360% increase in androgen receptor
   content of the ventral prostate gland was observed. No effects on ventral prostate or testicular weight, or on
   plasma testosterone level were observed.

10. Truhaut et al. (1975), as cited in ATSDR.
   a. Rats (male) were treated orally at 200 mg/kg, once. No histological lesions of the testes were observed.
   b. Mice (male) were treated orally at 200 mg/kg, once. No histological lesions of the testes were observed.
   c. Hamsters (male) were treated orally at 1,200 mg/kg, once. No histological lesions of the testes were observed.

   Rats were treated orally (food) at 0, 1, 5, or 25 ppm for 130 weeks. Daily dose levels of 0.045, 0.229, or 1.175
   mg/kg/d for males were calculated. Daily dose levels of 0.055, 0.273, or 1.409 mg/kg/d for females were
   calculated. No histopathological lesions of the reproductive tract were observed. (Khasawinah and Grutch
   1989a also cited in ATSDR.) (Also cited in the Female reproductive toxicity in animals section.)

12. Velsicol Chemical Co. (1983b), as cited in ATSDR.
   ATSDR: Mice were treated orally (food) with 1.21 mg/kg/d for 24 months. No histopathological lesions (of
   reproductive organs implied) were observed. (Khasawinah and Grutch (1989b) also cited.) (Also cited in the
   Female reproductive toxicity in animals section.)

   a. Rats were treated by inhalation at 28.2 mg/m3, 8 hr/d, 5 d/wk, for 28 days. No histopathological effects on
      reproductive organs were observed. (Khasawinah et al. (1989) also cited).
   b. Rats or monkeys were treated by inhalation at 10 mg/m3, 8 hr/d, 5 d/wk, for 90 days. No histopathological
      effects on reproductive organs were observed. (Khasawinah et al. (1989) also cited.) (Also cited in the Female
      reproductive toxicity in animals section.)

Other relevant data

Chlordane is metabolized to several products, including principally oxychlordane. Chlordane and its metabolites are
accumulated in fat and excreted slowly (via bile) in feces. Chlordane and its metabolites are also secreted in milk,
resulting in exposure of the nursing young. Chlordane metabolites (especially oxychlordane) were found in
numerous samples of human milk 1977 to 1983, and have been found as recently as 1991. Chlordane metabolites
were found in blood of occupationally exposed workers. In general, chlordane and its metabolites bioaccumulate
and biomagnify, although the pattern of metabolites changes among different trophic levels and species (ATSDR).

Secondary Sources


Carcinogenic Risk To Humans, Volume 20. World Health Organization.

Carcinogenic Risk To Humans, Volume 53. World Health Organization.

Organization, Geneva.

Reprotox™. Dr. Anthony M. Scialli. (TOMES APRIL 30, 1995)

Reprotext®. Micromedex, Inc. (TOMES APRIL 30, 1995)


Shepard’s Catalog of Teratogenic Agents. Dr. Thomas H. Shepard. (TOMES JULY 31, 1995)

ETHYLENE DIBROMIDE:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Ethylene dibromide (formula C₂H₄Br₂, CAS No. 106-93-4), also known as 1,2-dibromoethane, was previously used as a soil fumigant, and as an additive to leaded gas. It currently has some uses as a chemical intermediate. Ethylene dibromide is on the Proposition 65 list as a carcinogen.

Overview of Developmental/Reproductive Toxicity Concern

There is a MEDIUM-HIGH level of developmental/reproductive toxicity concern over ethylene dibromide due to reports of testicular toxicity in workers and in several species of animals (rats, mice, bulls, rams). The testicular toxicity includes effects on sperm morphology number and motility as well as testicular degeneration and infertility. Ethylene dibromide has been widely studied as a testicular toxicant. In developmental toxicity studies, increased intrauterine death, but no malformations, have been reported.

**Developmental toxicity**

No human studies with in utero exposure were located. Animal studies demonstrate embryotoxicity and developmental delay at maternally toxic doses.

**Female reproductive toxicity**

Only one animal study is available, which reported resorptions at maternally toxic inhalation exposures.

**Male reproductive toxicity**

Several studies have demonstrated effects on sperm parameters (numbers, viability, motility) in worker populations. One small study in workers reported a reduced fertility rate, but the effect was not statistically significant. Ethylene dibromide has been widely studied as a testicular toxicant. Fifteen studies in 5 species using oral, injection and inhalation routes reported on sperm parameters, testicular and associated reproductive organ morphology and pathology. Male mediated effects on offspring behavior and biochemical measures were also noted, but no full study of effects on fertility was identified from the secondary sources. One dominant lethal study was reported as finding no effects.

Overview of Exposure Toxicity Concern

There is a LOW level of concern over exposure due to ethylene dibromide. Ethylene dibromide’s use as a soil fumigant was canceled in 1984 by USEPA. It was used as gasoline additive in leaded automotive gas, but this use has been phased out in California. It has some uses as a chemical intermediate. EDB volatilizes readily from water and soil and has a half-life in air of 40 days. It is a persistent ground water contaminant, but it does not bioaccumulate in the food chain. Production and release of EDB have been declining since the 1980's.

Data on developmental and reproductive toxicity

NOTE: Unless otherwise indicated, all information, including the citation, is obtained from secondary sources. Full citations of all studies are not provided here.

**Developmental toxicity in humans**

No studies were identified.
Developmental toxicity in animals

   Rats were injected with 55 mg/kg ethylene dibromide on gd 1-15. No teratogenicity or maternal toxicity noted.
   No effects on “major birth defects” in rats or mice (unclear) were reported. No information was given regarding route, dose or period of exposure.
3. Short et al. (1978), as cited in ATSDR, RTECS®, Reprotox™, Barlow and Sullivan.
   Rats were exposed via inhalation to 20, 32, 38 or 80 ppm on gd 6-15 for 23 h/day. “Skeletal anomalies” (including “reduced” and “incomplete” ossification) were reported as low as 20 ppm as well as reduced maternal food consumption and weight gain. Reduced “viability of embryos and fetuses” was reported at 80 ppm, though there was 50% maternal mortality at this dose. Increased resorptions were reported at 38 ppm. Reduced fetal weight was reported at an unspecified dose.
   Rats were exposed via inhalation to 0, 0.43, 6.67, 66.7 ppm on gd 3-20. “Growth statistics” and a decrease in gestational weight gain were reported at 66.7 ppm. Enhanced rotorod and brightness discrimination acquisition as well as no effect on DRL-20, straight alley running nor passive avoidance were reported.

Female reproductive toxicity in humans

No studies identified.

Female reproductive toxicity in animals

1. Short et al. (1978), as cited in ATSDR, RTECS®, Reprotox™, Barlow and Sullivan.
   Mice were exposed via inhalation to 20, 32, 38 or 80 ppm on gd 6-15 for 23 h/day. Increased resorptions were reported at 38 ppm and reduced maternal food intake and weight gain were reported at doses as low as 20 ppm. Mice were reportedly more sensitive than rats.

Male reproductive toxicity in humans

1. Ratcliffe et al. (1987), as cited in ATSDR, HSDB, RTECS®, Reprotox™, Reprotext®.
   The study reported decreased sperm count, sperm viability and sperm motility as well as increased sperm abnormalities in agricultural workers compared to a control population. Reprotext cited exposure levels at 88 ppb.
2. Schrader et al. (1988), as cited in Reprotext®.
   The study reported decrease sperm velocity and semen volume in timber workers.
3. Takahashi et al. (1981), as cited in ATSDR and Reprotox™.
   The study reported reduced sperm counts in agricultural workers as compared to “reference controls” confounded with marijuana use and dibromochloropropane exposure.
   Men exposed to 0.5-5 ppm in a manufacturing plant showed a 42% incidence of sperm counts < 4 million compared to a low exposure (0.05 ppm) group’s 20% incidence. There was no control group.
5. Wong et al. (1979), as cited in ATSDR, Reprotox™, Schardein.
   Workers in a manufacturing plant showed a 29% reduction in fertility (small n, p>0.05).

Male reproductive toxicity in animals

1. Amir (1975), as cited in ATSDR.
   Bulls exposed orally showed sperm effects greater in the adult than in the young animal.
2. Amir and Ben-David (1973), as cited in ATSDR, RTECS®, Barlow and Sullivan.
   Bulls were exposed orally to 2 mg/kg and 4 mg/kg EDB at 10 doses on alternate days. The animals showed 79% abnormal sperm at 4 mg/kg and no effect at 2 mg/kg/day.
3. Amir and Lavon (1976), as cited in ATSDR.
   Bulls were exposed to 2 mg/kg/day throughout development to 14-16 months. Low sperm density, motility and increased abnormalities were reported. Effects were reversible. [Note: This may be same study as Amir and Volcani (1965)].

   Bulls were exposed to 2 mg/kg/day throughout development to 14-16 months. Low sperm density, motility and increased abnormalities were reported. Effects were reversible.

5. Amir et al. (1983), as cited in ATSDR.
   Bulls were exposed to 2 mg/kg/day throughout development to 14-16 months. Low sperm density, motility and increased abnormalities were reported. Effects were reversible. [Note: This may be same study as Amir and Volcani (1965)].

   Rats were exposed via i.p. injection. The study reported that EDB “interfered with sperm production”. RepROTOX did not give the dose.

7. Eljack and Hrudka (1979), as cited in IRIS®, RTECS®.
   Rams were exposed via s.c. injection to 7.8, 9.6, 13.3 mg/kg/day for 12 days. Decreased sperm motility, increased morphological abnormalities and degenerating sperm were reported. The changes were dose dependent.

8. Epstein et al. (1972), as cited in Reprotox™.
   Mice were exposed via i.p. and oral routes. No effects on “reproductive performance” were reported.

   Offspring of exposed rats showed male-mediated alterations in behavior.

    Offspring of exposed rats showed male-mediated alterations in brain enzymes.

11. NCI (1978), as cited in ATSDR.
    Rats and mice exposed via gavage showed testicular atrophy. Mortality and tumors were also reported.

12. NTP (1982), as cited in ATSDR.
    Rats exposed via inhalation showed testicular degeneration and interstitial cell tumors. No dose was given in secondary source.

13. Rowe (1957), as cited in Barlow and Sullivan.
    Rats were exposed to 0 and 50 ppm at 7 hr/day, 5 day/wk for 13 weeks. The study reported decreased relative testicular weights (10%). Showed no effects in small numbers of guinea pigs (n=8), rabbits (n=3) or monkey (n=1).

14. Short et al. (1979), as cited in ATSDR, Reprotox™ and Barlow and Sullivan.
    Rats were exposed via inhalation to 89 ppm for 10 weeks. Atrophy of the testes, epididymus, prostate and seminal vesicles, as well as infertility, were reported. Mortality and morbidity were also reported.

15. Williams et al. (1991), as cited in RTECS®, Reprotox™, Reprotext®.
    Rabbits were exposed via s.c. injection to up to 45 mg/kg/day of ethylene dibromide. No effects on sperm velocity, motility, pH or volume were reported.

16. Wong et al. (1982), as cited in ATSDR.
    Rats were exposed via inhalation to 20 ppm ethylene dibromide (w/ disulfiram). The study reported testicular atrophy and mortality.

Other relevant data

Labeled EDB has been shown to reach sperm in testes. Ethylene dibromide is activated by glutathione S-transferase. A possible mechanism of action is increased unscheduled DNA synthesis in sperm.
Secondary Sources

ATSDR. (1992) Agency for Toxic Substances and Disease Registry. Toxicological Profile for 1,2-Dibromoethane.


Reprotext®. Micromedex, Inc. (TOMES April 30, 1996)

Reprotox™. Dr. Anthony M. Scialli. (TOMES April 30, 1996)


Shepard’s Catalog of Teratogenic Agents. Dr. Thomas H. Shepard. (TOMES April 30, 1996)
HEPTACHLOR:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Heptachlor (formula C_{10}H_{5}Cl_{7}, CAS No. 76-44-8) was first used as a pesticide in 1952. Its agricultural uses were canceled in 1974 and, in 1988, all sales in the US were canceled. Heptachlor is on the Proposition 65 list as a carcinogen.

Overview Developmental/Reproductive Toxicity Concern

There is a MEDIUM-HIGH level of developmental/reproductive toxicity concern over heptachlor due to clear evidence of a dramatic reduction in the viability of offspring of heptachlor treated rats, dogs and mink. Human studies are limited to a milk poisoning incident in Hawaii where no adverse effects were reported. There is also evidence of marked effects on fertility in multigeneration studies, but it is not clear whether males or females were responsible.

Developmental toxicity

No effects on pregnancy outcome were found in follow-up studies of Hawaiian women exposed to heptachlor-contaminated milk products. There were no reports of malformation from animal studies with pregnancy exposures. Although no standard FIFRA studies have been done, a number of early multigeneration studies in several species have consistently reported elevated postnatal mortality. Exposure of offspring in these studies occurred both prenatally and postnatally via lactation. This effect is consistent with developmental toxicity of other chlorinated pesticides.

Female reproductive toxicity

No effects on fertility were found in follow-up studies of Hawaiian women exposed to heptachlor-contaminated milk products. Reduced fertility in rats and dogs was reported in multigeneration studies in which both male and female breeders were dosed. It is not clear whether females were affected. Altered estrus cycles and vaginal bleeding were described in separate studies.

Male reproductive toxicity

Reduced fertility was reported in several multigeneration studies (rats, dogs) in which both male and female breeders were dosed. It is not clear whether males were affected, but this was suggested in one secondary source. No effects on testes were seen in a chronic study, and dominant lethal studies in rats and mice did not demonstrate effects. No relevant studies in humans were located.

Overview of Exposure Concern

There is a LOW level of concern over the extent of exposure to heptachlor. Heptachlor was first used in 1952. Its agricultural uses were canceled in 1974 and, in 1988, all sales in US were canceled as well. Consumption in 1982 was 45,400 kilograms. It was not produced commercially in the US in 1991. Heptachlor has strong soil adsorption with little migration to groundwater. It is readily oxidized \textit{in vivo} and by sunlight to heptachlor oxide. It can vaporize from contaminated soil and from termite control applications. It can bioaccumulate (mainly as heptachlor oxide). Milk (breast and commercial) is an important route of exposure (since it is lipophilic). All exposure data are pre-1988 (when it was banned). It can be detected in tissues 3 years after exposure. A 1986 breast milk survey in North America showed minimal heptachlor oxide and no heptachlor. No breast milk data was located after 1990.
Data on developmental and reproductive toxicity

NOTE: Unless otherwise indicated, all information, including the citation, is obtained from secondary sources. Full citations of all studies are not provided here.

Developmental toxicity in humans

1. Chadduck et al. (1987), as cited Reprotox™, ATSDR.
   In a case study, gliosarcoma was described in a neonate exposed to heptachlor in association with a milk contamination incident in Oklahoma. The mother drank 0.5 gal contaminated milk per day.

2. Le Marchand et al. (1986), as cited in ATSDR, Reprotox™, Shepard’s Catalog of Teratogenic Agents, TERIS, IARC.
   This study found no increase in birth defects, fetal and neonatal death low birthweight, in offspring of women who drank contaminated milk (0.1 ppm, 27-29 mos.) in Hawaii. However, IARC reported this study as showing a statistically significant increase in cardiovascular malformation and hip dislocations, comparing Oahu, where the contamination occurred, to other Hawaiian islands.

Developmental toxicity in animals

1. Crum et al. (1993), as cited in TERIS.
   Mink were fed 12.5 or 25 mg/kg during pregnancy. Increased death in offspring and severe maternal toxicity were reported.

2. Eisler (1968), as cited in TERIS.
   No congenital anomalies in were reported in rats fed 0.3-10 ppm heptachlor during pregnancy.

3. FAO/WHO (1967), as cited IPCS.
   In a 3 generation study, rats were fed 6.9 mg/kg BW/day from 3 mos prior to mating. Cataracts were found in pups on pnd 19-26, and also in parents after 4-9 mos. Citation is a secondary source and may refer to one of the other studies described in this section.

4. Green et al. (1970), as cited in ATSDR.
   Rats were given 0.25 mg/kg/day in diet for 60 days prior to mating and during gestation. Increased resorptions and dramatically decreased postnatal survival (only 19 of 122 heptachlor treated offspring survived) in the F1 generation were reported.

5. IRDC (1973), as cited in IPCS.
   In a 2 generation study, dogs were fed 1, 3, 5, 7, or 10 mg/kg in diet. All but 1 of the F1 pups died before 10 weeks of age. No malformations were reported. This is a secondary source, no identification of the original study report was provided.

6. Mestitzova (1967), as cited in ATSDR, Reprotox™, TERIS.
   Rats were fed 6 mg/kg/day during pregnancy. Increased postnatal mortality occurred during the first 24 to 48 weeks after birth in the heptachlor treated offspring. Cataracts were also noted in the postnatal period.

7. Ruttkay-Nedecka et al. (1972), as cited in Schardein, IPCS.
   In a 3 generation study, rats were given 1-10 mg/kg BW/day in feed. Resorptions, lower viability index, lower lactation index and postnatal cataracts were reported.

8. Velsicol Chemical (1955), as cited in IRIS®.
   In a 1 generation study, rats were fed heptachlor in diet. At a dose of 0.35 mg/kg/day (7 ppm in diet), increased pup death was reported. The NOAEL was 0.25 mg/kg/day. There was no reproductive or growth effects. The same study was apparently described in IPCS as Witherup et al. 1955, unpublished data, and may have been an initial stage of the 3 generation study of Witherup, 1976 and Witherup et al. 1976a.

9. Witherup (1976a), as cited in IPCS.
   In a 3 generation study rats were given diets containing 0, 0.3, 3, or 7 mg/kg mixed heptachlor and heptachlor epoxide (3:1). The number of pregnancies in the F1 and F2 generation was “slightly reduced”. No fertility effects were reported in offspring. Increased postnatal mortality occurred 2-3 weeks after birth in the 3 mg/kg group.
10. Witherup et al. (1976b), as cited in IPCS. 
   In a 3 generation study, rats were fed 0, 0.3, 6, or 10 mg/kg in diet. Increased postnatal mortality occurred 2-3 weeks after birth at the 10 mg/kg dose in the second generation.
11. Yamaguchi (1987), as cited in Shepard’s Catalog of Teratogenic Agents, TERIS. 
   Rats were fed 5-10 mg/kg during embryogenesis. No teratogenic effects were seen. Maternal toxicity occurred at the highest dose.

Female reproductive toxicity in humans

1. Le Marchand et al. (1986), as cited in ATSDR. 
   No effect on fertility or fetal loss in was identified in women who drank heptachlor-contaminated milk in Hawaii.
2. Wasserman (1982), as cited in ATSDR. 
   Higher levels of heptachlor as well as other organochlorine pesticides were found in serum of mothers with premature deliveries.

Female reproductive toxicity in animals

1. Akay and Alp (1981), as cited in ATSDR. 
   Male and female mice were fed 6.5 or 13.26 mg/kg/day heptachlor for 10 weeks. No ovary or testes histopathology and no effects on reproduction were identified. Limited detail was provided in the report.
2. Cerey et al. (1971), as cited in IPCS. 
   Altered estrus cycles were reported in this study in rats. No exposure information was provided in the secondary source.
3. Green (1970), as cited in ATSDR. 
   Rats were given 0.25 mg/kg/day in diet for 60 days prior to mating and during gestation in a 2 generation study. Marked decrease in pregnancy rates were reported. No pregnancies occurred in the second generation. An effect on male fertility was indicated.
4. Mestitzova (1967), as cited in ATSDR. 
   Male and female rats were fed 6 mg/kg/day during an 18 month study (exact period of exposure unspecified). There was a 23% decrease in the size of successive generations.
5. NCI (1977), as cited in ATSDR. 
   Rats were fed 1.28 mg/kg/day for 80 weeks. Vaginal bleeding was reported during this chronic toxicity study.
6. Witherup et al. (1955), as cited in ATSDR. 
   In a 2 year study, rats were fed 0, 0.38(sic), 0.075, 0.125, 0.175, 0.25 mg/kg/day heptachlor in diet. The study reported failure to reproduce, as well as high mortality in the offspring at the three highest doses. The secondary source described “severe deficiencies” in the study.

Male reproductive toxicity in humans

No studies were identified

Male reproductive toxicity in animals

1. Akay and Alp (1981), as cited in ATSDR. 
   Male and female mice were fed 6.5 or 13.26 mg/kg/day heptachlor for 10 weeks. No ovary or testes histopathology and no effects on reproduction were identified. Limited detail was provided in the report.
2. Arnold et al. (1977), as cited in ATSDR. 
   Mice were given single oral doses of 7.5 or 15 mg/kg of a heptachlor/heptachlor epoxide mixture and were bred for 6 wks. No adverse effect on reproductive capacity was found.
3. Epstein et al. (1972), as cited in ATSDR, Reprotox™. 
   Male mice were given 5 daily oral doses of 5 or 10 mg/kg. No dominant lethal effect on fetal deaths or post implantation loss was identified.
4. Green (1970), as cited in ATSDR.
   Rats were given 0.25 mg/kg/day in diet for 60 days prior to mating and during gestation. A 2 generation study
   was also conducted with this dose. There was a marked decrease in pregnancy rate in both generations, which
   was attributed to the males, because treated females mated with untreated males conceived and had normal
   litters. Absence of viable sperm in the vaginal smear and presence of normal spermatogenesis in the males
   suggest that sperm were killed.
5. Mestitzova (1967), as cited in ATSDR.
   Male and female rats were fed 6 mg/kg/day during an 18 month study (exact period of exposure unspecified).
   There was a 23% decrease in the size of successive generations.

Other relevant data

Heptachlor is a metabolite of chlordane. Heptachlor is rapidly converted to heptachlor oxide in vivo. Heptachlor
does not concentrate in milk to the same degree as some organochlorines. DART effects generally occur at lower
exposure levels than cancer. In vitro heptachlor metabolism is similar in rats and humans. Unlike other
organochlorines, distributes to milk at a low constant amount. Breast milk heptachlor did not exceed ADI in 1986
(Klein et al. 1986, Reprotox™, in French). General toxicity in multigeneration studies is unknown due to limited
description of the studies.

Secondary Sources


Carcinogenic Risk To Humans, Volume 53. World Health Organization.

Health Organization.


Reprotox™. Dr. Anthony M. Scialli. (TOMES JULY 31, 1995)


Shepard’s Catalog of Teratogenic Agents. Dr. Thomas H. Shepard. (TOMES JULY 31, 1995)

BUTADIENE, 1,3-:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Butadiene, 1,3- (CAS No. 106-99-0) is used as a monomer for synthetic rubber polymers, xerographic toner, adhesives, plastics, and as an asphalt modifier. It is also found in gasoline. 1,3-butadiene forms epoxides and can form DNA adducts, and is on the Proposition 65 list as a carcinogen.

Overview of Developmental/Reproductive Toxicity Concern

There is a MEDIUM level of developmental/reproductive toxicity concern over 1,3-butadiene. There are reports of effects on sperm and dominant lethal effects after inhalation exposure of male mice. Reproductive organ pathology has also been reported. Evaluation of the severity of effect, dose response relationships, and coexistence of general toxicity is not possible based on review at this level. No multigeneration fertility studies in animals were available that would allow evaluation of fertility effects. No human studies were identified for any endpoint.

Developmental toxicity

Inhalation studies in mice and rats using a broad range of concentrations reported either no effects or developmental retardation at maternally toxic doses.

Female reproductive toxicity

No multigeneration studies were described in the secondary sources. Ovarian atrophy was reported in a chronic inhalation toxicology study.

Male reproductive toxicity

Sperm abnormalities and dominant lethal effects in mice were found after inhalation exposure. Testicular atrophy was reported in a chronic inhalation toxicology study (mice), but no reproductive organ pathology was reported in a subchronic study (rats). No multigeneration studies were described in the secondary sources to evaluate effects on fertility.

Overview of Exposure Concern

There is a MEDIUM level of concern over the extent of exposure. Butadiene is used as a monomer for synthetic rubber, xerographic toner, adhesives, plastics, and as an asphalt modifier. It is also found in gasoline. There are 12 manufacturer/processors in California (total production for California was 18.8 million lb/year (in 1984). According to ATSDR, >63,000 workers were potentially exposed in 1984. According to the 1994 California TRI, 14,900 lb were released (with the majority being as “disposal” and 3,797 lb released to the air).

Data on developmental and reproductive toxicity

NOTE: Unless otherwise indicated, all information, including the citation, is obtained from secondary sources. Full citations of all studies are not provided here.

Developmental toxicity in humans

No studies were identified.
Developmental toxicity in animals

1. Hackett et al. (1987a), as cited in ATSDR, IARC, Shepard’s Catalog of Teratogenic Agents. Rats were exposed via inhalation to 1, 40, 200 or 1000 ppm for 6 hr/day on gd 6-15. No effects were reported. This was an NTP contract study conducted at Pacific Northwest Labs. Other components of the study are described below and under the section on male reproductive toxicity. The study results were also reported in Morrissey et al. (1990) as cited in RTECS®, Reprotox™, Shepard’s Catalog of Teratogenic Agents, IARC.

2. Hackett et al. (1987b), as cited in ATSDR, IARC, Shepard’s Catalog of Teratogenic Agents. Mice were exposed via inhalation to 0, 40, 200 or 1000 ppm for 6 hr/day on gd 6-15. Decreased fetal weight in males occurred at 40 ppm and extra ribs were reported at 200 ppm. Reduced sternal ossification was reported at 1000 ppm. Maternal toxicity was noted at 200 ppm and 1000 ppm.

3. Irvine (1981), as cited in ATSDR, HSDB, RTECS®. Rats were exposed via inhalation to 200, 1000 or 8000 ppm for 6 hr/day on gd 6-15. “Skeletal abnormalities” were reported at 8000 ppm. No maternal toxicity was mentioned.

4. Murphy et al. (1975), as cited in Reprotox™. Hamsters were exposed to adhesive which contained butadiene. No teratogenic effects were reported.

Female reproductive toxicity in humans

No studies were identified.

Female reproductive toxicity in animals

1. Carpenter et al. (1944), as cited in ATSDR, Shepard’s Catalog of Teratogenic Agents. Rats, rabbits and guinea pigs were exposed to butadiene 7.5 hrs/day, 6 days/week at concentrations “up to 6700 ppm”. When this exposure was given to rats during pregnancy, no decrease in offspring was reported. No evidence for infertility was noted in either rabbits or guinea pigs (male and female) exposed at the same concentrations and mated freely.

2. Melnick et al. (1989), as cited in ATSDR. Mice were exposed via inhalation to 6.25 or 625 ppm butadiene 5 day/week for 65 weeks in a chronic toxicity and cancer study. Ovarian atrophy was reported at 6.25 ppm. There was no mention of general toxicity.

Male reproductive toxicity in humans

No studies were identified.

Male reproductive toxicity in animals

1. Carpenter et al. (1944), as cited in ATSDR, Shepard’s Catalog of Teratogenic Agents. Rabbits and guinea pigs (male and female) were exposed to butadiene 7.5 hrs/day, 6 days/week at concentrations “up to 6700 ppm”. No evidence for infertility was noted in either rabbits or guinea pigs. No further details of the study were provided.

2. Crouch (1979), as cited in ATSDR, HSDB. Rats exposed to 0, 1000, 2000, 4000, or 8000 ppm butadiene 6 hr/day, 5 days/week for 13 weeks showed no reproductive pathology.

3. Hackett et al. (1988b), as cited in ATSDR. Mice exposed via inhalation showed a dominant lethal effect at 200 ppm. The study was considered inconclusive due to lack of a dose-response association.

4. Hackett et al. (1988a), as cited in ATSDR. Mice were exposed via inhalation to 200, 1000 or 5000 ppm butadiene 6 hr/day for 5 days. Sperm head abnormalities were reported at 1000 ppm and 5000 ppm.
5. NTP (1984), as cited in ATSDR. Mice were exposed via inhalation to 6.25 or 6250 ppm butadiene 5 d/week for 61 weeks. Gonadal (testicular) atrophy was reported (dose not specified).

Other relevant data

Butadiene inhalation causes nasal and lung irritation and lung and kidney pathology. Chronic exposures cause cancer in laboratory animals.

Secondary Sources

Reprotox™. Dr. Anthony M. Scialli. (TOMES JULY 31, 1995)
Shepard’s Catalog of Teratogenic Agents. Dr. Thomas H. Shepard. (TOMES JULY 31, 1995)
CARBON TETRACHLORIDE:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Carbon tetrachloride (formula CCl₄, Cas No. 56-23-5) was previously used extensively as a fumigant, as a solvent in consumer products, dry cleaning, and industrial applications, and also in fire extinguishers. Use in consumer products and as a fumigant have been banned. Carbon tetrachloride is on the Proposition 65 list as a carcinogen.

Overview of Developmental/Reproductive Toxicity Concern

There is a MEDIUM level of developmental/reproductive toxicity concern. This is due to reports of developmental toxicity, including embryonic, fetal, or postnatal death, and retarded growth. Concern is tempered by the use of less relevant routes and very high dosages; extensive maternal hepatotoxicity at developmentally toxic doses has also been reported.

Developmental toxicity

There are two related epidemiological studies which found adverse developmental effects (birth defects and retarded growth) associated with CCl₄ in drinking water over 1 ppb. However this concentration is far lower than those causing adverse effects on development in animal models. Confounders may not have been adequately accounted for.

The effects of carbon tetrachloride exposure have been studied extensively in animals. Embryonic or fetal death has been observed in oral and injection studies at high dosages (gram/kg). Concurrent maternal toxicity was reported in some studies (death, hepatotoxicity, and reduced weight gain). Several studies have examined animals for malformations: no increases were observed. There is one report of postnatal death following prenatal exposure by inhalation. Reduced fetal weight has been found by inhalation and injection; concurrent maternal toxicity (hepatotoxicity and reduced weight gain) was also reported. Fetal liver damage was observed in injection studies, but maternal liver damage was more severe. Injection studies may be of less relevance due to "first pass" processing of orally ingested carbon tetrachloride by the maternal liver and greater maternal liver toxicity.

Female reproductive toxicity

In animals, there is one report of reduced fertility by inhalation (both males and females were exposed). Increased pre- and post-implant losses have been reported from injection at high dosages. There are two reports of altered estrus by injection. Potentiation of the effect of exogenous estrogens has been reported by CCl₄ by the oral route. These effects may result from altered estrogen metabolism secondary to liver damage.

Male reproductive toxicity

In animals, reduced weight of testes, abnormal testicular histopathology, and/or effects on spermatogenesis have been observed by oral and injection routes at high (gram/kg) dosages. By inhalation, a single study reported reduced fertility (both males and females were exposed), one study reported reduced testes weight at anaesthetizing concentrations, and two studies reported testicular damage at lethal dosages.
Overview of Exposure Concern

There is a MEDIUM level of concern over the extent of exposure. Carbon tetrachloride was previously used extensively as a fumigant, as a solvent in consumer products, dry cleaning, and industrial applications, and also in fire extinguishers. Use in consumer products and as a fumigant have been banned. It is manufactured in several locations in U.S. and is presently used mainly in synthesis of fluorocarbons and for export. Eight facilities manufacture or use CCl₄ in California. It is present at at least 27 National Priority List hazardous waste sites. There is widespread, low level exposure from carbon tetrachloride in the atmosphere, but high level exposures could occur in occupational settings or at contaminated sites. Degradation is very slow in the environment, but there is little or no bioconcentration or bioaccumulation.

Data on developmental and reproductive toxicity

NOTE: Unless otherwise indicated, all information, including the citation, is obtained from secondary sources. Full citations of all studies are not provided here.

Developmental toxicity in humans

1. Bove et al. (1992a), as cited in ATSDR.  
Two related human epidemiological studies using the same database were conducted in New Jersey (see Bove et al. 1992b)].
A cross-sectional study (no interviews) of 81,055 singleton live births and 599 singleton fetal deaths found an association between an estimated concentration of >1 ppb CCl₄ in drinking water and the following developmental outcomes:
- full term birth weight < 2,500 grams (OR 2.26, 95% CI 1.41-3.6, p<0.001)
- small for gestational age (OR 1.35, 95% CI 1.03-1.8, p<0.025)
- central nervous system defects (OR 4.64, 95% CI 0.93-14.2, p<0.065)
- neural tube defects (OR 5.39, 95% CI 1.31-22.2, p<0.025)
- cleft lip or palate (OR 3.60, 95% CI 0.88-14.7, p<0.08).
ATSDR notes that these levels seem low for a causative agent, and that possible confounders could be addressed in future studies.

2. Bove et al. (1992b), as cited in ATSDR.  
Two related human epidemiological studies using the same database were conducted in New Jersey (see Bove et al. 1992a)].
A case-control study of 43-49 cases/outcome, and 138 controls (with interviews) found an association between an estimated concentration of >1 ppb CCl₄ in drinking water and the following developmental outcomes:
- cleft lip or palate (OR 5.39, 95% CI 0.81-36.0, p<0.085)
- ventricular septal defects without other cardiac defects (OR 9.19, 95% CI 1.18-71.8, p<0.035)
ATSDR notes that these levels seem low for a causative agent, and that possible confounders could be addressed in future studies.

Developmental toxicity in animals

1. Adams et al. (1961), as cited in Barlow and Sullivan, Shepard’s Catalog of Teratogenic Agents.
   a. Rabbits were treated by injection (ip) at 1.0 ml/kg/d on gd 4 and 5. Cellular degeneration of embryonic discs and trophoblasts with very large nuclei were observed.
   b. Rabbits were treated by injection (ip) at 0.6 ml/kg on gd 5. No effect on blastocysts recovered on gd 6.5 was observed.

2. Alumot et al. (1976), as cited in ATSDR, Barlow and Sullivan, Reprotox™.
   Rats (males and females) were treated orally (food) at 6, 15, or 36 mg/kg/d, from 5 weeks of age through 5 successive pregnancies. No effects on parental body weight or liver damage were observed. No effects on percent conception, percent with litters, litter size, birth weight, or weaning weight were observed. An increase in neonatal mortality was observed at 6 mg/kg/d, but not at 15 mg/kg/d.
3. Author not provided (1971), as cited in RTECS®.
   Rats, oral, 2 gram/kg, female 7-8 D of pregnancy. Toxic effects: Effects on Fertility - Post-implantation mortality.

4. Author not provided (1976), as cited in RTECS®.
   Rat, oral, 3 gram/kg, female 14 d of pregnancy. Toxic effects: effects on embryo or fetus - extra embryonic structures. [Note: may be redundant to Tsirelnikov and Tsirelnikova (1976), although reported dose is different.]

5. Bhattacharyya (1965), as cited in Barlow and Sullivan, USEPA HAD.
   a. Rats (female) were treated by injection (sc) at 0.5-2.0 ml/kg on gd 19-20 kg [equivalent to 1.59 g/ml]. Extensive liver damage in adults, but only focal necrotic changes in fetal liver were observed.
   b. Rats (fetal) were treated by injection (direct fetal sc or intra-amniotic) at 0.04 ml (/animal?) once on the last 3 days of gestation. Liver changes, including paleness indicating fatty infiltration, lasting until at least 4 days after birth were observed. No necrosis, hemorrhage or degeneration were observed.

   Rats (female) were treated by inhalation at 250 ppm for 8 hr/d for 5 consecutive days between gd 10-15. There were 10 controls and 25 treated animals. Reduced pups/litter (9.2 vs 10.3 controls) (viability index 83% vs. 98% controls, p<0.1) and lactation index (postnatal survival?) (83% vs. 98% controls, statistical significance not reported) were observed. No teratogenic effects were observed. [Note: abstract of dissertation.]

7. Heine et al. (1964), as cited in Barlow and Sullivan.
   Rabbits were treated orally at 50 or 60 mg/kg on gd 6. No malformations were observed. [Considered to be an “Inadequately reported study”. Neumann (1977) also cited.]

   a. Rats (female) were treated by injection (sc) at 3 ml/kg, 4 times on one day. Over the next month, the estrus phase was prolonged by 1 day, and the mean length of the estrus cycle was increased from 4.56 to 5.21 days.
   b. Rats (female) were treated by injection (sc) at 3 ml/kg, 4 times on one day. They were mated 7 or more days later. Increased pre-implantation loss (21% treated vs. 5% controls) and post-implantation loss (18% treated vs. 7% in controls) were observed. [Note: liver damage and altered corticosterone levels were thought to be involved.]
   c. Rats (female) were treated before pregnancy at “hepatotoxic doses”. Offspring were more susceptible to liver damage from oral CCl₄ treatment at 4 weeks of age.
   (Also cited under Female reproductive toxicity in animals section.)

   Rats (female) were treated by injection (ip) at 0.3 ml/kg on gd 13 or 17. Dams were killed on gd 16 or 20, respectively. Altered liver enzyme levels in mother and fetus were observed. Maternal levels were more severely affected than fetal levels were.

    Rabbits (female) were treated orally at 50 or 60 mg/kg on gd 6. No malformations were observed. [Considered to be an “Inadequately reported study”. Heine et al. (1964) also cited.]

    Mice (female) were treated by injection (ip or sc) at 150 mg/animal (or 0.04 ml/animal? conflicting sources) once on gd 16 or 18. Increased fetal mortality, and necrosis and circulatory damage of placentas, were observed. Fetal liver necrosis and dilation of sinusoids were observed. Effects on maternal liver were more pronounced than those on fetal liver.

    Rats (female) were treated by injection (sc) at 1 ml/kg during pregnancy for unknown period. No effect on resorptions or malformations was observed. (Barlow and Sullivan comment: study poorly reported in original.)

13. Schwetz et al. (1974), as cited in ATSDR, Barlow and Sullivan, IARC, Reprotext®, RTECS®, Shepard’s Catalog of Teratogenic Agents, USEPA HAD.
    Rats were treated by inhalation at 300 or 1,000 ppm for 7 hr/d on gd 6-15. Reduced maternal weight (7% at 300 ppm, 15% at 1,000 ppm compared to controls), reduced food consumption (up to 40% at 300 ppm, 55% at 1,000 ppm compared to controls), increased relative (but not absolute) liver weight, and increased serum SGPT (liver damage) were observed. No effect on resorptions (not statistically significant, 1/23 totally resorbed at 1,000 ppm), or malformations was observed. Reduced fetal body weight and crown-rump length (statistically significant) was observed. (ATSDR suggests fetal effects are “likely” secondary to maternal toxicity. Barlow
and Sullivan remark that “this is not unexpected in view of the severe effect on food consumption in the dams”. They also comment that this was a “well designed study using large numbers of animals”.

14. Smyth et al. (1936), as cited in ATSDR
Rats (male and female) were treated by inhalation at 100 or 200 ppm for 8 hr/d, 5 d/wk, 10.5 months (3 generations). Reduced fertility was observed at 200 ppm. (Also cited under Female and Male reproductive toxicity sections.)

15. Tsirelnikov and Dobrovolskaya (1973), as cited in Barlow and Sullivan, RTECS®, Shepard’s Catalog of Teratogenic Agents.
Rats were treated by injection (ip) at 3 ml/kg once on gd 12 to 20. Dams were killed 2 days after dosing. Following treatment on gd 12-15, increased fetal death was observed. Following treatment on gd 16-20, fetal body weight was reduced (statistically significant). Following treatment on gd 15-16, relative fetal liver weight was lower, but following treatment on gd 17-20, it was higher. Following treatment on gd 19-20, morphological changes to fetal liver were observed. The authors noted that damage to the maternal liver was greater than to the fetal liver.

Rats were treated orally at 0.15 ml/kg once on gd 12, 14, 16, or 18. Following treatment on gd 12 or 14, destruction of the chorionic epithelium of the labyrinthine portion of the placenta was observed. No information on fetal death was reported.

17. Wilson (1954), as cited in ATSDR, Barlow and Sullivan, Reprotox™, Reprotext®, Schardein, Shepard’s Catalog of Teratogenic Agents, USEPA HAD
Rats were treated orally (gavage) at 0.3 ml/rat or by injection (sc) at 0.8 ml/rat on 2 or 3 days beginning between gd 7 and gd 11. A total of 29 rats were treated. Results discussed did not distinguish between routes of administration. Mortality occurred in 6 animals, and 11 animals lost entire litters from early resorption. Resorption rates for the remaining animals were “within normal limits”. No malformations were observed. Growth retardation in 1 litter was observed.

Female reproductive toxicity in humans

No studies were identified.

Female reproductive toxicity in animals

1. Alumot et al. (1976), as cited in ATSDR, Barlow and Sullivan, Reprotox™.
Rats (males and females) were treated orally (food) at 6, 15, or 36 mg/kg/d, from 5 weeks of age through 5 successive pregnancies. No effects on parental body weight or liver damage were observed. No effects on percent conception, percent with litters, litter size, birth weight, or weaning weight were observed. An increase in neonatal mortality was observed at 6 mg/kg/d, but not at 15 mg/kg/d.

2. Chatterjee and Mukherji (1966), as cited in Barlow and Sullivan.
Rats (female) were treated by injection (ip) at 1.5-2 ml/kg. Hepatotoxicity, but no effect on body weight was observed. Following injections during proestrus, persistent estrus (15 days) and increased uterine weight were observed. Following injections during dioestrus, persistent dioestrus (12 days) and reduced uterine weight were observed. All weight changes were significant. (Chatterjee (1967a, b) also cited.)

3. Chatterjee (1967a), as cited in Barlow and Sullivan.
Rats (female) were treated by injection (ip) at 1.5-2 ml/kg. Hepatotoxicity, but no effect on body weight was observed. Following injections during proestrus, persistent estrus (15 days) and increased uterine weight were observed. Following injections during dioestrus, persistent dioestrus (12 days) and reduced uterine weight were observed. All weight changes were significant. (Chatterjee and Mukherji (1966) and Chatterjee (1967b) also cited.)

Rats (female) were treated by injection (ip) at 1.5-2 ml/kg. Hepatotoxicity, but no effect on body weight was observed. Following injections during proestrus, persistent estrus (15 days) and increased uterine weight were observed. Following injections during dioestrus, persistent dioestrus (12 days) and reduced uterine weight were
observed. All weight changes were significant. (Chatterjee and Mukherji (1966) and Chatterjee (1967a) also cited.)

   Mice (female) were treated by injection at 2 ml/kg once before maturity. No potentiation of increase in uterine weight caused by exogenous estrogens was observed.

   a. Rats (female) were treated by injection (sc) at 3 ml/kg, 4 times on one day. Over the next month, the estrus phase was prolonged by 1 day, and the mean length of the estrus cycle was increased from 4.56 to 5.21 days.
   b. Rats (female) were treated by injection (sc) at 3 ml/kg, 4 times on one day. They were mated 7 or more days later. Increased pre-implantation loss (21% treated vs. 5% controls) and post-implantation loss (18% treated vs. 7% in controls) were observed.
   [Note: liver damage and altered corticosterone levels were thought to be involved.]
   c. Rats (female) were treated before pregnancy at “hepatotoxic doses”. Offspring were more susceptible to liver damage from oral CCl₄ treatment at 4 weeks of age.

7. Levin et al. (1970), as cited in Barlow and Sullivan.
   Rats (female) were treated orally (gavage) at 0.17-1.7 ml/kg before maturity. Inhibition of metabolism of estrogen by the liver was observed. Potentiation of increase in uterine weight caused by estrogen was observed. (Talbot (1939) also cited.)

8. Smyth et al. (1936), as cited in ATSDR.
   Rats (male and female) were treated by inhalation at 100 or 200 ppm for 8 hr/d, 5 d/wk, 10.5 months (3 generations). Reduced fertility was observed at 200 ppm. (Also cited under Developmental and Male reproductive toxicity sections.)

   Rats (female) were treated orally (gavage) at 0.17-1.7 ml/kg before maturity. Inhibition of metabolism of estrogen by the liver was observed. Potentiation of increase in uterine weight caused by estrogen was observed. (Levin et al. (1970) also cited.)

**Male reproductive toxicity in humans**

No studies were identified.

**Male reproductive toxicity in animals**

1. Adams et al. (1952), as cited in ATSDR, Barlow and Sullivan, Reprotox™.
   a. Rats (male) were exposed by inhalation to 400 ppm for 1 hr/d, 5 d/wk, for 6 weeks. A slight decrease in body weight gain and some liver toxicity were observed. No effect on testes weight was observed.
   b. Rats (male) were exposed by inhalation at 200 or 400 ppm for 7 hr/d, 5 d/wk, for 25 weeks. Mortality (9/15 at 200 ppm, 13/15 at 400 ppm) was observed. Moderate to marked degeneration of germinal elements was observed.
   c. Guinea pigs (male) were exposed by inhalation at 400 ppm for 7 hr/d, 5d/wk, for 4 wks. Mortality in most animals was observed. Minor, non-specific testes pathology was observed.

2. Alumot et al. (1976), as cited in ATSDR, Barlow and Sullivan, Reprotox™.
   Rats (males and females) were treated orally (food) at 6, 15, or 36 mg/kg/d, from 5 weeks of age through 5 successive pregnancies. No effects on parental body weight or liver damage were observed. No effects on percent conception, percent with litters, litter size, birth weight, or weaning weight were observed. An increase in neonatal mortality was observed at 6 mg/kg/d, but not at 15 mg/kg/d.

3. Chapman et al. (1992), as cited in ATSDR.
   Rats (male) were treated by inhalation at “anaesthetizing” concentrations (plus 0.6 ppm dietary sodium phenobarbitol) for 2 d/wk for 5 weeks. A small (5%) reduction in testes weight (p<0.05) was observed.

4. Chatterjee (1966), as cited in Barlow and Sullivan, Reprotox™, RTECS®, USEPA HAD.
   Rats (male) were treated by injection (ip) at 4,800 mg/kg/d for 15 days. No effect on body weight was observed. Reduced relative testes weight (atrophy) (9.8 vs. 15.5 g/kg controls), reduced relative seminal vesicle weight, and “some abnormality” in spermatogenesis was observed.
5. Chatterjee (1967a), as cited in Barlow and Sullivan.  
Rats (male) were treated by injection (ip) at 1.5 ml/kg (once). Hepatic damage, adrenal hypertrophy, but no effect on body weight was observed. Reduced testes and seminal vesicle weight, evidence of testicular atrophy, and abnormal spermatogenesis was observed. (Chatterjee (1966) and Chatterjee (1967b) also cited.)

Rats (male) were treated by injection (ip) at 1.5 ml/kg (once). Hepatic damage, adrenal hypertrophy, but no effect on body weight was observed. Reduced testes and seminal vesicle weight, evidence of testicular atrophy, and abnormal spermatogenesis was observed. (Chatterjee (1966) and Chatterjee (1967a) also cited.)

7. DeToranzo et al. (1978), as cited in Reprotox™, RTECS®.  
Rats (male) were injected (ip) at 5 g/kg, 1 day prior to mating. General and testicular toxicity were observed.

8. Kalla and Bansal (1975), as cited in Barlow and Sullivan, USEPA HAD.  
Rats (male) were treated by injection (ip) at 4,800 mg/kg/d (or possibly 2,400 mg/kg/d) for 10, 15, or 20 days. Reduced body weight was observed. Reduced relative testes, seminal vesicle, epididymus and prostate weights were observed in all groups. Damage to spermatids and increase in the size of the lumens of seminiferous tubules was observed at 15 days. Disruption of germ and interstitial cells, and complete absence of spermatids was observed at 20 days.

Mice (male) were treated orally at 2,000 mg/kg once. General and testicular toxicity were observed. Uptake of 3H-thymidine into testicular DNA was reduced to 50% of controls.

10. Smyth et al. (1936), as cited in ATSDR.  
Rats (male and female) were treated by inhalation at 100 or 200 ppm for 8 hr/d, 5 d/wk, 10.5 months (3 generations). Reduced fertility was observed at 200 ppm. (Also cited under Developmental and Female reproductive toxicity sections.)

Other relevant data

Carbon tetrachloride is readily absorbed by the oral and inhalation routes, and absorbed to a lesser extent dermally. Carbon tetrachloride is highly toxic to the liver, and also the kidney and central nervous system. The CCl₃ free radical is believed to be involved (ATSDR). In humans, CCl₄ was found in cord blood in amounts equal or greater than maternal blood (Barlow and Sullivan, USEPA HAD, Shepard’s Catalog of Teratogenic Agents, Reprotext®). Carbon tetrachloride does not bioconcentrate or biomagnify (ATSDR).

Secondary Sources


Reprotox™. Dr. Anthony M. Scialli. (TOMES APRIL 30, 1995)

Reprotox®. Micromedex, Inc. (TOMES APRIL 30, 1995)


Shepard’s Catalog of Teratogenic Agents. Dr. Thomas H. Shepard. (TOMES APRIL 30, 1995)
VINYL CHLORIDE:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Vinyl chloride (formula C₂H₃Cl, CAS No. 75-01-4) is used almost entirely for manufacturing polyvinyl chloride (PVC). Some vinyl chloride is used as an intermediate in various chemical syntheses. Vinyl chloride is on the Proposition 65 list as a carcinogen.

Overview of Developmental/Reproductive Toxicity Concern

There is a MEDIUM level of developmental/reproductive toxicity concern over vinyl chloride due to associations between vinyl chloride exposure and birth defects in humans, and reports of damage to the testes in rats. Evaluation of possible confounding and multiple exposures in human studies is not possible at this level of review. Developmental toxicity studies in animals reported embryotoxicity and developmental delay, sometimes in association with maternal toxicity. All animal studies use the inhalation route, the most relevant route for humans.

Developmental toxicity

A number of epidemiological studies of malformations have been conducted in communities adjacent to PVC manufacturing facilities. Results are not entirely consistent and the early positive studies have been criticized for their design and statistical analysis. Animal studies demonstrate embryotoxicity, developmental delay and hematomas at the higher doses which are frequently also associated with maternal toxicity.

Female reproductive toxicity

Human information appears to be scattered and derived from small and incompletely reported studies. Apparently, no standard fertility studies (multigeneration or continuous breeding) have been conducted in animals.

Male reproductive toxicity

Impotence was reported in three studies of worker populations, and increased fetal loss was reported in the wives of workers at a polymerization plant. Animal studies indicate damage to testes with vinyl chloride inhalation, but general toxicity was not discussed. Reports of studies of dominant lethal effects were inconsistent in different secondary sources and no male fertility study was located for animals.

Overview of Exposure Concern

There is a MEDIUM level of concern over the extent of exposure. 97% of vinyl chloride is used in PVC manufacturing. The other 3% is in assorted chemical synthesis. Major exposures can occur in manufacturing or fabrication of PVC. General population exposure can occur from releases from landfills, prefabricators, and water treatment. Small amounts are released from PVC packaging and pipes. There is a “minute amount” in cigarette smoke. Little exposure from food occurs since 1974 regulations requiring “cleaner” (decreased monomer content) PVC. At two landfills in California, emissions were detected in the ambient air of nearby areas. Vinyl chloride is not produced in California. Two facilities in California use vinyl chloride to produce PVC. In California, surface waters were “generally free” of vinyl chloride, but half of 947 wells tested had detectable levels. Vinyl chloride is not expected to bioconcentrate or bioaccumulate. It degrades rapidly in air, but more slowly in other media.
Data on developmental and reproductive toxicity

NOTE: Unless otherwise indicated, all information, including the citation, is obtained from secondary sources. Full citations of all studies are not provided here.

Developmental toxicity in humans

1. Bao (1988), as cited in ATSDR.
   No effects were reported in pregnant workers in China exposed to 0.2-130.7 ppm vinyl chloride.
2. Edmonds et al. (1975), (1978), as cited in ATSDR, Schardein.
   No relationship was found between malformations and distance from plant or parental occupation in a second study in the same area as Infante et al., 1976b.
3. Infante (1976), Infante et al. (1976b), as cited in ATSDR.
   Increased malformation rates (CNS, upper alimentary tract, genitals, club foot) were found in communities with vinyl chloride polymerization facilities compared to county and state averages.
4. Rosenman et al. (1989), as cited in ATSDR, HSDB, Schardein.
   The odds ratio for CNS defects was correlated with the amount of emissions from 2 polymerization facilities and also with the distance from the facilities. No overall increase in birth defects was detected in the community. It was concluded that the increase in CNS defects was probably associated with vinyl chloride emissions (HSDB)
5. Theriault et al. (1983), as cited in ATSDR, Schardein.
   There was an increased prevalence of malformations in a town with a polymerization facility vs. 3 matched control towns. Prevalence of malformation was correlated with seasonal changes in emissions but not with proximity to the plant or with parental occupation.

Developmental toxicity in animals

1. Bingham et al. (1979), as cited in Barlow and Sullivan.
   Rats were exposed by inhalation to 0, 600 or 6,000 ppm 4h/day on gd 9-21. Low birthweight was reported.
   Rats were exposed to 2.4 ppm by inhalation throughout gestation. Increased early postimplantation loss, fetal hematomas, and hydrocephaly with intracerebral hematoma were reported, but no statistics or information on maternal toxicity were provided.
   Rats were exposed by inhalation to 2.4 ppm vinyl chloride throughout gestation. Hepatotoxic effects in offspring including decreased bile enzyme activity, decreased bile secretion, and decreased cholic acid content were reported; increased hexobarbital sleep time was also reported in offspring. No information was provided concerning maternal toxicity or study methods.
   Rats were exposed via inhalation to 0, 1.9, or 13.9 ppm vinyl chloride, 4 h/day, throughout gestation. Alteration in blood vessel permeability, nervous system functional disturbance and other abnormalities were reported at 1.9 ppm. Maternal toxicity was reported at 13.9 ppm along with decreased erythrocyte count and urinary hippuric acid. Increased fetal hemorrhage was also seen at 1.9 and 13.9 ppm and fetal edema at 13.9 ppm. At 6 months postnatal, offspring had decreased hemoglobin and leukocytes, decreased nonreproductive organ weights, decreased ability to orient, and increased pentobarbital sleep time.
   a. Mice were exposed to 0, 50 or 500 ppm vinyl chloride by inhalation during embryogenesis (gd 6-15). Decreased litter size and fetal weight, delayed ossification, decreased maternal food consumption, decreased maternal weight gain and increased maternal mortality were reported.
   b. Rats and rabbits were exposed to 0, 500 or 2,500 ppm vinyl chloride during embryogenesis (gd 6-15 for rats, gd 6-18 for rabbits). In rats, decreased fetal weight, decreased maternal food consumption, decreased maternal
weight gain, increased maternal mortality, and dilated ureters (2500 ppm) were reported. In rabbits, litter size and maternal food consumption were affected.

6. Ungvary et al. (1978), as cited in RTECS®.
   Rats were exposed by inhalation to 1500 ppm, 24 h/day on gd 1-9. Postimplantation loss, altered growth, developmental delay, increased resorptions and increased maternal liver/body weight ratios were reported. Anophthalmia and microphthalmia were reported but these results were not statistically significant.

Female reproductive toxicity in humans

1. Bao (1988), Chinese, as cited in ATSDR.
   Pre-eclampsia was reported in Chinese workers exposed to 3.9-130.7 ppm.
2. Lindbohm et al. (1985), as cited in ATSDR.
   No increase in abortion was found in 44 plastics workers exposed to vinyl chloride, polyurethane and styrene.
3. Makarov (1984), Russian, as cited in ATSDR.
   Decreased "sexual function" was reported in women 41-50 years and in women exposed for >21 years to vinyl chloride. Menstrual irregularities were described with no effect on abortion. This study was confounded by acrylate exposure.

Female reproductive toxicity in animals

1. Ungvary et al. (1978), as cited in ATSDR, RTECS®.
   Rats were exposed by inhalation to 1500 ppm, 24 h/day on gd 1-9. The study found increased resorptions and preimplantation loss and increased maternal liver/body weight ratio.

Male reproductive toxicity in humans

1. Infante (1976), as cited in ATSDR, Reprotox™, Schardein.
   Increased fetal loss was reported in the wives of workers at a polymerization plant. The study has been criticized for statistics and methodology.
2. Lee and Harry (1974), as cited in ATSDR.
   In a case report, decreased testicular size was described in an exposed worker who died of angiosarcoma.
3. Makarov et al. (1984), as cited in ATSDR.
   A decrease in "sexual function" and reduced testosterone levels were reported in this study. Exposure to methyl methacrylate also occurred.
4. Suciu et al. (1975), as cited in ATSDR.
   Sexual impotence was reported in 24% of an exposed worker population. No further description of the study was provided.
5. Veltman et al. (1975), as cited in ATSDR.
   Male potency problems were reported in 20% of exposed workers. No further description of the study was provided.
6. Walker (1976), as cited in ATSDR.
   35% loss of libido, 8% impotence, and decreased testosterone production were reported. No further description of the study was provided.

Male reproductive toxicity in animals

1. Anderson et al. (1976), as cited in ATSDR, RTECS®, Shepard’s Catalog of Teratogenic Agents, Barlow and Sullivan.
   In a dominant lethal study, male mice were exposed by inhalation to 30,000 ppm, 6 hr/day, for 5 days prior to mating. One secondary source reported an effect on preimplantation loss (RTECS®), but another reported no pre or postimplantation loss and no fertility effect (ATSDR).
2. Bi et al. (1985), as cited in ATSDR.
   Rats were exposed by inhalation to 10, 100, 3000 ppm, for 6 h/day, 6 day/wk over 3, 6, 12 or 18 mos.
Decreased relative testes weight was seen with 6 months of exposure and damage to testicular seminiferous tubules was seen with 12 mos exposure in the 100 and 3000 ppm groups.

3. Short (1977), as cited in RTECS®, Reprotox™, Shepard’s Catalog of Teratogenic Agents, Barlow and Sullivan. In a dominant lethal study, rats were exposed by inhalation to 250 ppm vinyl chloride for 6 h/day, 55 d prior to mating. The vinyl chloride concentration in this study was also cited as 100 ppm. One secondary source (RTECS®) reported an effect on the female fertility index, but other secondary sources reported negative findings or no dominant level effect.

4. Sokal et al. (1980), as cited in ATSDR. Male rats were exposed via inhalation to 0, 50, 500, 20,000 ppm for 5 h/day, 5 days/wk, for 10 months. Morphological lesions in liver and testes and depression in body weight were reported at 500 ppm. Damage to spermatogenic epithelium and disorders of spermatogenesis were also mentioned.

5. Torkelson (1961), as cited in ATSDR. Rats, dogs, guinea pigs, and rabbits were exposed to 200 ppm 7 hr/day, 5 days/wk for 6 months (4.5 mos for rats). There were a small number of animals in each group. No effect on testes weight was found.

Other relevant data

Vinyl chloride is metabolized by alcohol dehydrogenase. Interactions with alcohol ingestion can occur (John (1977), Schwetz (1975), as cited in ATSDR).

Secondary Sources


Reprotox™. Dr. Anthony M. Scialli. (TOMES APRIL 30, 1996)


Shepard’s Catalog of Teratogenic Agents. Dr. Thomas H. Shepard. (TOMES APRIL 30, 1995)
Aldrin (CAS No. 309-00-2) is an organochlorine pesticide with molecular formula $\text{C}_{12}\text{H}_8\text{Cl}_6$. It was formerly used as pesticide in the U.S. Most uses were canceled by U.S. EPA in 1974. Its remaining uses were canceled by 1987. Aldrin is on the Proposition 65 list as a carcinogen.

Overview of Developmental/Reproductive Toxicity Concern

There is a MEDIUM level of developmental/reproductive toxicity concern. This is due to reports of developmental toxicity in animals, including preweaning death and postnatal neurobehavioral changes. Concern is tempered by the fact that the reports of preweaning death are old, and of questionable quality. Aldrin and its metabolite dieldrin are stored in fat and secreted in milk, which may be partly or wholly responsible for the observed postnatal effects.

**Developmental toxicity**

There is one report in humans of elevated levels of aldrin in blood or placenta in cases of spontaneous abortion and premature delivery. However, other organochlorine compounds were also elevated. There are reports in dogs, rats, and mice of preweaning death following prenatal or prenatal and lactational exposure. However, these reports are fairly old, and the studies in dogs used small numbers and appeared to have other methodological problems. There are also reports in rats and mice of neurobehavioral changes (increased locomotor activity and seizure threshold) in pups following exposure of the female during pregnancy and/or lactation. Aldrin and its immediate metabolite dieldrin are lipophilic, are stored in fat, and are expected to be secreted in milk, even when aldrin is administered prenatally. This may be partly or wholly responsible for the observed postnatal effects. There was also a report of malformations in mice and hamsters following single exposure to about 1/2 of the maternal LD$_{50}$ dose of aldrin during gestation. However, data on maternal toxicity in this report was not available.

**Female reproductive toxicity**

There is one report in humans of elevated levels of aldrin in blood or placenta in cases of spontaneous abortion and premature delivery. However, other organochlorines were also elevated. No consistent effects were observed in animal studies.

**Male reproductive toxicity**

There are reports of adverse effects on sperm and sexual organ histopathology in rats by injection. A dominant lethal study in mice by injection and oral routes found no effects.

Overview of Exposure Concern

There is a LOW level of concern over exposure to aldrin. Most uses of this organochlorine insecticide in the U.S. were banned in 1974, and remaining uses were banned in 1987. Small amounts remain in the environment, especially from prior termite applications. Most aldrin in the environment has been degraded to dieldrin.

Data on Developmental and Reproductive Toxicity

NOTE: Unless otherwise indicated, all information, including the citation, is obtained from secondary sources. Full citations of all studies are not provided here.

**Developmental toxicity in humans**
1. Saxena et al. (1980), as cited in ATSDR.  
In cases of spontaneous abortion and premature labor, aldrin levels were higher in the blood or placenta than in controls. However, other organochlorine compounds were also elevated. (Also cited under Female reproductive toxicity in humans.)

**Developmental toxicity in animals**

1. Al-Hachim (1971), as cited in ATSDR.  
Mice were treated with aldrin by oral gavage at 2 mg/kg/d for 5-7 d during the “3rd trimester”. Increased seizure threshold in offspring was observed. No effect on acquisition of conditioned avoidance response was observed.

Rats were treated with aldrin during lactation. Increased locomotor activity was observed in the offspring.

Rats were treated with aldrin during pregnancy. Increased locomotor activity was observed in the offspring.

4. Castro et al. (1992), as cited in Reprotox™.  
Rats were treated with aldrin during pregnancy. Increased locomotor activity was observed in the offspring.

5. Deichman et al. (1971), as cited in ATSDR.  
Dogs (beagle) were treated with aldrin at 0.15 mg/kg/d for 14 months, and mated 0.5 to 9 months later. Postnatal death was observed. Small numbers of animals were used in this study.

6. Keplinger et al. (1970), as cited in IPCS.  
Mice (male and female) were treated with aldrin orally (in food) at 0, 3, 5, 10, or 25 ppm for 6 generations. There were 2 litters per generation. At 25 ppm, there was high toxicity with few dams reaching gestation, and high litter mortality; this dose was discontinued. Reduced pre-weaning pup survival at 5 and 10 ppm was observed. (Also cited in the Female and Male reproductive toxicity in animals sections.)

Dogs (male and female) were treated with aldrin orally at 0, 0.2, 0.6, or 2 mg/kg/d for 44 weeks prior to mating and during gestation weeks 1-8. No abnormalities were observed, but reduced pup survival during nursing was observed. Dead pups had liver and kidney histopathological changes. This study was limited because maternal toxicity was not addressed, a small number of dogs were tested, and pregnancies were incidental to the main study protocol. (Also cited in Female and Male reproductive toxicity in animals sections.)

8. Kitselman et al. (1950), as cited in Schardein.  
Cattle fed hay containing a low dose of aldrin had no malformed calves.

a. Mice were treated with aldrin orally (gavage) at 25 mg/kg on gd 9. Malformations (webbed feet, cleft palate, and open eye in 25% of treated group), but no effect on fetal survival or weight was observed. The dose was about 1/2 of the LD$_{50}$ dose (this did not correspond to the LD$_{25}$ dose), but no information on maternal toxicity was given.

b. Hamsters were treated with aldrin orally (gavage) at 50 mg/kg once on gd 7, 8, or 9. Malformations (webbed feet, cleft palate, and open eye), post-implantation mortality, fetal death, and reduced fetal weight were observed. Effects were more pronounced on gd 7 and 8 than on gd 9. The dose was about 1/2 of the LD$_{30}$ dose (this did not correspond to the LD$_{25}$ dose).

10. Treon et al. (1954), as cited in ATSDR.  
Rats were treated with aldrin orally (food) at 0.125, 0.625, or 1.25 mg/kg/d for 3 generations. No maternal mortality was observed at up to 1.25 mg/kg/d. At 0.625 mg/kg/d, reduced numbers of litter were observed. At 0.125 mg/kg/d, increased mortality of offspring was observed. (Note: this is probably redundant to Treon and Cleveland (1955).) (Also cited in the Female and Male reproductive toxicity in animals sections.)

11. Treon and Cleveland (1955), as cited in IPCS, Reprotext®.  
Rats were treated with aldrin orally (food) at 2.5, 12.5, or 25 ppm for 3 generations. Increased pre-weaning pup mortality at 12.5 and 25 ppm was observed. An initial reduction in fertility at 12.5 and 25 ppm, which disappeared over successive generations, was observed. No effects on litter size or pup weight were observed. Increased preweaning pup mortality at 12.5 and 25 ppm was observed. (Note this is probably redundant to Treon et al. (1954)). (Also cited in the Female and Male reproductive toxicity in animals sections.)
Female reproductive toxicity in humans

1. Saxena et al. (1980), as cited in ATSDR.
   In cases of spontaneous abortion and premature labor, aldrin levels were higher in the blood or placenta than in controls. However, other organochlorine compounds were also elevated. (Also cited in the Developmental toxicity in humans section.)

Female reproductive toxicity in animals

1. Author not provided (1978), as cited in RTECS®.
   Rats (female) were treated with aldrin by injection (sc) at 10 mg/kg (total) 2 days prior to mating. Effects on uterus, cervix, or vagina were observed.
2. Ball et al. (1953), as cited in Reprotext®.
   Rats were treated with aldrin orally (in food) at 10-20 ppm. Disturbance of the estrus cycle was observed.
3. Gellert and Wilson (1979), as cited in HSDB.
   Rats (female) were treated with aldrin orally (in food) during gestation. Offspring were tested for reproductive function. No adverse reproductive effects were observed in male or female offspring of treated rats.
4. Keplinger et al. (1970), as cited in IPCS.
   Mice (male and female) were treated with aldrin orally (in food) at 0, 3, 5, 10, or 25 ppm for 6 generations. There were 2 litters per generation. At 25 ppm, there was high toxicity with few dams reaching gestation, and high litter mortality; this dose was discontinued. Reduced pre-weaning pup survival at 5 and 10 ppm was observed. (Also cited in the Developmental and Male reproductive toxicity in animals sections.)
5. Kitselman (1953), as cited in ATSDR, Reprotext®, RTECS®, Schardein.
   Dogs (male and female) were treated with aldrin orally at 0, 0.2, 0.6, or 2 mg/kg/d for 44 weeks prior to mating and during gestation weeks 1-8. No abnormalities were observed, but reduced pup survival during nursing was observed. Dead pups had liver and kidney histopathological changes. This study was limited because maternal toxicity was not addressed, a small number of dogs were tested, and pregnancies were incidental to the main study protocol. (Also cited in Developmental and Male reproductive toxicity in animals sections.)
6. Treon et al. (1954), as cited in ATSDR.
   Rats were treated with aldrin orally (food) at 0.125, 0.625, or 1.25 mg/kg/d for 3 generations. No maternal mortality was observed at up to 1.25 mg/kg/d. At 0.625 mg/kg/d, reduced numbers of litter were observed. At 0.125 mg/kg/d, increased mortality of offspring was observed. (Note this is probably redundant to Treon and Cleveland (1955)). (Also cited in the Developmental and Male reproductive toxicity in animals sections.)
7. Treon and Cleveland (1955), as cited in IPCS, Reprotext®.
   Rats were treated with aldrin orally (food) at 2.5, 12.5, or 25 ppm for 3 generations. Increased pre-weaning pup mortality at 12.5 and 25 ppm was observed. An initial reduction in fertility at 12.5 and 25 ppm, which disappeared over successive generations, was observed. No effects on litter size or pup weight were observed. Increased preweaning pup mortality at 12.5 and 25 ppm was observed. (Note this is probably redundant to Treon et al. (1954)). (Also cited in the Developmental and Male reproductive toxicity in animals sections.)

Male reproductive toxicity in humans

No studies were identified.
Male reproductive toxicity in animals

1. Chatterjee et al. (1988a), as cited in Reprotox™.
Rats (male) were treated (unknown route) with aldrin at 150 ug/kg (unknown duration). Reduced sperm concentration, degeneration of seminiferous tubules, reduced accessory sexual organ weight, and reduced plasma testosterone were also observed. (Chatterjee et al. 1988b also cited)

2. Chatterjee et al. (1988b), as cited in Reprotox™, RTECS®.
Rats were injected (ip) at 150 ug/kg/d for 13 or 26 days. After 13 days, “androgenic” effects were observed. After 26 days, effects on prostate, seminal vesicle, and Cowper's gland were observed.

3. Epstein et al. (1972), as cited in ATSDR, IARC, IPCS.
   a. Mice (male) were treated with aldrin by injection (ip) at 8 or 40 mg/kg (1 day). No dominant lethal effects were observed.
   b. Mice (male) were treated orally at 0.5 or 1 mg/kg/d for 5 days. No dominant lethal effects were observed.

4. Keplinger et al. (1970), as cited in IPCS.
Mice (male and female) were treated with aldrin orally (in food) at 0, 3, 5, 10, or 25 ppm for 6 generations. There were 2 litters per generation. At 25 ppm, there was high toxicity with few dams reaching gestation, and high litter mortality; this dose was discontinued. Reduced pre-weaning pup survival at 5 and 10 ppm was observed. (Also cited in the Developmental and Female reproductive toxicity in animals sections.)

5. Kitselman (1953), as cited in ATSDR, Reprotext®, RTECS®, Schardein.
   Dogs (male and female) were treated with aldrin orally at 0, 0.2, 0.6, or 2 mg/kg/d for 44 weeks prior to mating and during gestation weeks 1-8. No abnormalities were observed, but reduced pup survival during nursing was observed. Dead pups had liver and kidney histopathological changes. This study was limited because maternal toxicity was not addressed, a small number of dogs were tested, and pregnancies were incidental to the main study protocol. (Also cited in Developmental and Female reproductive toxicity in animals sections.)

6. Treon et al. (1954), as cited in ATSDR.
Rats were treated with aldrin orally (food) at 0.125, 0.625, or 1.25 mg/kg/d for 3 generations. No maternal mortality was observed at up to 1.25 mg/kg/d. At 0.625 mg/kg/d, reduced numbers of litter were observed. At 0.125 mg/kg/d, increased mortality of offspring was observed. (note this is probably redundant to Treon and Cleveland (1955).) (Also cited in the Developmental and Female reproductive toxicity in animals sections.)

7. Treon and Cleveland (1955), as cited in IPCS, Reprotext®.
   Rats were treated with aldrin orally (food) at 2.5, 12.5, or 25 ppm for 3 generations. Increased pre-weaning pup mortality at 12.5 and 25 ppm was observed. An initial reduction in fertility at 12.5 and 25 ppm, which disappeared over successive generations, was observed. No effects on litter size or pup weight were observed. Increased preweaning pup mortality at 12.5 and 25 ppm was observed. (Note this is probably redundant to Treon et al. (1954)). (Also cited in the Developmental and Female reproductive toxicity in animals sections.)

Other relevant data

Aldrin is readily metabolized to dieldrin (an epoxide). There is a considerable literature on the developmental and reproductive toxicity of dieldrin; the effects are similar to, and consistent with, the effects of aldrin. Aldrin and dieldrin are lipophilic, accumulate in fat, and are eliminated moderately slowly. Aldrin crosses the placenta and is found in cord blood. Aldrin and dieldrin have been found in some, but not all, samples of human milk. As lipophilic compounds, aldrin and dieldrin are expected to be secreted in the milk, which may be related to the observations of death during lactation and postnatal neurobehavioral effects in animal experiments.

Secondary Sources


Reprotext®. Micromedex, Inc. (TOMES APRIL 30, 1995)

Reprotox™. Dr. Anthony M. Scialli. (TOMES APRIL 30, 1995)


Shepard’s Catalog of Teratogenic Agents. Dr. Thomas H. Shepard. (TOMES APRIL 30, 1995)
2,4,5-T BUTYL ESTER:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

2, 4, 5-T butyl ester (formula C_{12}H_{13}Cl_{3}O_{3}, CAS No. 93-79-8) is a component of the commercial herbicide (2,4,5-trichlorophenoxy)acetic acid, or 2,4,5-T. In 1970, all uses of 2,4,5-T were canceled (except for use on rice in US). In 1983, all manufacture of 2,4,5-T was stopped and in 1984, all uses were canceled. It is not listed as a Proposition 65 carcinogen.

Overview of Developmental/Reproductive Toxicity Concern

There is a LOW level of developmental/reproductive toxicity concern over 2,4,5-T butyl ester due to lack of studies with agents of verified purity. While a number of studies of developmental toxicity were conducted in laboratory rodents in the 1970s, the chemicals used may have been contaminated with dioxin. In addition, most of these studies are foreign language reports, and no information on compound purity was provided in the secondary sources. Examination of the primary literature may lead to an increase in the level of concern. There are a number of human studies of 2,4,5-T but none of them attempt to isolate an effect of the butyl ester component.

Developmental toxicity

Two studies in mice reported fetotoxicity and craniofacial abnormalities when 2,4,5-T butyl ester was administered by the oral route during embryogenesis. In rat studies, more general effects on embryotoxicity, teratogenicity, and growth retardation were mentioned. Study descriptions are very limited in secondary sources. Human studies are limited to exposures where the butyl ester was a minor component of an herbicide.

Female reproductive toxicity

No studies were identified.

Male reproductive toxicity

No studies were identified.

Overview of Exposure Concern

There is a LOW level of concern over the extent of exposure to 2,4,5-T butyl ester. 2,4,5-T butyl ester was used as a herbicide until 1970, when all uses were canceled (except for use on rice in US). In 1983, all manufacture of 2,4,5-T were stopped and in 1984, all uses were canceled. It is not bioaccumulative.

Data on developmental and reproductive toxicity

NOTE: Unless otherwise indicated, all information, including the citation, is obtained from secondary sources. Full citations of all studies are not provided here.

Developmental toxicity in humans

No studies were identified.
Developmental toxicity in animals

   In this Russian language report, 2,4,5-T butyl ester was given by gavage at doses of 50, 100, or 200 mg/kg to rats and "embryotoxic" effects were reported.
2. Courtney (1977), as cited in RTECS.
   Mice were exposed by the oral route. At a dose of 748 mg/kg (total dose) on gd 11-13, fetotoxicity and craniofacial abnormalities were reported. At a dose of 1246 mg/kg on gd 12-15 fetal death was reported.
3. Konstantova (1976), as cited in RTECS, HSDB.
   Rats were exposed by the oral route. At a dose of 200 µg/kg on gd 7-8, urogenital abnormalities were observed. At a dose of 2 mg/kg on gd 1-20 post-implantation mortality, fetal death, and live birth index were affected. The low effective doses in this study were attributed by the secondary source (HSDB) to TCDD contamination.
4. Lima and Rodriguez (1979), as cited in HSDB.
   In rats, administration of 5, 150 or 200 mg/kg (route not stated) resulted in decreased body weight and length. At 150 mg/kg, increased fetal death and maternal mortality were seen. No teratogenic effects were observed.
5. Neubert and Dillmann (1972), as cited in RTECS.
   Mice were exposed to 120 mg/kg (total dose) by the oral route on gd 6-15. At a dose of 120 mg/kg fetotoxicity was reported and at a dose of 740 mg/kg craniofacial abnormalities were found.
   In this Russian language report, 2,4,5-T butyl ester was described as "teratogenic in rodents".

Female reproductive toxicity in humans

No studies were identified.

Female reproductive toxicity in animals

No studies were identified.

Male reproductive toxicity in humans

No studies were identified.

Male reproductive toxicity in animals

No studies were identified.

Other relevant data

1. Erickson (1984), as cited in HSDB.
   No overall increase in congenital defects in Vietnam veterans.
2. Field and Kerr (1979), as cited in Shepard's Catalog of Teratogenic Agents.
   Neural tube defects were correlated with commercial 2,4,5-T herbicide use.
   The mechanism of toxicity in animals is "poorly understood". 2,4,5-T is rapidly excreted in urine.
   For commercial 2,4,5-T, no effect on cleft palate incidence was found.
5. Smith (1981), (1982); Townsend (1982), as cited in HSDB.
   No congenital defects were reported in wives of 2,4,5-T exposed workers.
   For commercial 2,4,5-T, no effects on congenital defects were found in a study in Hungary.
Secondary Sources


Shepard’s Catalog of Teratogenic Agents. Dr. Thomas H. Shepard. (TOMES APRIL 30, 1995)
METHYLENE CHLORIDE:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Methylene chloride (formula CH₂Cl₂, CAS No. 75-09-2) is used as a paint stripper, a solvent and a degreaser. It has also been used in drug manufacturing, in some coffee decaffeinating processes, and in some fire extinguishers. Its use in hair spray was banned in 1989. Overall, its use is declining. It is not listed as a Proposition 65 carcinogen.

Overview of Developmental/Reproductive Toxicity Concern

There is a LOW level of developmental/reproductive toxicity concern over methylene chloride due to an absence of effects reported in standard developmental toxicity and reproductive toxicity study designs in animals. Details concerning these primarily negative studies were not provided in the secondary sources.

Developmental toxicity

One recent study reported reduced birthweight in women exposed via emissions from a nearby factory. No information was available concerning the design and quality of this study. Two standard developmental toxicity studies and one standard multigeneration study have been conducted in rodents via the inhalation route. Developmental delay was reported at maternally toxic doses.

Female reproductive toxicity

An increased risk of spontaneous abortion was reported in a small case-control study. Another briefly mentioned occupational study also reported increased spontaneous abortion. No effects were reported in a single generation (oral route) and a multiple generation (inhalation route) study in rodents.

Male reproductive toxicity

One briefly mentioned study in workers reported decreased sperm counts in workers. In animals studies, no fertility effects were found in a multigeneration study by the inhalation route, and no testes pathology was identified in a subchronic inhalation study.

Overview of Exposure Concern

There is a HIGH level of concern over the extent of exposure. Methylene chloride is used as a paint stripper solvent and as a degreaser, although this use is declining. It is also used in drug manufacturing, decaffeinating coffee, and in fire extinguishers. The 1994 TRI figures indicate that 2,921,225 lbs were released in California, of which 1,365,771 lbs were released to air. There is a relatively high amount of consumer exposure. In 1983, 24,000 tons/yr were used in California according to the ARB. There were no manufacturers in CA in 1983 according to the ARB.

Data on developmental and reproductive toxicity

NOTE: Unless otherwise indicated, all information, including the citation, is obtained from secondary sources. Full citations of all studies are not provided here.
Developmental toxicity in humans

1. Bell et al. (1991), as cited in Reprotext®,
   Decreased birthweights were reported in women exposed via emissions from a nearby factory. No information on design or sample size was provided.

Developmental toxicity in animals

1. Bornschein et al. (1980), as cited in ATSDR, HSDB, Reprotox™, Reprotext®, Shepard’s Catalog of Teratogenic Agents, Barlow and Sullivan, IARC, IPCS.
   Rats were exposed by inhalation to 0 or 4500 ppm methylene chloride for 6 h/day on or before gd 1-17. In behavioral studies a habituation effect was identified, but there were no effects on activity or avoidance learning. This report was based on the same study as Hardin and Manson, as described below.
2. Hardin and Manson (1980), as cited in ATSDR, HSDB, RTECS®, Reprotox™, Reprotext®, Shepard’s Catalog of Teratogenic Agents, Barlow and Sullivan, IARC, IPCS.
   Rats were exposed by inhalation to 0 or 4500 ppm methylene chloride for 6 h/day before, or before and during gd 1-17. Decreased fetal weight, rib malformations and dilated renal pelvis were reported at maternally toxic doses.
3. IRDC, 1976 (secondary source, primary source not identified) as cited in HSDB.
   Rats were given methylene chloride by gavage at doses of 0, 25, 75, or 225 mg/kg/day for 18 weeks in the F0 generation and 90 days in the F1 generation. No effects on fertility, litter size or pup survival were found.
4. Nitschke et al. (1988b), as cited in ATSDR, HSDB; also called "Dow Chemical Study", as cited in HSDB.
   In a 2-generation study, rats were exposed via inhalation to 0, 100, 500, 1500 ppm 6 hr/day, 5 d/wk. No effects on neonatal growth, survival, or major skeletal variations were seen. ATSDR stated that fetal body weights were decreased. There were no maternal toxicity effects or pathological changes in adults or weanlings.
5. Schwetz et al. (1975), as cited in ATSDR, RTECS®, Reprotox™, Reprotext®, Shepard’s Catalog of Teratogenic Agents, Barlow and Sullivan, IARC, USEPA HAD. (Also reported in Leong et al. (1975), as cited in Reprotext®, Schardein.
   Mice and rats were exposed by inhalation to 0 or 1225 ppm methylene chloride for 7 h/day on gd 6-15. Retarded growth, developmental delay (delayed ossification) and skeletal variants (extra sternal ossification centers) were reported. Observed effects were reported to occur at maternally toxic doses. This study was also described as finding no teratogenic effects

Female reproductive toxicity in humans

1. Axelson et al. (1984), as cited in Reprotext®.
   Increase in spontaneous abortion in an occupational study. No further information on the study was provided.
2. Bell et al. (1991), as cited in Reprotext®.
   Infants of women exposed to methylene chloride emissions from a nearby factory had lower birthweights than those of unexposed women.
3. Taskinen et al. (1986), as cited in Reprotox™, Reprotext®, Shepard’s Catalog of Teratogenic Agents, USEPA HAD.
   In a case-control study (11 cases and 3 controls per case) an increased odds ratio (about 2.5) for abortion was reported in workers exposed to methylene chloride through employment in the pharmaceutical industry.
   An incidence of 31% gynecological and obstetrical complaints was reported in this Russian language article. There was also exposure to gasoline in the population.
Female reproductive toxicity in animals

1. Bornmann and Loesser (1967), as cited in IRIS®, IPCS.
   In a 1 generation study, rats were exposed to 125 mg/L methylene chloride in drinking water for 13 weeks before mating. No effects were reported.
2. Nitschke et al. (1988b), as cited in ATSDR, HSDB; also called "Dow Chemical Study", as cited in HSDB.
   In a 2-generation study, rats were exposed via inhalation to 0, 100, 500, 1500 ppm 6 hr/day, 5 d/wk. No parental or developmental toxicity was found.

Male reproductive toxicity in humans

1. Kelly (1988), as cited in ATSDR.
   In a case series, decreased sperm counts were recorded in a group of workers exposed by inhalation and dermal contact.

Male reproductive toxicity in animals

1. Nitschke et al. (1988b), as cited in ATSDR, HSDB; also called "Dow Chemical Study", as cited in HSDB.
   In a 2-generation study, rats were exposed via inhalation to 0, 100, 500, 1500 ppm 6 hr/day, 5 d/wk. No parental or developmental toxicity was found
2. Raje et al. (1988), as cited in ATSDR.
   Rats were exposed to methylene chloride at concentrations of 200 ppm or less. There were no microscopic lesions in the testes.

Other relevant data.

Anesthetic properties of methylene chloride limit doses that can be examined by inhalation. Elevated maternal carboxyhemoglobin has been noted with maternal exposure (Anders and Sunram (1982), as cited in ATSDR, IPCS). Carbon monoxide is a metabolite of methylene chloride and could be involved in its toxic effects. Methylene chloride causes dopamine depletion which could affect gonadotropins (HSDB). In humans, there is a genetically at-risk group (25% of population) composed of nonconjugators (Reprotext®). Reprotext also stated that “the EPA regards methylene chloride as having ‘minimal’ teratogenic potential”.

Secondary Sources


Reprotox™. Dr. Anthony M. Scialli. (TOMES JULY 31, 1995)

Reprotext®. Micromedex, Inc. (TOMES JULY 31, 1995)


Shepard’s Catalog of Teratogenic Agents. Dr. Thomas H. Shepard. (TOMES JULY 31, 1995)


PROGESTERONE:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Note: This chemical is now included for consideration in another group of chemicals.

Progesterone (Cas No. 57-83-0) was formerly used to treat bleeding during pregnancy, for infertility and for habitual abortion. Birth control pills use synthetic progestins, rather than progesterone. Only one current therapeutic use of progesterone was found, and this was as a component of an intrauterine device (IUD). It is used as a veterinary drug. Progesterone is on the Proposition 65 list as a carcinogen.

Overview of Developmental/Reproductive Toxicity Concern

There is a DRAFT HIGH level of developmental/reproductive toxicity concern over progesterone due to effects on fertility and pregnancy loss in females, reproductive organ toxicity in males, and effects on development of the external genitalia in offspring. These effects have been demonstrated in laboratory animals with supportive data in humans. Progesterone does not appear to produce malformations in laboratory animals when administered during embryogenesis, although some suggestive data for this toxic effect have been produced in human studies.

Developmental toxicity

Concern has been raised in human studies about an association between progestin use in pregnancy and incidence of hypospadia in males and masculinization of the external genitalia in females. Detailed review of the studies would be necessary to determine if progesterone, rather than synthetic progestins, was implicated in the effect and whether confounding factors were controlled. Several large scale studies have failed to find a more general association between progestin use in pregnancy and birth malformations. In rats and guinea pigs, progesterone administration during pregnancy has been reported to cause abnormalities of the urogenital system. With respect to concerns of an association of in utero exposure to progestin and hypospadias and masculinization of external genitalia in humans, because of differences in timing of development of the external genitalia in rats and mice, it might not be expected to observe hypospadia and masculinization as a result of in utero exposure in these species.

Female reproductive toxicity

It is generally accepted, based on extensive contraceptive development research, that progesterone has a contraceptive effect, producing disruption of menstrual cycle, inhibition of ovulation and ovarian and endometrial atrophy. When administered during pregnancy, pregnancy loss (including pre and post implantation loss and abortion) is produced in both humans and animals. Various other indices of fertility have been reported to be disrupted by progesterone administration prior to mating or during pregnancy in animal studies.

Male reproductive toxicity

In two studies, progesterone was administered by injection (i.m.) to men. Impotence, breast development and effects on spermatogenesis were reported. In animal studies (including rats, mice, rabbits, guinea pigs, cattle and monkeys) progesterone administered by injection, oral, dermal, or inhalation routes was shown to have toxic effects on the reproductive tract and, in some studies, on spermatogenesis and mating performance. No evaluations of fertility were identified.
Overview of Exposure Concern

There is a DRAFT LOW level of concern over the extent of exposure. Progesterone was formerly used therapeutically for bleeding during pregnancy, infertility and habitual abortion. Currently, birth control pills use synthetic progestins, rather than progesterone. The current PDR reported that one IUD uses progesterone. No production data after 1979 was available from secondary sources.

Data on developmental and reproductive toxicity

NOTE: Unless otherwise indicated, all information, including the citation, is obtained from secondary sources. Full citations of all studies are not provided here. A large number of animal studies were performed in the 1950’s and 60’s in connection with contraceptive development. These studies were found primarily in RTECS and are described below with text modified from the RTECS entries.

Developmental toxicity in humans

1. Author not provided, as cited in RTECS®.
   Women were exposed via a parenteral route to 600 µg/kg on 67-71d of pregnancy. Toxic effects included: Specific Developmental Abnormalities- urogenital system. Reference: Mayo Clinic Proceedings 33:200, 1958.
2. Author not provided, as cited in RTECS®.
   Women were exposed via an unreported route to 386 mg/kg on weeks 18-34 of pregnancy. Toxic effects included: Specific Developmental Abnormalities- urogenital system. Reference: AMA Journal of Diseases of Children 95:9, 1958.
3. Author not provided, as cited in RTECS®.
   Women were exposed orally to 113 mg/kg in weeks 6-32 of pregnancy. Toxic effects included: Specific Developmental Abnormalities- urogenital system. Reference: Journal of Clinical Endocrinology and Metabolism 19:1369, 1959.
4. Check et al. (1986), as cited in Reprotox™.
   No increase in birth defects was seen in progesterone exposed pregnancies.
5. Hayles and Nolan (1957), as cited in Shepard’s Catalog of Teratogenic Agents.
   Two cases were reported of masculinized female infants whose mothers received progesterone (10 mg by injection for 3 days, and up to 60 mg orally).
6. Heinonen et al. (1977), as cited in Reprotox™.
   In more than 500 pregnancies with progesterone exposure, no relationship was shown with birth defects in offspring.
7. Kallen et al. (1992), as cited in Reprotox™.
   No increase in birth defects was seen in progesterone exposed pregnancies.
8. Michaelis et al. (1983), as cited in Reprotox™.
   In 186 progesterone exposed pregnancies, no increase in birth defects could be identified.
   No increase in birth defects was seen in progesterone exposed pregnancies.
10. Rock et al. (1985), as cited in Shepard’s Catalog of Teratogenic Agents, HSDB.
    In 42 pregnancies treated with progesterone suppositories (average total dose 2236), 28% abortions but no malformations were found. In 45 pregnancies treated with i.m. progesterone (average total dose 1009 mg), 5.8% spontaneous abortions and 2 malformations (a unilateral undescended testes and a meningomyelocele) were reported.

Developmental toxicity in animals

1. Adams et al. (1961), as cited in IARC.
   Rabbits were given 1 mg via injection on gd 1-4. there were no discernible effects on 6.5 day old blastocysts.
2. Author not provided, as cited in RTECS®.
   Hamsters were exposed via subcutaneous injection to 80 mg/kg on gd 1. Toxic effects included: Maternal Effects- Parturition; Effects On Newborn- Live birth index. Reference: Biology of Reproduction 6:281, 1972.

3. Author not provided, as cited in RTECS®.
   Mice were exposed via subcutaneous injection to 240 mg/kg on gd 14-16. Toxic effects included: Effects On Newborn- Biochemical and metabolic; - Delayed effects; Effects On Newborn. Reference: Developmental Pharmacology and Therapeutics 10:385, 1987.

4. Author not provided, as cited in RTECS®.
   Rabbits were exposed via an unreported route to 120 µg/kg on gd 6-29. Toxic effects included: Effects On Newborn- Weaning or lactation index. Reference: Contraception 17:489, 1978.

5. Author not provided, as cited in RTECS®.
   Rats were exposed via intramuscular injection to 110 mg/kg on gd 1-22. Toxic effects included: Effects On Newborn. Reference: Journal of Clinical Investigation 41:710, 1962.

6. Author not provided, as cited in RTECS®.
   Rats were exposed via intramuscular injection to 30 mg/kg on gd 1-6. Toxic effects included: Effects On Embryo Or Fetus- Fetotoxicity. Reference: Folia Biologica 16:343, 1968.

7. Author not provided, as cited in RTECS®.
   Rats were exposed via intramuscular injection to 35 mg/kg on gd 4-20. Toxic effects included: Effects On Embryo Or Fetus- Extra embryonic structures. Reference: Folia Biologica 16:343, 1968.

8. Author not provided, as cited in RTECS®.
   Rats were exposed via parenteral route to 36,300 µg/kg on gd 7-17. Toxic effects included: Specific Developmental Abnormalities- Central nervous system; Effects On Newborn- Biochemical and metabolic. Reference: Brain Research 170:194, 1979.

9. Author not provided, as cited in RTECS®.
   Rats were exposed via a parenteral route to 60 µg/kg on gd 16-19. Toxic effects included: Specific Developmental Abnormalities- Blood and lymphatic systems (including spleen and marrow). Reference: Bulletin of Experimental Biology and Medicine 82:1561, 1976.

10. Author not provided, as cited in RTECS®.

11. Author not provided, as cited in RTECS®.
    Rats were exposed via subcutaneous injection to 4 mg/kg on gd 9. Toxic effects included: Specific Developmental Abnormalities- Central nervous system. Reference: Bulletin of Experimental Biology and Medicine 74:1255, 1972.

12. Author not provided, as cited in RTECS®.
    Rats were exposed via subcutaneous injection to 420 mg/kg on gd 15-17. Toxic effects included: Effects On Embryo Or Fetus- Fetal death. Reference: Endocrinology 75:145, 1964.

13. Author not provided, as cited in RTECS®.
    Rats were exposed via subcutaneous injection to 9 mg/kg on gd 15-20. Toxic effects included: Specific Developmental Abnormalities- Urogenital system. Reference: Journal of Reproduction and Fertility 5:331, 1963.

14. Foote et al. (1968), as cited in IARC, RTECS®.
    Female guinea pigs were administered s.c. injections of 1 mg progesterone from day 18 after mating to day 60. No masculinization was reported in fetuses, but abnormalities (undefined) of the urogenital system were reported.

    Mice were injected with 0.25 mg from gd 16-19. No effects on female external genitalia were found.

16. Keeler and Binns (1968), as cited in IARC.
    Ewes were given oral doses of 1.3-1.8 mg on gd 14. No toxic or teratogenic effects on the offspring were found.

17. Lerner et al. (1962), as cited in IARC.
    Rats were administered 2.5-10 mg on gd 14-19 and no apparent virilizing effects were reported.
18. McCarthy et al. (1977), as cited in IARC.
   Rabbits were administered injections of 0.5, 1.0 and 1.0 mg progesterone 2 days before mating, 1 day before
   mating or on the day of mating (respectively). This led to embryonic deaths by day 4 of gestation.
19. Piotrowski (1969), as cited in IARC.
   Rabbits were administered injections of 30 mg/kg on gd 8-16. Virilization of fetuses (increased anourethral
distance in both sexes) and an excess of males were reported.
20. Revesz et al. (1960), as cited in Shepard’s Catalog of Teratogenic Agents, IARC.
   Rats were exposed to up to 5-200 mg per day on gd 15-20. No abnormalities of the external genitalia of
   offspring were found.
   No virilizing effects were found in rat fetuses exposed to progesterone.
22. Wharton and Scott (1964), as cited in IARC.
   Monkeys (rhesus) were given i.m. doses of 50 mg 5 days/week from gd 24-28 to term. No change in duration
   of pregnancy and no anomalies in the offspring were reported.

Female reproductive toxicity in humans

1. Author not provided, as cited in RTECS®.
   Women were exposed intravaginally to 210 mg/kg on 3W prior to mating. Toxic effects included: Maternal
   Effects- Menstrual cycle changes or disorders. Reference: American Journal of Obstetrics and Gynecology
   76:626, 1958.
2. Author not provided, as cited in RTECS®.
   Women were exposed intravaginally to 475 µg/kg for 1Y prior to mating. Toxic effects included: Maternal
   Effects- Menstrual cycle changes or disorders; Effects On Fertility - Female fertility index. Reference:
3. Author not provided, as cited in RTECS®.
   Women were exposed orally to 100 mg/kg on 20D prior to mating. Toxic effects included: Maternal Effects-
4. Author not provided, as cited in RTECS®.
   Women were exposed orally to 120 mg/kg on 20D prior to mating. Toxic effects included: Effects On Fertility
5. Author not provided, as cited in RTECS®.
   Women were exposed orally to 120 mg/kg on 20D prior to mating. Toxic effects included: Maternal Effects-
   Menstrual cycle changes or disorders; Effects On Fertility - Female fertility index; Effects On Fertility - Other
6. Author not provided, as cited in RTECS®.
   Women were exposed orally to 200 mg/kg on 20D prior to mating. Toxic effects included: Maternal Effects-
7. Author not provided, as cited in RTECS®.
   Women were exposed via a parenteral route to 32 mg/kg on 3W prior to mating. Toxic effects included:
   Maternal Effects- Menstrual cycle changes or disorders. Reference: American Journal of Obstetrics and

Female reproductive toxicity in animals

1. Author not provided, as cited in RTECS®.
   Dogs were exposed via implant to 360 mg/kg on 34W prior to mating. Toxic effects included: Effects On
2. Author not provided, as cited in RTECS®.
   Goats/Sheep were exposed via intramuscular injection to 2545 µg /kg on 7D prior to mating. Toxic effects
   included: Maternal Effects- Menstrual cycle changes or disorders; Effects On Fertility - Female fertility index.
3. Author not provided, as cited in RTECS®.
   Goats/Sheep were exposed via subcutaneous injection to 1.273 mg/kg for 14 days. Toxic effects included:
   Maternal Effects: menstrual cycle changes or disorders; Effects On Fertility - Other measures of fertility.

4. Author not provided, as cited in RTECS®.
   Hamsters were exposed via a parenteral route to 2400 µg/kg on 3D prior to mating. Toxic effects included:

5. Author not provided, as cited in RTECS®.
   Hamsters were exposed via subcutaneous injection to 240 µg/kg on 1D prior to mating. Toxic effects included:

6. Author not provided, as cited in RTECS®.
   Hamsters were exposed via subcutaneous injection to 32 mg/kg on 1D prior to mating. Toxic effects included:

7. Author not provided, as cited in RTECS®.
   Mice were exposed via subcutaneous injection to 100 mg/kg on 1D of pregnancy. Toxic effects included:

8. Author not provided, as cited in RTECS®.
   Mice were exposed via subcutaneous injection to 20 mg/kg on gd 6-9. Toxic effects included: Effects On Fertility - Post-implantation mortality; Effects On Embryo Or Fetus - Fetotoxicity. Reference: Oyo Yakuri. Pharmacometrics 15:955, 1978.

9. Author not provided, as cited in RTECS®.
   Mice were exposed via an unreported route to 10 mg/kg on 1D prior to mating. Toxic effects included: Effects On Fertility - Other measures of fertility. Reference: Fertility and Sterility 12:346, 1961.

10. Author not provided, as cited in RTECS®.
    Monkeys were exposed via inhalation to 4 µg/kg on 10D prior to mating. Toxic effects included: Effects On Fertility - Other measures of fertility. Reference: Nature 270:532, 1977.

11. Author not provided, as cited in RTECS®.
    Monkeys were exposed via intramuscular injection to 12 mg/kg on 8D prior to mating. Toxic effects included:

12. Author not provided, as cited in RTECS®.
    Monkeys were exposed via subcutaneous injection to 900 µg/kg on 9D prior to mating. Toxic effects included:

13. Author not provided, as cited in RTECS®.
    Pigs were exposed via subcutaneous injection to 1667 µg/kg on 1D prior to mating. Toxic effects included:

14. Author not provided, as cited in RTECS®.
    Pigs were exposed via subcutaneous injection to 2250 µg/kg on gd 1-5. Toxic effects included: Effects On Fertility - Other measures of fertility. Reference: Journal of Animal Science 18:163, 1959.

15. Author not provided, as cited in RTECS®.
    Rabbits were exposed via intramuscular injection to 2500 mg/kg on 2D prior to mating. Toxic effects included:

16. Author not provided, as cited in RTECS®.

17. Author not provided, as cited in RTECS®.
    Rabbits were exposed via an intrauterine route to 105 µg/kg on 21D prior to mating. Toxic effects included:
18. Author not provided, as cited in RTECS®.
Rabbits were exposed via an intrauterine route to 260 µg/kg on 21D prior to mating and gd 1-31. Toxic effects included: Effects On Fertility - Post-implantation mortality. Reference: Contraception 17:465, 1978.

19. Author not provided, as cited in RTECS®.

20. Author not provided, as cited in RTECS®.
Rabbits were exposed orally to 1 mg/kg on 1D prior to mating and gd 1. Toxic effects included: Effects On Fertility - Other measures of fertility. Reference: Endocrinology 79:939, 1966.

21. Author not provided, as cited in RTECS®.
Rabbits were exposed orally to 100 mg/kg on 1D prior to mating. Toxic effects included: Effects On Fertility - Mating Performance; Effects On Fertility - Other measures of fertility. Reference: Acta Endocrinologica, Supplementum 73:17, 1963.

22. Author not provided, as cited in RTECS®.
Rabbits were exposed orally to 1 mg/kg on 1D prior to mating. Toxic effects included: Effects On Fertility - Other measures of fertility. Reference: Steroids 5:699, 1965.

23. Author not provided, as cited in RTECS®.
Rabbits were exposed via subcutaneous injection to 100 µg/kg on 1D prior to mating. Toxic effects included: Maternal Effects- Ovaries, fallopian tubes. Reference: Journal of Physiology 181:568, 1965.

24. Author not provided, as cited in RTECS®.

25. Author not provided, as cited in RTECS®.

26. Author not provided, as cited in RTECS®.
Rabbits were exposed via subcutaneous injection to 50 µg/kg on 1D prior to mating. Toxic effects included: Effects On Fertility - Other measures of fertility. Reference: Acta Endocrinologica, Supplementum 73:3, 1963.

27. Author not provided, as cited in RTECS®.
Rats were exposed intracerebrally to 250 µg/kg on 1D prior to mating. Toxic effects included: Effects On Fertility - Other measures of fertility. Reference: Journal of Reproduction and Fertility 27:445, 1971.

28. Author not provided, as cited in RTECS®.
Rats were exposed via intramuscular injection to 900 µg/kg on gd 6-14. Toxic effects included: Effects On Fertility - Post-implantation mortality. Reference: Folia Biologica 16:343, 1968.

29. Author not provided, as cited in RTECS®.
Rats were exposed orally to 25 mg/kg on 1D prior to mating. Toxic effects included: Effects On Fertility - Mating Performance. Reference: Fertility and Sterility 5:282, 1954.

30. Author not provided, as cited in RTECS®.
Rats were exposed orally to 50 mg/kg on 1D prior to mating. Toxic effects included: Effects On Fertility - Mating Performance. Reference: Acta Endocrinologica, Supplementum 28:18, 1956.

31. Author not provided, as cited in RTECS®.
34. Author not provided, as cited in RTECS®. Cattle were exposed via intramuscular injection to 1700 µg/kg on 39-41W of pregnancy. Toxic effects included: Maternal Effects- Parturition. Reference: Theriogenology 20:267, 1983.
35. Author not provided, as cited in RTECS®. Dogs were exposed via implant to 600 mg/kg on week 60 prior to mating. Toxic effects included: Maternal Effects- Breasts, lactation (prior to or during pregnancy). Reference: Fertility and Sterility 36:373, 1981.
36. Author not provided, as cited in RTECS®. Dogs were exposed via subcutaneous injection to 16 mg/kg on 5D prior to mating. Toxic effects included: Maternal Effects- Uterus, cervix, vagina. Reference: Contraception 12:529, 1975.
37. Author not provided, as cited in RTECS®. Goats/Sheep were exposed via subcutaneous injection to 1273 µg/kg on 14D prior to mating. Toxic effects included: Maternal Effects. Reference: Endocrinology 43:208, 1948.
38. Author not provided, as cited in RTECS®. Hamsters were exposed via subcutaneous injection to 2 mg/kg on 1D prior to mating. Toxic effects included: Maternal Effects- Uterus, cervix, vagina. Reference: Journal of Reproduction and Fertility 42:341, 1975.
40. Author not provided, as cited in RTECS®. Mice were exposed via implant to 3 g/kg on 5D prior to mating. Toxic effects included: Maternal Effects- Uterus, cervix, vagina. Reference: Contraception 16:357, 1977.
41. Author not provided, as cited in RTECS®. Mice were exposed via subcutaneous injection to 1500 µg/kg on 3D prior to mating. Toxic effects included: Maternal Effects- Uterus, cervix, vagina. Reference: Journal of Reproduction and Fertility 5:331, 1963.
42. Author not provided, as cited in RTECS®. Monkeys were exposed intravaginally to 17155 µg/kg on 52W prior to mating. Toxic effects included: Maternal Effects- Ovaries, fallopian tubes. Reference: Contraception 20:339, 1979.
43. Author not provided, as cited in RTECS®. Monkeys were exposed intravaginally to 85410 µg/kg on 52W prior to mating. Toxic effects included: Maternal Effects- Uterus, cervix, vagina; Effects On Fertility - Other measures of fertility. Reference: Contraception 20:339, 1979.
44. Author not provided, as cited in RTECS®. Monkeys were exposed via subcutaneous injection to 2600 µg/kg on 13D prior to mating. Toxic effects included: Maternal Effects- Menstrual cycle changes or disorders. Reference: Proceedings of the Society for Experimental Biology and Medicine 94:298, 1957.
45. Author not provided, as cited in RTECS®. Pigs were exposed via a parenteral route to 5833 µg/kg on 14D prior to mating. Toxic effects included: Maternal Effects- Menstrual cycle changes or disorders. Reference: Journal of Animal Science 10:665, 1951.
46. Author not provided, as cited in RTECS®. Pigs were exposed via subcutaneous injection to 40 mg/kg on 16D prior to mating. Toxic effects included: Maternal Effects- Ovaries, fallopian tubes. Reference: Journal of Reproduction and Fertility 19:541, 1969.
47. Author not provided, as cited in RTECS®. Rabbits were exposed via intramuscular injection to 8 mg/kg on 25-32D of pregnancy. Toxic effects included: Maternal Effects- Postpartum. Reference: Journal of Animal Science 42:131, 1976.
48. Author not provided, as cited in RTECS®. Rabbits were exposed via subcutaneous injection to 50 µg/kg on 5D prior to mating. Toxic effects included: Maternal Effects- Uterus, cervix, vagina. Reference: Anatomical Record 142:469, 1962.
49. Author not provided, as cited in RTECS®. Rats were exposed via implant to 250 µg/kg on 2D after birth. Toxic effects included: Maternal Effects- Postpartum. Reference: Biology of Reproduction 7:109, 1972.
50. Author not provided, as cited in RTECS®.  
Rats were exposed via implant to 30 mg/kg on 24D prior to mating. Toxic effects included: Maternal Effects- Ovaries, fallopian tubes. Reference: Biology of Reproduction 2:315, 1970.

51. Author not provided, as cited in RTECS®.  
Rats were exposed via a parenteral route to 8750 µg /kg on 7D prior to mating. Toxic effects included: Maternal Effects- Uterus, cervix, vagina. Reference: Journal of Experimental Medicine 102:347, 1955.

52. Author not provided, as cited in RTECS®.  
Rats were exposed via subcutaneous injection to 20 mg/kg on gd 23. Toxic effects included: Maternal Effects- Parturition; Maternal Effects- Postpartum; Effects On Newborn- Growth statistics. Reference: Proceedings of the Society for Experimental Biology and Medicine 145:1047, 1974.

53. Author not provided, as cited in RTECS®.  
Rats were exposed via an unreported route to 100 mg/kg on gd 20-24. Toxic effects included: Maternal Effects- Parturition. Reference: Biology of Reproduction 16:479, 1977.

54. Author not provided, as cited in RTECS®.  
Rats were exposed orally to 700 mg/kg on day 14 prior to mating. Toxic effects included: Maternal Effects- Uterus, cervix, vagina. Reference: Fertility and Sterility 24:284, 1973.

55. Author not provided, as cited in RTECS®.  
Rats were exposed via subcutaneous injection to 188 mg/kg on 30D prior to mating. Toxic effects included: Paternal Effects- Menstrual cycle changes or disorders. Reference: Proceedings of the Society for Experimental Biology and Medicine 108:3, 1961.

Male reproductive toxicity in humans

1. Author not provided, as cited in RTECS®.  
Men were exposed via intramuscular injection to 15 mg/kg on 21D prior to mating. Toxic effects included: Paternal Effects - Impotence. Reference: Annals of the New York Academy of Sciences 71:649, 1958.

2. Author not provided, as cited in RTECS®.  
Men were exposed via intramuscular injection to 50 mg/kg on 70D prior to mating. Toxic effects included: Paternal Effects - Spermatogenesis; Paternal Effects - Breast Development. Reference: Annals of the New York Academy of Sciences 71:649, 1958.

Male reproductive toxicity in animals

1. Author not provided, as cited in RTECS®.  
Cattle were exposed via subcutaneous injection to 3 mg/kg on 30D prior to mating. Toxic effects included: Paternal Effects - Spermatogenesis; Paternal Effects - Other effects on. Reference: Endocrinology 77:203, 1965.

2. Author not provided, as cited in RTECS®.  
Guinea pigs were exposed via intramuscular injection to 1480 mg/kg on 70D prior to mating. Toxic effects included: Paternal Effects - Testes, epididymis, sperm duct; Effects On Fertility - Mating Performance. Reference: Nature 209:1322, 1966.

3. Author not provided, as cited in RTECS®.  
Mice were exposed via subcutaneous injection to 2400 mg/kg on 20D prior to mating. Toxic effects included: Paternal Effects - Testes, epididymis, sperm duct. Reference: Endocrinology 28:129, 1941.

4. Author not provided, as cited in RTECS®.  
Monkeys were exposed via inhalation to 30 µg /kg/30 min on 60D prior to mating. Toxic effects included: Paternal Effects - Spermatogenesis; Paternal Effects - Testes, epididymis, sperm duct. Reference: Biology of Reproduction 22:935, 1980.

5. Author not provided, as cited in RTECS®.  
Rabbits were exposed via subcutaneous injection to 70 mg/kg on 14D prior to mating. Toxic effects included: Paternal Effects - Spermatogenesis; Paternal Effects - Other effects on. Reference: Nature 204:261, 1964.
6. Author not provided, as cited in RTECS®.
   Rats were exposed via intramuscular injection to 200 mg/kg on 48D prior to mating. Toxic effects included:
   PATERNAL EFFECTS - Testes, epididymis, sperm duct; PATERNAL EFFECTS - Prostate, seminal vesicle.
   Cowper's gland, accessory glands; PATERNAL EFFECTS - Other effects on. Reference: Indian Journal of
   Experimental Biology 5:45, 1967.

7. Author not provided, as cited in RTECS®.
   Rats were exposed orally to 180 mg/kg on 9D prior to mating. Toxic effects included: PATERNAL EFFECTS

8. Author not provided, as cited in RTECS®.
   Rats were exposed dermally to 240 mg/kg on 30D prior to mating. Toxic effects included: PATERNAL
   EFFECTS - Prostate, seminal vesicle. Cowper's gland, accessory glands; PATERNAL EFFECTS - Prostate,

Secondary Sources


Carcinogenic Risk To Humans, Volume 21. World Health Organization.

Reprotox™. Dr. Anthony M. Scialli. (TOMES APRIL 30, 1995)

(TOMES APRIL 30, 1995)

Shepard’s Catalog of Teratogenic Agents. Dr. Thomas H. Shepard. (TOMES APRIL 30, 1995)
CARBAMAZEPINE:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Note: This chemical is now included for consideration in another group of chemicals.

Carbamazepine (Tegretol, 5H-Dibenz(b,f)azepine-5-carboxamide; CAS no. 298-46-4) is a iminostilbine used as an anticonvulsant, primarily in the treatment of grand mal seizures, and as a specific analgesic for trigeminal neuralgia. It has the chemical formula C₁₅H₁₂N₂O. Carbamazepine is an FDA pregnancy category C drug, and is not a Proposition 65 carcinogen. (Note: the compound 6H-Dibenz(b,f)oxiren(d)azepine-6-carboxamide, 1a, 10b-dihydro-; CAS no. 36507-30-9, chemical formula C₁₅H₁₂N₂O is also identified as carbamazepine in some sources.)

Overview of Developmental/Reproductive Toxicity Concern

There is a DRAFT HIGH level of developmental/reproductive toxicity concern over carbamazepine, due to reports of its developmental toxicity from clinical and epidemiological human studies, and supporting animal studies. The incidence of malformations in children of women taking carbamazepine during pregnancy is reported to be 2-3 times that in general population. Very few studies have investigated effects of carbamazepine on male or female reproduction.

Developmental toxicity

A large body of data from human clinical and epidemiological studies and reports indicates an association between carbamazepine treatment during pregnancy and adverse developmental effects, including the possible existence of a fetal carbamazepine syndrome. Similar results from studies in rats and mice support this association.

Female reproductive toxicity

No data on human female reproductive toxicity associated with carbamazepine were identified. A small number of studies in animals have reported associations between carbamazepine exposure and parameters such as pre- and post-implantation mortality, litter size and live birth index.

Male reproductive toxicity

A single study in human males involving semen analysis revealed no abnormalities other than elevated semen fructose levels, which were considered unlikely to indicate an effect on fertility. A study in rats exposed by injection for 3 months post weaning revealed lowered epididymal sperm count but no effect on fertility.

Overview of Exposure Concern

There is a DRAFT LOW level of concern over exposure to carbamazepine, since it is a drug that is available only under prescription. The therapeutic dose range for carbamazepine is 200-1200 mg/day, resulting in plasma levels of 4-8 µg/ml.

Data on developmental and reproductive toxicity

NOTE: Unless otherwise indicated, all information, including the citation, is obtained from secondary sources. Full citations of all studies are not provided here.
Developmental toxicity in humans

   Women were exposed to a total of 3492 mg/kg throughout pregnancy and to day 17 postnatal. Undefined biochemical and metabolic effects on the newborns were reported.

   Women were exposed to a total of 3492 mg/kg from weeks 26-42 of pregnancy. Undefined abnormalities of skin and appendages in offspring were reported.

   Women were exposed to a total of 96 mg/kg for 3 weeks during pregnancy (period undefined). Undefined abnormalities of the CNS in offspring were reported.

4. Battino et al. (1992), as cited in TERIS.
   Several cohort studies, each involving <100 epileptic women treated with carbamazepine during the first trimester, showed a frequency of malformations 2-3 times higher than normal populations. (This was similar to the incidence in populations of epileptics treated with other anticonvulsants). (See also Lindhout et al. (1982); Lindhout et al. (1992); Kaneko et al. (1988); Nakane et al. (1980); Starreveld-Zimmerman et al. (1973)).

5. Bertollini et al. (1985), as cited in TERIS.
   No association with maternal carbamazepine treatment during pregnancy in 7607 infants with congenital abnormalities in a case-control study.

   Reduced head circumference, body weight and length in offspring of mothers who were treated with carbamazepine during pregnancy.

7. Bod (1989), as cited in TERIS.
   Features of a fetal carbamazepine syndrome of growth and developmental delay associated with minor facial and other anomalies were seen in most of 35 children born to women treated with carbamazepine monotherapy. Malformations included hypoplastic fingernails and craniofacial abnormalities (upslanting eyes, long philtrum, short nose); no increase in major birth defects was observed. The basis for these results has been questioned by some. (See also Jones et al. (1989a); Gladstone et al. (1992); Lindhout et al. (1992b); Rosa (1991)).

8. Czeizel et al. (1992), as cited in Reprotox™, TERIS.
   No association with maternal carbamazepine use was found in a Hungarian case-control study of 10,698 infants with congenital malformations.

9. Gaily et al. (1990a), as cited in TERIS.
   Normal intellectual function and IQ was reported for children aged 5.5 years who had had significantly reduced head circumference at birth, and who’s mothers had been treated with Carbamazepine during pregnancy. Head circumference was not significantly decreased at age 5.5 years. (See also Hiilesma et al., (1981); Gaily et al., (1988); (1990b)).

10. Gaily et al. (1990b), as cited in TERIS.
    Normal intellectual function and IQ was reported for children aged 5.5 years who had had significantly reduced head circumference at birth, and who’s mothers had been treated with Carbamazepine during pregnancy. Head circumference was not significantly decreased at age 5.5 years. (See also Hiilesma et al., (1981); Gaily et al., (1988); (1990a)).

11. Gaily et al. (1988), as cited in TERIS.
    Normal intellectual function and IQ was reported for children aged 5.5 years who had had significantly reduced head circumference at birth, and who’s mothers had been treated with Carbamazepine during pregnancy. Head circumference was not significantly decreased at age 5.5 years. (See also Hiilesma et al., (1981); Gaily et al., (1990a); (1990b)).

12. Gladstone et al. (1992), as cited in Reprotox™, Shepard’s Catalog Of Teratogenic Agents, TERIS.
    In a prospective study, one of 23 women treated with carbamazepine give birth to an infant with myelomeningocele. (See also Bod (1989); Jones et al. (1989a); Lindhout et al. (1992b); Rosa (1991)).
    Hiilesmaa et al. (1981), as cited in Shepard’s Catalog of Teratogenic Agents, Schardein, TERIS.
    Reduced head circumference, but no increase in congenital anomalies or mental retardation, in offspring of mothers who were treated with carbamazepine during pregnancy.

13. Jones et al. (1989a), as cited in RTECS®, Reprotox™, Shepard’s Catalog of Teratogenic Agents, Schardein, TERIS.
Features of a fetal carbamazepine syndrome of growth and developmental delay associated with minor facial and other anomalies were seen in most of 35 children born to women treated with carbamazepine monotherapy. Malformations included hypoplastic fingernails and craniofacial abnormalities (upslanting eyes, long philtrum, short nose); no increase in major birth defects was observed. The basis for these results has been questioned by some. (See also Bod (1989); Gladstone et al. (1992); Lindhout et al. (1992b); Rosa (1991)).

14. Jones et al. (1989b), as cited in TERIS. Rebuttal to the criticisms offered to Jones et al. (1989a).

15. Jones et al. (1988), as cited in Reprotox™, Schardein. Increased risk to the unborn baby and association with a number of abnormalities similar to those seen in the fetal hydantoin syndrome suggested. (Abstract only).

16. Kallen et al. (1989), as cited in TERIS. A putative association between gestational carbamazepine exposure and neural tube defects was not statistically confirmed. (See also Bertollini et al. (1985); Czeizel et al. (1992); Omtzigt et al. (1992)).

17. Kallen (1994), as cited in Reprotox™, Shepard’s Catalog of Teratogenic Agents. A nested case-control study found an association between carbamazepine treatment during pregnancy and spina bifida, with an odds ration of 6.0 (C.I. 0.9 - 56.9). Although not statistically significant, this finding was considered very suggestive by the authors of the study.

18. Kaneko et al. (1988), as cited in TERIS. Several cohort studies, each involving <100 epileptic women treated with carbamazepine during the first trimester, showed a frequency of malformations 2-3 times higher than normal populations. (This was similar to the incidence in populations of epileptics treated with other anticonvulsants). (See also Battino et al. (1992); Lindhout et al. (1982); Lindhout et al. (1992); Nakane et al. (1980); Starreveld-Zimmerman et al. (1973)). Higher frequencies of anomalies have also been observed among infants born to mothers treated with carbamazepine in combination with other anticonvulsants, especially valproic acid. (See also Lindhout et al. (1984); Kaneko et al. (1988); Shakir and Abdulwahab (1991); Kaneko et al. (1992)).

19. Kaneko et al. (1986), as cited in Shepard’s Catalog of Teratogenic Agents. Statistically significant increase in malformations in offspring of women treated with carbamazepine and another drug (except valproic acid). Kaneko et al. (1992), as cited TERIS. Higher frequencies of anomalies have been observed among infants born to mothers treated with carbamazepine in combination with other anticonvulsants, especially valproic acid. (See also Lindhout et al. (1984); Kaneko et al. (1988); Shakir and Abdulwahab (1991); Kaneko et al. (1992)).

20. Legido et al. (1991), as cited in Reprotox™, Schardein. Case report of effects that included some or all of the following: spina bifida, rib anomalies, optic nerve hypoplasia, retardation. No comparison was done with successful pregnancies in the same time span. (See also West et al. (1990); Vestermark and Vestermark (1991); Oakeshott and Hunt (1991)).

21. Lindhout et al. (1984), as cited in Reprotox™, TERIS. Higher frequencies of anomalies have been observed among infants born to mothers treated with carbamazepine in combination with other anticonvulsants, especially valproic acid. This increased risk may putatively be due to an accumulation of carbamazepine epoxide. (See also Kaneko et al. (1988); Shakir and Abdulwahab (1991); Kaneko et al. (1992)).

22. Lindhout et al. (1982), as cited in TERIS. Several cohort studies, each involving <100 epileptic women treated with carbamazepine during the first trimester, showed a frequency of malformations 2-3 times higher than normal populations. (This was similar to the incidence in populations of epileptics treated with other anticonvulsants). (See also Battino et al. (1992); Lindhout et al. (1992); Kaneko et al. (1988); Nakane et al. (1980); Starreveld-Zimmerman et al. (1973)).

23. Lindhout et al. (1992a), as cited in TERIS. Several cohort studies, each involving <100 epileptic women treated with carbamazepine during the first trimester, showed a frequency of malformations 2-3 times higher than normal populations. (This was similar to the incidence in populations of epileptics treated with other anticonvulsants). (See also Battino et al. (1992); Lindhout et al. (1982); Kaneko et al. (1988); Nakane et al. (1980); Starreveld-Zimmerman et al. (1973)).

24. Lindhout et al. (1992b), as cited in TERIS. Increased frequency of neural tube defects suggested in offspring of women treated with carbamazepine during
pregnancy. (See also Bod (1989); Gladstone et al. (1992); Jones et al. (1989a); Lindhout et al. (1992b); Rosa (1991)).

   Case report of an infant with myelomeningocele that was gestationally exposed to phenobarbital and carbamazepine.

26. Nakane et al. (1980), as cited in Schardein, TERIS.
   Several cohort studies, each involving <100 epileptic women treated with carbamazepine during the first trimester, showed a frequency of malformations 2-3 times higher than normal populations. (This was similar to the incidence in populations of epileptics treated with other anticonvulsants). (See also Battino et al. (1992); Lindhout et al. (1982); Lindhout et al. (1992); Kaneko et al. (1988); Starreveld-Zimmerman et al. (1973)).

27. Niebyl et al. (1979), as cited in Reprotox™, Schardein.
   No obvious teratogenic potential of the drug was noted in humans (no information provided on the type of study).

28. Oakeshott and Hunt (1991), as cited in Reprotox™
   Case report of effects that included some or all of the following: spina bifida, rib anomalies, optic nerve hypoplasia, retardation. No comparison was done with successful pregnancies in the same time span. (See also Legido et al. (1991); West et al. (1990); Vestermark and Vestermark (1991)).

29. Omtzigt et al. (1992), as cited in TERIS.
   A putative association between gestational carbamazepine exposure and neural tube defects was not statistically confirmed. (See also Bertollini et al. (1985); Czeizel et al. (1992); Kallen et al. (1989)).

30. Rosa (1991), as cited in Reprotox™, Shepard’s Catalog of Teratogenic Agents, Schardein, TERIS.
   Increased frequency of neural tube defects suggested in offspring of women treated with carbamazepine during pregnancy; 2 of 107 infants born to women who took carbamazepine during pregnancy had spina bifida (estimated risk from this and other data was 1%). (See also Bod (1989); Gladstone et al. (1992); Jones et al. (1989a); Lindhout et al. (1992b)).

31. Shakir and Abdulwahab (1991), as cited in TERIS.
   Higher frequencies of anomalies have been observed among infants born to mothers treated with carbamazepine in combination with other anticonvulsants, especially valproic acid. (See also Kaneko et al. (1992); Lindhout et al. (1984); Kaneko et al. (1988)).

32. Starreveld-Zimmerman et al. (1973), as cited in TERIS.
   Several cohort studies, each involving <100 epileptic women treated with carbamazepine during the first trimester, showed a frequency of malformations 2-3 times higher than normal populations. (This was similar to the incidence in populations of epileptics treated with other anticonvulsants). (See also Battino et al. (1992); Lindhout et al. (1982); Lindhout et al. (1992); Kaneko et al. (1988); Nakane et al. (1980)).

33. Van Allen et al. (1988), as cited in Shepard’s Catalog of Teratogenic Agents, Schardein, TERIS.
   Use of carbamazepine during pregnancy poses a risk of a developmental syndrome including round faces, upslanting palpebral fissures, hypertelorism, hypoplastic nasal bridge, short upturned nose, flamus nevus, large anterior fontanel and variable nail hypoplasia.

34. van der Pol et al. (1991), as cited in TERIS.
   The frequency of neurological dysfunction and school problems were no greater than expected in offspring of epileptic women treated with carbamazepine during pregnancy.

   Case reports of effects that included some or all of the following: spina bifida, rib anomalies, optic nerve hypoplasia, retardation. No comparison was done with successful pregnancies in the same time span. (See also Legido et al. (1991); West et al. (1990); Oakeshott and Hunt (1991)).

36. West et al. (1990), as cited in Reprotox™.
   Case report of effects that included some or all of the following: spina bifida, rib anomalies, optic nerve hypoplasia, retardation. No comparison was done with successful pregnancies in the same time span. (See also Legido et al. (1991); Vestermark and Vestermark (1991); Oakeshott and Hunt (1991)).

Developmental toxicity in animals
Rats were administered a total of 765 mg/kg orally over the period of gd 9-17 (presumably 85mg/kg/d). Fetal death and fetotoxicity (undefined) were reported. (Also cited under animal female reproductive toxicity).

Male and female mice were administered a total of 92 g/kg orally over the period beginning 2 weeks prior to mating and continuing to gd 18 in females. Effects on pre- and post-implantation mortality were reported, as well as fetotoxicity (undefined). (Also cited under animal female reproductive toxicity).

Mice were administered a total of 765 mg/kg orally over the period of gd 7-12. Craniofacial abnormalities including eye, ear, nose and tongue were reported. (Abstract only).

Female rats were administered a total of 3600 mg/kg orally over the period beginning 2 weeks prior to mating and continuing to gd 22. Effects on the live birth index, weaning/lactation index and growth statistics in the newborns were reported. (Abstract only). (Also cited under animal female reproductive toxicity).

5. Finnell and Dansky (1991), as cited in TERIS. 
Offspring of mice treated with 5-100 times the therapeutic dosage had CNS and other anomalies. Teratology studies in mice exposed to 2-10 human therapeutic doses produces inconsistent results. (No information on period, duration or route of exposure).

6. Finnell et al. (1986), as cited in TERIS. 
Offspring of mice treated with 5-100 times the therapeutic dosage had CNS and other anomalies (no information on period, duration or route of exposure).

7. Fritz et al. (1976), as cited in TERIS. 
Teratology studies in mice exposed to 2-10 human therapeutic doses produces inconsistent results (no information on period, duration or route of exposure).

Reported to be teratogenic in mice (no information on dose, route, period or duration of exposure).

Rats exposed to 250 mg/kg/d (period and route not given) had an incidence of 2/135 malformed fetuses.

10. Paulson et al. (1979), as cited in RTECS®, TERIS. 
Offspring of mice treated orally with a total of 9984 mg/kg over gd 8-13 had fetotoxicity described in TERIS as CNS and other anomalies.

11. Sullivan and McElhatton (1977), as cited in RTECS®, TERIS. 
Offspring of mice treated orally with a total of 440 mg/kg over gd 6-16 had abnormalities of the musculoskeletal system.

12. Vorhees et al. (1990), as cited in RTECS®, Shepard’s Catalog of Teratogenic Agents, Schardein, TERIS. 
Rats were gavaged with 200, 400 or 600 mg/kg/d on gd 7-18 (17-25 times human therapeutic doses, produced blood level 2-3 times higher than therapeutic levels in humans). Maternal toxicity occurred at the two higher doses, and fetal weight was reduced at those doses. A dose-dependent increase in congenital anomalies (generalized edema and musculoskeletal abnormalities) was reported, but these may have occurred only at the higher doses. Fetotoxicity (undefined) was reported at the lowest dose level. An increase in post-implantation mortality was reported at the highest dose level. (Also cited under animal female reproductive toxicity).

13. Wray et al. (1982), as cited in TERIS. 
Teratology studies in mice exposed to 2-10 human therapeutic doses produces inconsistent results (no information on period, duration or route of exposure).

Female reproductive toxicity in humans

No studies identified.

Female reproductive toxicity in animals
1. Author not provided. (E. Afr. Med. J. 60:407. 1983), as cited in RTECS®. Rats were administered a total of 765 mg/kg orally over the period of gd 9-17 (presumably 85 mg/kg/d). Effects on litter size (undefined) were reported. (Also cited under animal developmental toxicity).

2. Author not provided. (Terat. Carcinog. Mutag. 6:393. 1986), as cited in RTECS®. Male and female mice were administered a total of 92 g/kg orally over the period beginning 2 weeks prior to mating and continuing to gd 18 in females. Effects on pre- and post-implantation mortality were reported. (Also cited under animal developmental toxicity).

3. Author not provided. (Teratology 29(3):33A. 1984), as cited in RTECS®. Female rats were administered a total of 3600 mg/kg orally over the period beginning 2 weeks prior to mating and continuing to gd 22. Effects on the live birth index, weaning/lactation index and growth statistics in the newborns were reported. (Abstract only). (Also cited under animal developmental toxicity).

4. Vorhees, CV et al. (1990), as cited in RTECS®, Shepard’s Catalog of Teratogenic Agents, Schardein, TERIS. Rats were gavaged with 200, 400 or 600 mg/kg/d on gd 7-18 (17-25 times human therapeutic doses, produced blood level 2-3 times higher than therapeutic levels in humans). Maternal toxicity occurred at the two higher doses, and an increase in post-implantation mortality was reported at the highest dose level. (Also cited under animal developmental toxicity).

Male reproductive toxicity in humans

1. Shechter-Amir et al. (1993), as cited in Reprotox™. Semen analysis in a small number of men who had received carbamazepine for at least three months revealed no abnormalities other than elevated semen fructose levels, which were considered unlikely to indicate an effect on fertility.

Male reproductive toxicity in animals

1. Cohn et al. (1982), as cited in HSDB. Rats exposed by injection (specific route and dose not specified) for 3 months post weaning had lowered epididymal sperm count but no effect on fertility.

Other relevant data

1. Chemical Society (1979), as cited in HSDB. Carbamazepine crosses the placenta rapidly and yields fetal:maternal plasma level ratios of 0.5 - 0.8 (species not defined). Carbamazepine 10,11 epoxide is also present in fetal plasma and tissues.

2. Froesher et al. (1984); Kaneko et al. (1979); Kuhnz et al. (1983); Niebyl et al. (1979); Pynnonen et al. (1977)), as cited in Reprotox™. Carbamazepine enters breast milk at levels 25-70% of that in maternal blood, and accumulation in nursing infants has been reported.


4. Lindhout et al. (1984), as cited in Reprotox™, TERIS. Carbamazepine in combination with other anticonvulsants has been suggested to increase the risk of teratogenesis due to accumulation of carbamazepine epoxide.

5. Omtzigt et al. (1993), as cited in Reprotox™. Suggested that it has not been established whether the presence of carbamazepine epoxide in carbamazepine monotherapy is associated with adverse fetal effects.

Secondary Sources

Reprotox™. Dr. Anthony M. Scialli. (TOMES J ULY 31, 1995)


Shepard’s Catalog of Teratogenic Agents. Dr. Thomas H. Shepard. (TOMES J ULY 31, 1995)