AVAILABILITY OF DRAFT DATA SUMMARIES AND DRAFT PRIORITIES FOR CHEMICALS WITH RESPECT TO THEIR POTENTIAL TO CAUSE BIRTH DEFECTS OR OTHER REPRODUCTIVE HARM

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

OEHHA prioritizes chemicals for consideration by the Developmental and Reproductive Toxicant (DART) Identification Committee of OEHHA's Science Advisory Board by 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 proposed chemicals and evaluating the potential for each chemical to cause birth defects or other reproductive harm 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*. Any information submitted to OEHHA by interested parties was also reviewed. Draft data summaries, which provide a concise overview of the data available from these sources, are prepared for each of these chemicals, and each chemical is given a draft level of hazard concern as a result of this initial evaluation. The particular set of chemicals evaluated below were previously identified as priority candidates for evaluation through an earlier prioritization process, and were prioritized under the present process.

It should be noted that this prioritization process reflects a preliminary, rather than an in-depth review of developmental/reproductive toxicity and exposure data. The purpose of this initial screen is to identify those chemicals of highest toxicological concern so that these can be evaluated in greater detail and then brought before OEHHA's Science Advisory Board. Chemicals are identified on an ongoing basis and will be similarly evaluated by this prioritization process.

Two chemicals (carbamazepine and progesterone) which previously had been postponed, are now being considered in this group. One chemical (phenol) that previously had been considered for administrative listing is now being considered in this group. Finally, five chemicals in this group have been identified as potential candidates for listing through administrative mechanisms (boric acid (including sodium tetraborate), benzo[a]pyrene, carbon dioxide (by inhalation), dichlorophenoxyacetic acid, 2,4 butyl ester [2,4-D butyl ester], endrin). Should it be determined that any or all of these five chemicals are not appropriate candidates for such action, they will resume their status as potential candidates for consideration by the DART Identification Committee.

Name of Chemical and Draft Level of Developmental/Reproductive Toxicity Concern	Draft Level of Exposure Concern	Page
HIGH Developmental/Reproductive Toxicity Concern		
chloroform	high	3
manganese	high	9
phenol	high	17
progesterone	medium	21
carbamazepine •	low	30
MEDIUM-HIGH Developmental/Reproductive Toxicity Concern		
n-hexane	high	37
styrene	high	40
xylenes (mixtures)	high	47
1,1-dichloroethylene	medium	51
folpet	low	55
MEDIUM Developmental/Reproductive Toxicity Concern		
chromium (includes tri and hexavalent forms)	high	58
copper sulfate	medium	62
formamide	low	65
methyl butyl ketone	low	68
toxaphene	low	70
LOW Developmental/Reproductive Toxicity Concern		
1,2-dichloropropane	medium	74
INSUFFICIENT DATA		
beryllium	medium	79
toluene-2,4-diisocyanate	medium	82
Postponed	**Status -** potential candidate for listing through administrative mechanisms	
boric acid [a] sodium tetraborate [a]	1993 U.S EPA documents under evaluation by OEHHA	84
benzo[a]pyrene [a]	1983 IARC review under evaluation by OEHHA	91
carbon dioxide by inhalation [a]	1991 U.S EPA documents under evaluation by OEHHA	95
dichlorophenoxy-acetic acid, 2,4 butyl ester (2,4-D butyl ester) [a]	1988 and 1994 U.S EPA documents under evaluation by OEHHA	99
endrin [a]	1980 U.S EPA document under evaluation by OEHHA	102

• 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.

[a] Potential listing via authoritative bodies provision (22 CCR § 12306)

CHLOROFORM: DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Chloroform (CAS No.67-66-3) is a simple organic compound with the formula $CHCl_3$. It is a liquid at room temperature, with a vapor pressure of 200 mm at 25.9°C. Chloroform is primarily used as a chemical intermediary in the production of fluorocarbon-22 (a fluorocarbon that is not regulated by the Montreal Protocol). It is a by-product of chlorination of water for drinking, swimming, etc., and is widely used as a laboratory and industrial solvent. Chloroform is a Proposition 65 carcinogen. Chloroform's previous use as an anesthetic was discontinued because of its carcinogenicity.

Overview of Developmental/Reproductive Toxicity Concern

OEHHA staff have found that there is a DRAFT **HIGH** level of developmental/reproductive toxicity concern over chloroform due to reports of developmental toxicity including prenatal death, growth retardation and malformations in mice, rats and rabbits. Where exposure parameters have been reported, exposure to atmospheric concentrations between 30 and 37,000 ppm for varying periods and durations have resulted in adverse developmental effects. Oral exposures to between 20 and 400 mg/kg/day have also resulted in adverse developmental effects.

Developmental toxicity

Very few data are available from human studies. A single epidemiological study indicated an association between chloroform concentrations in drinking water, and intrauterine growth retardation. Chloroform crosses the placenta in humans, resulting in concentrations in fetal blood that are greater than maternal blood concentrations.

Studies in several species of laboratory animals have demonstrated that exposure of dams to chloroform during gestation can result in death or growth retardation of the conceptus. There are also studies indicating the potential for *in utero* chloroform exposure via inhalation to induce malformations such as imperforate anus and cleft palate. In several studies, these developmental effects occurred in conjunction with no or minimal reported maternal toxicity, while varying indices of maternal toxicity were reported to co-occur in other studies. Oral exposure of dams to chloroform has also been shown to cause death or growth retardation of the conceptus, but less information is available on potential co-occurrence of maternally toxicity with these developmental outcomes.

Female reproductive toxicity

Several studies in animals that demonstrated developmental toxicity also showed effects on indices of female reproduction, including fertility and conception rate. One recent 2-generation reproduction study reported no effects on fertility in either generation.

Male reproductive toxicity

A small number of studies in animal species have reported various indices of male reproductive toxicity including effects on sperm morphology, conception rate and gonadal atrophy. Other studies have failed to demonstrate such effects, but the comparability of the studies is not clear.

Overview of Exposure Concern

OEHHA staff have found that there is a DRAFT **HIGH** level of concern over exposure to chloroform. The primary environmental source of exposure to chloroform is as a by-product of disinfection by chlorination of drinking water. Chloroform is well absorbed following ingestion of contaminated water, and by inhalation of vapor release from water. Occupational exposures to chloroform may occur due to its large production volume and use in California. A

total of 523.6 million pounds of chloroform was produced in the US in 1989, including production by 10 facilities in California. Under the Toxic Release Inventory (TRI), 110,334 pounds were reported released in California in 1991, and 6,750 pounds in 1993. Chloroform was detected in 116 of 2947 wells sampled in California in 1986. It persists only for a short time due to its tendency to off-gas. It does not bioconcentrate. Chloroform in air has a half-life of approximately 80 days. 22 CCR § 12703(b)(2) provides a categorical exemption for chlorine disinfection from the requirements of the statute as they pertain to levels of exposure that pose no significant risk of cancer.

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. Axelsson *et al*. (1984), as cited in TERIS.
   Epidemiological study of occupational exposures to organic solvents, including chloroform, during the first trimester of pregnancy. No reported increase in frequency of anomalies (n=128 for those reporting exposure to chloroform)).
2. Kramer *et al*. (1992), as cited in TERIS.
   Case-control study. Weak association (adj. OR 1.8, CI 1.1-2.9) with growth retardation in communities with higher than usual drinking water chloroform levels (levels not defined). The study was considered to have serious methodological limitations.
3. Tylleskar-Jensen (1967), as cited in Reprotext®, Barlow and Sullivan.
   Two case reports of eclampsia in women who had worked in laboratories with measured concentration of 100-1,000 ppm chloroform (compared to the recommended exposure limit of 50 ppm at the time). The background incidence in the population was reported to be 1 case per 4,000 pregnancies.

Developmental toxicity in animals

1. Author not provided (1982), as cited in RTECS®.
   Mice were exposed orally to a total of 2115 mg/kg of chloroform over the period beginning 3 weeks prior to mating (both males and females) and continuing until 5 days post-partum (females). Undefined effects on the neonates were reported.
2. Baeder and Hofmann (1988), as cited in ATSDR.
   Rats were exposed to 30, 100 or 300 ppm via inhalation for 7h/day on gd 7-16. Slight growth retardation and empty implantation sites were reported following exposure to 300 ppm.
3. Burkhalter and Balster (1979), as cited in ATSDR, HSDB, RTECS®, Schardein, USEPA HAD, USEPA HEAD.
   Mice were exposed to 31.1 mg/kg/day orally from 21 days prior to mating (males and females) through 7 days post-partum (females). Undefined effects on growth statistics and metabolic and biochemical parameters in newborns were reported. No effects on postnatal behavior of offspring were observed.
4. Dilley *et al*. (1977), as cited in Reprotox™, Reprotext®, Barlow and Sullivan, IARC, USEPA HAD.
   Rats were exposed to 4080 ppm via inhalation on gd 7-14 (daily duration of exposure not defined). Increased post-implantation mortality and decreased fetal weights were reported, but no teratogenic effects. No information on maternal toxicity was provided.
5. Gulati *et al*. (1988), as cited in ATSDR.
   Mice were exposed to chloroform via gavage in a 2-generation reproduction study (dose and period of exposure not reported). No developmental effects on offspring were reported.
6. McKinney *et al*. (1976), as cited in Barlow and Sullivan.
   Mice were exposed orally to chloroform in drinking water at concentrations of 152, 760 or 3,800 ppb prior to mating and during pregnancy. There was a dose-dependent (but unspecified) decrease in embryonic development.

7. Murray *et al*. (1979), as cited in ATSDR, RTECS®, Reprotox™, Reprotext®, TERIS, USEPA HAD, USEPA HEAD.
   Mice were treated with chloroform via inhalation of 100 ppm/7h/day on gd 1-7, gd 8-15 or gd 6-15. Animals treated on gd 1-7 exhibited pre-implantation and post-implantation embryomortality (resorptions). Offspring of animals treated on gd 8-15 exhibited craniofacial abnormalities (including cleft palate, nose and tongue abnormalities), decreased ossification and decreased crown-rump length. Maternal toxicity was reported in some secondary sources.
8. National Toxicology Information Services (NTIS) (date unknown), as cited in RTECS®.
   Rats exposed to 20.1 mg/m^3/1h on gd 7-14 exhibited fetotoxicity and fetal death.
9. Ruddick *et al*. (1980), as cited in Reprotox™, Shepard's Catalog of Teratogenic Agents.
   Rats were treated by gavage with 100 mg/kg on gd 6-15. Maternal and fetal toxicity were reported. (Abstract only).
10. Ruddick *et al*. (1983), as cited in ATSDR, RTECS®, Reprotext®, TERIS, USEPA HAD, USEPA HEAD.
    a. Rats were exposed via oral gavage to 50, 200 or 400 mg/kg/day on gd 5-15. Decreased fetal weight was reported at 400 mg/kg/day, as was maternal toxicity. A higher incidence of sternebral anomalies was also reported at this dose level.
    b. Rabbits were exposed via oral gavage to 50, 200 or 400 mg/kg/day on gd 5-15. The same effects were reported as had been reported for rats.
11. Schwetz (1970), as cited in Reprotox™, Barlow and Sullivan, Schardein.
    a. Mice were exposed via inhalation to 25,000 or 37,000 ppm chloroform for 15 min/day on gd 8-10 or 12-14. These exposures resulted in increased incidence of skeletal and visceral anomalies and cleft palate, and were reported to be embryotoxic but not highly teratogenic. No information on maternal toxicity was provided.
    b. Rats were exposed via inhalation to 25,000 or 37,000 ppm chloroform for 1h/day on gd 9-11 or 13-15. As with mice, these exposures resulted in increased incidence of skeletal and visceral anomalies and cleft palate, and were reported to be embryotoxic but not highly teratogenic. No information on maternal toxicity was provided.
    (Abstract only)
12. Schwetz *et al*. (1974), as cited in IRIS, RTECS®, Reprotox™, Reprotext®, Barlow and Sullivan, TERIS, IARC, USEPA HAD, USEPA HEAD.
    Rats were exposed via inhalation to 30, 100 or 300 ppm for 7h/day on gd 6-15. At the lowest dose tested, decreased fetal crown-rump length and delayed ossification was reported. The intermediate dose resulted in acaudate fetuses with imperforate anuses, and missing ribs, while the highest dose tested caused decreased fetal weight and increased resorptions. Maternal toxicity occurred at the two highest doses tested, but not the lowest.
13. Thompson *et al*. (1974), as cited in ATSDR, IRIS, RTECS®, Reprotox™, Reprotext®, Schardein, TERIS, IARC, USEPA HAD, USEPA HEAD.
    a. Rats were exposed by oral gavage to 20, 50 or 126 mg/kg/day on gd 6-15, in a teratology study. (Doses of 79, 126, 300, 316 and 501 mg/kg/day were used in a preliminary range-finding study). Fetotoxicity including effects on the musculoskeletal system were seen at doses of 50 mg/kg/day and above, concurrent with signs of maternal toxicity (e.g., reduced food consumption, lowered body weight gain). No malformations were reported.
    b. Rabbits were exposed orally to 20, 35 or 50 mg/kg/day on gd 6-18, in a teratology study. (Doses of 63, 100, 159, 251 and 398 mg/kg/day were used in a preliminary range-finding study). Reduced mean fetal weight was observed at doses of 20 and 50 mg/kg/day, and reduced maternal weight gain was observed in the group exposed to 50 mg/kg/day. Resorptions were also reported, but no malformations were observed.
14. York *et al*. (1982), as cited in Reprotox™.
    Developmental delays associated with maternal toxicity were reported following inhalation of methyl chloroform. No information on species, dose or period of exposure was provided.

Female reproductive toxicity in humans

1. Tylleskar-Jensen (1967), as cited in Reprotext®, Barlow and Sullivan.
   Two case reports of eclampsia in women who had worked in laboratories with measured concentration of 100-1,000 ppm chloroform (compared to the recommended exposure limit of 50 ppm at the time). The background incidence in the population was reported to be 1 case per 4,000 pregnancies.

Female reproductive toxicity in animals

1. Baeder and Hofmann (1988), as cited in ATSDR.
   Rats were exposed to 30, 100 or 300 ppm via inhalation for 7h/day on gd 7-16. Decreased conception rate reported following gestational exposure to 300 ppm, but not 100 ppm.
2. Burkhalter and Balster (1979), as cited in ATSDR, HSDB, RTECS®, Schardein, USEPA HAD, USEPA HEAD.
   Mice were exposed to 31.1 mg/kg/day orally from 21 days prior to mating (males and females) through 7 days post-partum (females). No effects on female reproductive parameters were reported.
3. Gulati *et al*. (1988), as cited in ATSDR.
   Mice were exposed to chloroform via gavage in a 2-generation reproduction study (dose and period of exposure not reported). No effects on fertility in either generation were reported.
4. Heywood *et al*. (1979), as cited in ATSDR.
   Dogs were chronically exposed orally to 30 mg/kg/day. No effects on reproductive organs were reported.
5. Murray *et al*. (1979), as cited in ATSDR, RTECS®, Reprotox™, Reprotext®, TERIS, USEPA HAD, USEPA HEAD.
   Mice were treated with chloroform via inhalation at 100 ppm/7h/day on gd 1-7, gd 8-15 or gd 6-15. Animals treated on gd 1-7 exhibited pre-implantation and post-implantation embryomortality (resorptions). Females exposed to this level of chloroform showed decreased ability to maintain pregnancy (consistent with effects reported under developmental toxicity, above).
6. National Cancer Institute (NCI) (1976), as cited in ATSDR.
   a. Rats were exposed chronically via gavage to 200 or 477 mg/kg/day. No histopathological changes in reproductive organs of females were observed.
   b. Mice were also exposed chronically via gavage to 200 or 477 mg/kg/day. Again, no histopathological changes in reproductive organs of females were observed.
7. Palmer *et al*. (1979), as cited in ATSDR, USEPA HEAD.
   Rats were exposed via gavage to chloroform (contained in toothpaste) at levels of 150 and 410 mg/kg/day (duration of exposure not reported). Gonadal atrophy was observed at 410 mg/kg/day exposure, but not 150 mg/kg/day exposure.
8. Schwetz *et al*. (1974), as cited in IRIS, RTECS®, Reprotox™, Reprotext®, Barlow and Sullivan, TERIS, IARC, USEPA HAD, USEPA HEAD.
   Rats were exposed via inhalation to 30, 100 or 300 ppm for 7h/day on gd 6-15. Effects on female fertility index were reported at 300 ppm, but not 30 or 100 ppm, exposure.
9. Thompson *et al*. (1974 , as cited in ATSDR, IRIS, RTECS®, Reprotox™, Reprotext®, Schardein, TERIS, IARC, USEPA HAD, USEPA HEAD.
   Rabbits were exposed orally to 20, 35 or 50 mg/kg/day on gd 6-18. Resorptions were reported (as noted under developmental toxicity, above).
10. Whipple *et al*. (1912), as cited in Barlow and Sullivan.
    Dogs subjected to 2 hours of anesthesia during pregnancy exhibited placental necrosis, sometimes accompanied by placental separation, hemorrhage and prenatal delivery. Hepatotoxicity was observed in the dams.

Male reproductive toxicity in humans

No studies identified.

Male reproductive toxicity in animals

1. Burkhalter and Balster (1979), as cited in ATSDR, HSDB, RTECS®, Schardein, USEPA HAD, USEPA HEAD.
   Mice were exposed to 31.1 mg/kg/day orally from 21 days prior to mating (males and females) through 7 days post-partum (females). No effects on male reproductive parameters were reported.
2. Gulati *et al*. (1988), as cited in ATSDR.
   Mice were exposed to chloroform via gavage in a 2-generation reproduction study (dose and period of exposure not reported). No effects on fertility in either generation were reported.
3. Heywood *et al*. (1979), as cited in ATSDR.
   Dogs were chronically exposed orally to 30 mg/kg/day. No effects on reproductive organs were reported.
4. Jorgenson and Rushbrook (1980), as cited in ATSDR.
   Rats were subacutely exposed via drinking water to 160 mg/kg/day. No histopathological effects were observed in the testes.
5. Land *et al*. (1979), as cited in ATSDR.
   Abstract - appears to be the same study as Land *et al*. (1981).
6. Land *et al*. (1981), as cited in ATSDR, HSDB, Reprotext®.
   Mice were exposed via inhalation to 400 ppm for 4h/day on 5d/week for a total of 28 days exposure. This exposure resulted in a significant increase in the proportion of abnormal sperm observed.
7. National Cancer Institute (NCI) (1976), as cited in ATSDR.
   a. Rats were exposed chronically via gavage to 200 or 477 mg/kg/day. No histopathological changes in reproductive organs of males were observed.
   b. Mice were also exposed chronically via gavage to 200 or 477 mg/kg/day. Again, no histopathological changes in reproductive organs of males were observed.
8. Palmer *et al*. (1979), as cited in ATSDR, USEPA HEAD.
   Rats were exposed via gavage to chloroform (contained in toothpaste) at levels of 150 and 410 mg/kg/day (duration of exposure not reported). Gonadal atrophy was observed at 410 mg/kg/day exposure, but not 150 mg/kg/day exposure.
9. Topham (1981), as cited in HSDB.
   Mice were exposed to chloroform via i.p. injection of 5ml/kg 5 times per day (duration of exposure not reported). These animals tested negative in a sperm morphology assay, with no increase in structural abnormalities in sperm observed.
10. Torkelson *et al*. (1976), as cited in Barlow and Sullivan.
    a. Rats were exposed via inhalation to 25, 50 or 85 ppm for 7h/day, 5d/week for 6 months. At the end of the exposure period, relative testicular weights were increased in the 50 and 85 ppm groups, although no histopathological effects were reported. (Control testicular weights were reported to be unusually low, but the authors still considered the observed effect to be biologically significant).
    b. Guinea pigs were exposed under the same protocol as were the rats. At the end of the exposure period, relative testicular weights were increased in this species also in the 50 and 85 ppm groups, but not statistically significantly. Again, no histopathological effects were reported.
    c. Rabbits were exposed under the same protocol as were the rats. Too few animals were used for effects to be evaluated.
    d. Dogs were exposed under the same protocol as were the rats. Too few animals were used for effects to be evaluated.

Other relevant data

1. American Congress of Government Industrial Hygienists (ACGIH) (1986), as cited in Reprotext®.
   Embryotoxicity of chloroform was taken into account in setting the TLV.
2. Dowty *et al.* (1976), as cited in Reprotox™, Reprotext®, Barlow and Sullivan.
   Chloroform has been demonstrated to cross the placenta in humans, with concentrations in fetal blood exceeding concentrations in maternal blood.

Secondary Sources

ATSDR. (1993) Agency for Toxic Substances and Disease Registry. Toxicological Profile for Chloroform.

Barlow S.M. and Sullivan F.M. (1982) *Reproductive Hazards Of Industrial Chemicals*, Academic Press.

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES JULY 31, 1995)

IARC. International Agency for Research on Cancer (IARC, 1979). *Monographs On The Evaluation Of Carcinogenic Risk To Humans, Volume 20.* World Health Organization.

IRIS®. Integrated Risk Information System. US Environmental Protection Agency. (TOMES JULY 31, 1995)

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

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

RTECS®. Registry of Toxic Effects of Chemical Substances. National Institute of Occupational Safety and Health. (TOMES JULY 31, 1995)

Schardein J. L. (1993) *Chemically Induced Birth Defects*. Second Edition, Marcel Dekker.

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

TERIS. Teratogen Information System. University of Washington. (TOMES JULY 31, 1995)

USEPA HAD. US Environmental Protection Agency. Health Assessment Document for Chloroform. (EPA-600/8-84-004A, 1984).

USEPA HEAD. US Environmental Protection Agency. Health Effects Assessment for Chloroform. (EAP/600/8-89/090, 1988).

MANGANESE:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Manganese (Mn) is a transition metal in the Periodic Table of the elements, which forms numerous compounds. Manganese and its compounds are abundant in the earth's crust (0.1%) and ubiquitous in soils and water. Its main uses are in steel and other alloys. It is also used in dry cell batteries, matches, fireworks, glasses and ceramics, fertilizers, animal feed, fungicides, algaecides, and disinfectants, and also as an oxidizing agent and an organic catalyst. Manganese is an essential nutrient.

Overview of Developmental/Reproductive Toxicity Concern

OEHHA staff have found that there is a DRAFT **HIGH** level of developmental/reproductive toxicity concern. This is primarily due to reports of male reproductive toxicity. Exposure to manganese in human males is known to cause a syndrome which includes loss of libido and impotence. Reduced fertility and adverse effects on male reproductive organs have been reported in experimental animals. There is also evidence for learning disabilities in human children, likely from postnatal exposures. There are reports of developmental toxicity in animals. However, concern for developmental effects is tempered by several reports which have observed no effects, and the use of less relevant routes in some studies.

Developmental Toxicity

There are three reports of an association between elevated Mn levels in children's hair and learning disabilities. However, this likely results from postnatal exposure, and it is not clear what the role of other metals is, or whether other confounders were adequately accounted for. Manganese deficiency has been associated with birth defects in humans in two studies.

There are several reports of adverse developmental effects of high levels of Mn in experimental animals. By oral or inhalation routes, reduced litter and pup weight, postnatal survival and weight gain, and neurobehavioral alterations have been observed. No reports of increased resorptions or malformations by these routes have been found. By injection (or unknown routes) increased resorptions, malformations, and fetal growth retardation have been observed. Several reports have observed no effects on developmental endpoints at high dosages. Manganese deficiency has been shown to be teratogenic in the mouse, rat, rabbit, guinea pig and cow.

Female reproductive toxicity

There is one report in humans of an association between toxicosis of late pregnancy and elevated levels of Mn, Cu, and Ni in blood. The role of other metals and confounding factors is not clear. One study in rats, where females and males were treated at high levels, showed reduced fertility. This may be due to male mediated effects.

Male reproductive toxicity

It is widely accepted that exposure to high levels of Mn dust or in water can cause Mn poisoning (manganism) in humans. This is a neurobehavioral disorder which progresses from vague symptoms including anorexia and insomnia to speech disturbances and emotionalism to major problems with co-ordination and activity. One consistent element of this disorder is early hyposexuality progressing to loss of libido in males. This may be preceded by a temporary increase in libido. In milder cases it may be reversible, but generally not in severe cases. The more severe cases are mostly from Mn miners in other countries. However, one report of battery workers in a European country found reduced fertility at levels where only very subtle neurobehavioral effects were found.

In experimental animals, adverse effects on males have also been found. In two studies in rabbits by intratracheal instillation, degeneration of seminiferous tubules was observed; sterility was also observed in one of these studies. In a study in mice treated with Mn at high levels in food, reduced testes and other sexual organ weight was observed. In a study in rats, where both sexes were treated with Mn in water at high levels, reduced fertility was observed, and reduced serum testosterone in males was observed. Numerous studies using injection have found degeneration of seminiferous tubules and biochemical effects. However, most studies have found no dominant lethal effects. The "manganism" observed in humans does not appear to occur in rodents. It has been hypothesized that manganism involves accumulation of Mn in the "pigmented" regions of the human brain, which are lacking in rodents, and so no effect is observed.

Overview of Exposure Concern

OEHHA staff have found that there is a DRAFT **MEDIUM** level of concern over the extent of exposure to manganese. Manganese is abundant in the earth's crust (0.1%) and ubiquitous in soils and water. Its main uses are in steel and other alloys. It is also used in dry cell batteries, matches, fireworks, glasses and ceramics, fertilizers, animal feed, fungicides, algaecides, disinfectants, and also as an oxidizing agent and an organic catalyst. Essentially all of the US supply of manganese is imported (1.1 billion lbs. were imported in 1988). There are 27 facilities in CA which manufacture or process manganese and manganese compounds. The OSHA permissible exposure limit is 1.0 mg Mn/m^3 (Time Weighted Average).

Manganese is an essential trace element, and "adequate and safe" human intakes are currently established at 2.5-5.0 mg/d for adults and 0.7-1.0 mg/d for infants. The general population exposure from food is approximately 3.8 mg/d (but values may be higher for vegetarians). Several manganese compounds are on the FDA Generally Recognized As Safe (GRAS) list.

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. Barlow and Kapel (1979), as cited in IRIS®.
   An association was reported between elevated Mn levels in hair and learning disabilities in children. (Pihl and Parks (1977) also cited.) (Elevated levels in hair may reflect postnatal exposures).
2. Collipp *et al*. (1983), as cited in IRIS®.
   The level of Mn in hair from learning-disabled children was significantly increased compared to normal children. The level of Mn in hair was shown to increase several fold from birth to 4 months of age. (Elevated levels in hair may reflect postnatal exposure).
3. Kawamura *et al*. (1941), as cited in IRIS®, IPCS.
   Contamination of well water from nearby disposal of dry-cell batteries led to a high level of Mn (estimated at 28 mg/L) in the well water. Intake was estimated at up to 0.8 mg/kg/d for a 70 kg adult. There were 25 cases of Mn poisoning identified, with 3 deaths (1 suicide). Elderly people were most affected, but children appeared unaffected.
4. Kilburn (1987), as cited in ATSDR, TERIS.
   Among 293 Australian aboriginal children born on an island with high levels of Mn, the frequency of congenital abnormalities did not appear to be unusual.
5. Pihl and Parks (1977), as cited in IRIS.
   An association was reported between elevated Mn levels in hair and learning disabilities in children. (Barlow and Kapel (1979) also cited.) (Elevated levels in hair may reflect postnatal exposure).

Developmental toxicity in animals

1. Anotonova (1978), as cited in Barlow and Sullivan.
   Rats were treated with Mn orally (gavage) at 4 - 42.5 mg/kg/d through pregnancy. The 4 mg/kg/d level was regarded as control. Also, there was about 4 - 5 mg/kg/d in the diet of all groups. At 30 and 42.5 mg/kg/d, postnatal survival and weight gain was lower than in groups given 17.5 mg/kg/d and lower. Mean litter size was increased in 7.5-42.5 mg/kg/d groups, and mean weight of pups increased in 7.5 - 17.5 mg/kg/d groups. This may reflect the role of Mn as an essential nutrient.
2. Benya *et al*. (1981), as cited in Schardein.
   Rats were treated with Mn in the form of cyclopentadienyl manganese tricarbonyl (MMT) (at unknown dosage, etc.). No teratogenicity was observed.
3. Cotzias *et al*. (1976), as cited in IRIS®, Barlow and Sullivan.
   Mice were treated with Mn orally (food) during lactation. At 40 ppm and higher, reduction in body weight at 30 days of age was observed. At 1000 ppm and higher, postnatal death occurred. Neurochemical alterations were also noted at unknown dosage.
4. Ferm (1972), as cited in Barlow and Sullivan, Schardein, TERIS.
   Hamsters were treated with Mn by injection (iv) at 10-35 mg/kg on gd 8. At 35 mg/kg, 2/3rds of the mothers died. Increased resorptions but no malformations were observed.
5. Food and Drug Laboratories Inc. (1973), as cited in Barlow and Sullivan, TERIS.
   a. Rats were treated with Mn orally (gavage) up to 78.3 mg/kg for gd 6-15. No effect on maternal body weight, implants/dam, resorptions/dam, live fetuses/dam, malformations, or fetal weight was observed.
   b. Hamsters were treated with Mn orally (gavage) up to 136 mg/kg for gd 6-10. No effect on maternal body weight, implants/dam, resorptions/dam, live fetuses/dam, malformations, or fetal weight was observed.
   c. Rabbits were treated with Mn orally (gavage) up to 112 mg/kg for gd 6-18. No effect on maternal body weight, implants/dam, resorptions/dam, live fetuses/dam, malformations, or fetal weight was observed.
6. Hanlon *et al*. (1975), as cited in Barlow and Sullivan.
   Hamsters were treated with Mn at 1.36 mg/kg on gd 8. No embryolethality or teratogenicity was observed.
7. Hoppe *et al*. (1979), as cited in Schardein.
   Rats were treated with Mn in the form of bis(3,4,5-trimethoxy-B-phenethylammonium) tetrachloromanganate (II) (dosage etc. unknown). No teratogenicity was observed.
8. Jarvinen and Ahlstrom (1975), as cited in Barlow and Sullivan, USEPA HAD.
   Rats (female) were treated with Mn orally (food) at 4-1004 ppm from weaning to 8 weeks of age, mated with untreated males, and treatment continued through pregnancy. No effects on maternal weight gain, implants/dam, resorptions/dam, dead fetuses/dam, or malformations were observed. (Also cited under female repro.)
9. Kimmel *et al*. (1974), as cited in Barlow and Sullivan.
   Rats were treated with Mn by injection (ip) at 10 mg/kg/d for gd 8-10. No significant effect on implantations, resorptions, malformations, or fetal weight was observed.
10. Kontur and Fechter (1985, 1988), as cited in ATSDR, IRIS®, Reprotox™.
    Rats were treated with Mn orally (water) at up to 20,000 ppm on gd 1-20. No significant effects on litter size or neurotoxicity were observed. At 20,000 ppm reduced maternal water intake, and reduced litter weight was observed. No effect on litter size or neurotoxicity was observed. (Also cited under female repro.)
11. Laskey *et al*. (1982), as cited in ATSDR, Reprotox™, Reprotext®, USEPA HAD.
    Rats were treated with Mn orally (food) at 0, 350, 1,050, or 3,500 ppm added to normal diet (50 ppm). Pregnant females were treated from gd 2 through birth and offspring to 224 days of age. In male offspring, a dose-related decrease in serum testosterone, but no effect on serum LH was observed. When males and females were mated within dose groups, reduced fertility at 3,500 ppm, but no effect on litter size, number of ovulations, resorptions, preimplantation loss, or fetal weight was observed. (Also cited under male and female repro sections.)
12. Lown *et al*. (1984), as cited in ATSDR, IRIS®, Reprotox™.
    Mice were treated with Mn (as MnO_2) by inhalation at 49.1 mg/m^3 for the first 12 weeks and 85.3 mg/m^3 thereafter for 7 hr/d, 5 d/wk for 16 weeks prior to conception and for 18 days following conception (gd 1-18). Cross-fostering was used to separate pre- and post-natal exposure effects. Reduced pup weight was observed. In prenatally exposed offspring, reduced scores on activity measures (open field, roto-rod, and exploration) and retarded growth persisting into adulthood were observed. In offspring of non-exposed mice cross-fostered to exposed mothers, a reduction in roto-rod performance was observed. (Also cited in female reproductive section.)
13. Massaro *et al*. (1980), as cited in Reprotox™, Schardein, TERIS.
    Mice were treated with Mn (as Mn oxide) by inhalation at 949 mg/m^3 for 7 hr/d during pregnancy. Postnatal

behavioral effects, but no structural defects were observed. (Note: abstract, some of the same authors as Lown et al. (1984).)

14. Sanchez *et al*. (1993a), as cited in Reprotext®.
    Mice were treated with Mn (by unknown route) at 2, 4, 8, or 16 mg/kg/d during pregnancy. At 4-16 mg/kg/d late resorptions were increased, at 8-16 mg/kg/d fetotoxicity (undefined) was increased, and signs of maternal toxicity were observed. A NOAEL of 2 mg/kg/d for embryo- or fetotoxicity was observed.
15. Sanchez *et al*. (1993b), as cited in TERIS.
    Mice were treated with Mn (by unknown route) at 8-16 mg/kg/d during pregnancy. Increased death, malformations, and growth retardation were observed in offspring. (Note: probably abstract, probably redundant to Sanchez et al. (1993a).)
16. Seth *et al*. (1977), as cited in Barlow and Sullivan.
    Rats were treated with Mn (as $MnCl_2$) orally (gavage) at 15 mg/kg/d from lactation day 2 to the end of lactation. In pups, elevated brain levels of Mn, and some changes in enzyme levels in the brain were observed. No effect of body weight or developmental landmarks was observed.
17. Tsujii and Hoshishima (1979), as cited in Reprotext®.
    Mice (not clear if pregnant females or young pups) were treated with Mn by injection of trace amounts. Improved learning in the offspring was observed.
18. Wade (1975), as cited in Barlow and Sullivan.
    Pigs were treated with Mn by injection (ip) at 0.5 mg/kg/d for 1 or 2 weekly doses during the last month of pregnancy. Reduced live births, 35-day survival, and 35-day old weight were observed. {Dissertation abstract}
19. Webster and Valios (1987), as cited in ATSDR, TERIS.
    Mice were treated with a single dose of Mn by injection (ip) at 12.5-50 mg/kg during pregnancy. Increased exencephaly, embryonic loss and fetal growth retardation were observed.

Female reproductive toxicity in humans

1. Leonov *et al*. (1971), as cited in Barlow and Sullivan.
   Toxicosis in late pregnancy was associated with higher maternal blood levels of Mn, Cu, and Ni. There was no association between toxicosis in the first half of pregnancy and Mn blood levels.

Female reproductive toxicity in animals

1. Jarvinen and Ahlstrom (1975), as cited in Barlow and Sullivan, USEPA HAD.
   Rats (female) were treated with Mn orally (food) at 4-1004 ppm from weaning to 8 weeks of age, mated with untreated males, and treatment continued through pregnancy. No effects on maternal weight gain, implants/dam, resorptions/dam, dead fetuses/dam, or malformations were observed. (Also cited under developmental.)

2. Kontur and Fechter (1985, 1988), as cited in ATSDR, IRIS®, Reprotox™.
   Rats were treated with Mn orally (water) at up to 20,000 ppm on gd 1-20. No significant effects on litter size or neurotoxicity were observed. At 20,000 ppm reduced maternal water intake, and reduced litter weight was observed. No effect on litter size or neurotoxicity was observed. (Also cited under developmental section.)
3. Laskey *et al*. (1982), as cited in ATSDR, Reprotox™, Reprotext®, USEPA HAD.
   Rats were treated with Mn orally (food) at 0, 350, 1,050, or 3,500 ppm added to normal diet (50 ppm). Pregnant females were treated from gd 2 through birth and offspring to 224 days of age. In male offspring, a dose-related decrease in serum testosterone, but no effect on serum LH was observed. When males and females were mated within dose groups, reduced fertility at 3,500 ppm, but no effect on litter size, number of ovulations, resorptions, preimplantation loss, or fetal weight was observed. (Also cited under developmental and male repro sections.)
4. Lown *et al*. (1984), as cited in ATSDR, IRIS®, Reprotox™.
   Mice were treated with Mn (as MnO_2) by inhalation at 49.1 mg/m^3 for the first 12 weeks and 85.3 mg/m^3 thereafter for 7 hr/d, 5 d/wk for 16 weeks prior to conception and for 18 days following conception (gd 1-18). Cross-fostering was used to separate pre- and post-natal exposure effects. Reduced pup weight was observed. In prenatally-exposed offspring, reduced scores on activity measures (open field, roto-rod, and exploration) and

retarded growth persisting into adulthood were observed. In offspring of non-exposed mice cross-fostered to exposed mothers, a reduction in roto-rod performance was observed. (Also cited under developmental section.)

Male reproductive toxicity in humans

1. Alessio *et al*. (1989), as cited in IRIS®.
   A study of 14 workers exposed to Mn at <1 mg/m^3 showed that FSH and LH levels were not significantly different from controls, although prolactin and cortisol levels were significantly higher.
2. Chandra *et al*. (1974), as cited in USEPA HAD.
   Impaired sexual behavior (diminished libido or impotence) was reported in workers showing symptoms of manganism (manganese poisoning).
3. Cook *et al*. (1974), as cited in IRIS®, USEPA HAD.
   Impaired sexual behavior (diminished libido or impotence) was reported in workers showing symptoms of manganism (manganese poisoning).
4. Emara *et al*. (1971), as cited in ATSDR, USEPA HAD.
   Impotence and loss of libido were reported in cases of manganism in the dry battery industry.
5. Gennert (1992), as cited in IRIS®.
   Alkaline battery plant workers (n=70) exposed to 0.215 mg/m^3 (respirable dust, TWA) for 5.3 years average were evaluated. Fertility was not different from controls, and no difference in serum FSH, LH or prolactin levels was found. (Note: same population as Roels et al. (1992).)
6. Lauwerys *et al*. (1985), as cited in ATSDR, IRIS®,Reprotext®.
   Male workers were exposed to Mn dust at 0.07-8.61 mg/m^3 (median 0.97 mg/m^3) for 1-19 years (average 7.9 years). A decrease in the number of children born to workers in the 16-25 and 26-35 year old groups when compared to controls was reported. A LOAEL of 0.34 mg/m^3 was identified. This corresponds to the LOAEL reported for neurobehavioral disturbances in another study of the same population (Roels et al. (1987): not cited here).
7. Mandzgaladze (1967), as cited in IPCS.
   The wives of workers in various manganese processing plants found that spontaneous abortions were increased (13.8% vs. 8.1% control) and stillbirths increased (3.2% vs. 1.7% control). The frequency of spontaneous abortions increased with duration of exposure. No information on the work status of wives was given. (Note: study also appears to contain animal experimental data: see Mandzgaladze (1966).)
8. Mena *et al*. (1967), as cited in ATSDR, Barlow and Sullivan, USEPA HAD.
   A study of 13 Chilean miners with chronic, severe manganese poisoning found that 8 complained of sexual impotence. This symptom was not found in 14 healthy miners of the same age range.
9. Rodier (1955), as cited in ATSDR, IRIS®, Barlow and Sullivan, USEPA HAD, IPCS.
   A study of Moroccan miners with manganese poisoning found that 150 cases were reported out of about 4,000 employees. Miners engaged in drilling blast holes accounted for 132 of these cases. The concentration of Mn in the air was reported to be about 450 mg/m^3 in one mine, and 250 mg/m^3 in another mine. Of the miners with manganese poisoning, impotence was reported in 80%, and urinary ketosteroids were reduced, suggesting reduced testosterone secretion, in 81%.
10. Roels *et al*. (1992), as cited in IRIS®.
    A group of alkaline battery plant workers was evaluated. Serum levels of certain reproductive hormones (FSH, LH, and prolactin) were not significantly different from controls. (Note: this is the same population studied by Gennart et al. (1992).)
11. Schuler *et al*. (1957), as cited in ATSDR, Barlow and Sullivan.
    A study of 15 Chilean workers with severe Mn poisoning found that 4 reported diminution or abolition of libido with delay in ejaculation in 3 of the 4.

Male reproductive toxicity in animals

1. Chandra (1971), as cited in Barlow and Sullivan, USEPA HAD.
   Rats (male) were treated with Mn by injection (ip) at 8 mg/kg/d for up to 180 days. After 150 days, marked

degeneration of seminiferous tubules, depletion or absence of spermatids and spermatocytes and degenerated spermatogenic cells were observed.

2. Chandra *et al*. (1973), as cited in ATSDR, Barlow and Sullivan, USEPA HAD.
   Rabbits (male) were treated with Mn by intratracheal injection at 250 mg/kg. After 4 months, testicular edema, degeneration of seminiferous tubules, and reduced activity of some enzymes was observed. Females kept with treated males did not become pregnant (no details available).
3. Chandra *et al*. (1975), as cited in ATSDR, Reprotext®, Barlow and Sullivan, IPCS.
   Rats (male) were treated with Mn by injection (ip) at 25-30 days at 6 mg/kg/d. Degeneration of seminiferous tubules, decreased enzyme activity, and increased Mn concentration in testes were observed.
4. Correla Vargus (1984), as cited in Reprotox™.
   Rats (male) treated with manganese (unknown dosage etc.) developed testicular toxicity.
5. Dikshith and Chandra (1978), as cited in Barlow and Sullivan, USEPA HAD.
   Rats (male) were treated with Mn orally at 50 ug/kg/d for 180 days. No chromosomal damage to bone marrow or spermatogonial cells was observed. This dosage is considerably lower than the daily requirement for Mn.
6. Epstein *et al*. (1972), as cited in Barlow and Sullivan, USEPA HAD.
   Mice (male) were treated with Mn by a single injection (ip) at 20 or 100 mg/kg, followed by serial mating. No effects on fertility, or pre- or post-implantation losses were observed.
7. Gray and Laskey (1980), as cited in ATSDR, Reprotext®, Barlow and Sullivan, USEPA HAD.
   Mice (male) were treated with Mn orally (food) at 1040 ppm on postnatal days 15 to 90. Reduced weight of preputial glands, seminal vesicles, and testes was observed.
8. Hejtmancik *et al*. (1978a, 1978 b), as cited in ATSDR.
   Mice and rats were treated with Mn in a chronic toxicity study (NTP study: dosages etc. unknown). No effect on sperm morphology was observed.
9. Imam and Chandra (1975), as cited in Barlow and Sullivan, USEPA HAD, IPCS.
   Rabbits (male) were treated with Mn by injection (iv) at 3.5 mg/kg/d for up to 30 days. Degeneration of seminiferous tubules and alterations in enzyme activity were observed.
10. Joardar and Sharma (1990), as cited in Reprotox™.
    Mice were treated with Mn (dosage etc. unknown). Clastogenic effects and abnormal sperm head formation were observed.
11. Jorgenson *et al*. (1978), as cited in USEPA HAD.
    Rats (male) were treated with Mn orally (gavage) at 3 dose levels (unspecified) 1 or more times in a dominant lethal test procedure. No dominant lethal effects were observed.
12. Laskey *et al*. (1982), as cited in ATSDR, Reprotox™, Reprotext®, USEPA HAD.
    Rats were treated with Mn orally (food) at 0, 350, 1,050, or 3,500 ppm added to normal diet (50 ppm). Pregnant females were treated from gd 2 through birth and offspring to 224 days of age. In male offspring, a dose-related decrease in serum testosterone, but no effect on serum LH was observed. When males and females were mated within dose groups, reduced fertility at 3,500 ppm, but no effect on litter size, number of ovulations, resorptions, preimplantation loss, or fetal weight was observed. (Also cited under developmental and female repro sections.)
13. Laskey *et al*. (1985), as cited in ATSDR, Reprotext®.
    Rats (male) were treated with Mn orally (dosage etc. unknown). Reduced testosterone levels, but no effect on LH or FSH were observed.
14. Mandzgaladze (1966), as cited in IPCS.
    Rats (male) were treated with Mn orally or by inhalation for various periods. Changes in spermatogenesis and effects on embryogenesis were observed. (Mandzgaladze (1967) also cited.)
15. Saakadze and Vasiolov (1977), as cited in Reprotext.
    Mice (male) treated with Mn did not show dominant lethal effects (dosage etc. unknown).
16. Seth *et al*. (1973), as cited in ATSDR, Reprotext®, USEPA HAD.
    Rabbits (male) were treated with Mn by a single intratracheal instillation at 160 mg/kg . After 2 months, degenerative changes in seminiferous tubules, which increased in severity after 8 months, were observed.
17. Shukla and Chandra (1977), as cited in USEPA HAD.
    Rats (male) were treated with Mn by injection (ip) at 15 mg/kg/d for 15, 30, or 45 days. Degenerative changes of the testes were observed.
18. Shukla and Chandra (1979), as cited in Barlow and Sullivan, USEPA HAD.
    Rats (male) were treated with Mn by multiple injections. Degenerative changes of the testes were observed.

19. Singh *et al*. (1974), as cited in Barlow and Sullivan, USEPA HAD.
    Rats (male) were treated with Mn by injection (ip) at 6 mg/kg/d for 25 days. Degenerative and biochemical changes of the seminiferous tubules were observed.
20. Singh *et al*. (1975), as cited in USEPA HAD.
    Rats (male) were treated with Mn by injection (ip) at 6 mg/kg/d for 25-30 days. Degenerative and biochemical changes of the seminiferous tubules were observed. Zn was protective, but chelating agents were not. (Singh et al. (1974) and Tandon et al. (1975) also cited.)
21. Tandon *et al*. (1975), as cited in USEPA HAD.
    Rats (male) were treated with Mn by injection (ip) at 6 mg/kg/d for 25-30 days. Degenerative and biochemical changes of the seminiferous tubules were observed. Zn was protective, but chelating agents were not. (Singh et al. (1974, 1975) also cited.)

Other relevant data

Manganese is an essential nutrient. Under normal circumstances, Mn levels are tightly controlled by homeostatic mechanisms. Manganese deficiency has been shown to be teratogenic to mouse, rat, rabbit, guinea pig and cow (as cited in Schardein) and has been associated with birth defects in humans in 2 studies (Barlow et al. (1985) and Saner et al. (1985), as cited in Reprotox™). Neonates may be relatively sensitive to Mn toxicity due to reduced ability to eliminate Mn (biliary secretion) and consequent weakness of normal homoeostatic systems.
The requirements for dietary Mn in rats is estimated to be about 50 times higher than humans (as cited in IRIS®). Adverse male reproductive effects in humans are part of a larger neurological disturbance ("manganism"). This is a neurobehavioral disorder which progresses from vague symptoms including anorexia and insomnia to speech disturbances and emotionalism to major problems with co-ordination and activity. Depending upon extent of exposure and individual variability, this disturbance may or may not be reversible. Rodents do not exhibit similar neurological deficits following manganese exposure. This has been hypothesized to be related to the concentration of Mn in pigmented regions of the human brain; rodents have a relative lack of pigmented regions.

Secondary Sources

ATSDR. (1993) Agency for Toxic Substances and Disease Registry. Toxicological Profile for Manganese and Compounds.

Barlow S.M. and Sullivan F.M. (1982) *Reproductive Hazards Of Industrial Chemicals*, Academic Press.

IRIS®. Integrated Risk Information System. US Environmental Protection Agency. (TOMES JULY 31, 1995)

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

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

Schardein J. L. (1993) *Chemically Induced Birth Defects*. Second Edition, Marcel Dekker.

TERIS. Teratogen Information System. University of Washington. (TOMES JULY 31, 1995)

USEPA HAD. US Environmental Protection Agency. Health Assessment Document for Manganese. (EPA Report No. EPA-600/8-83-013F, Accession No. PB 84-229954. 1984)

IPCS. International Programme on Chemical Safety (1981) Environmental Health Criteria No. 17. World Health Organization, Geneva, Switzerland.

PHENOL:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Phenol (CAS No. 108-95-2) is a colorless or white solid when pure, but is usually sold and used in liquid form. Its molecular formula is C_6H_6O. The primary use of phenol is in plastics; it is also used in the production of certain man-made fibers as well as bisphenol-A. Phenol is also used as a slimicide (i.e., for removing molds, etc.), a disinfectant, in medical products, and as a reagent in research laboratories. The USEPA is currently requiring additional testing of developmental neurotoxicity and reproductive toxicity of phenol.

Overview of Developmental/Reproductive Toxicity Concern

OEHHA staff have found that there is a DRAFT **HIGH** level of developmental/reproductive toxicity concern for phenol, based on evidence for developmental toxicity in animals. Prenatal exposure to phenol has been associated with reductions in fetal weight and viability, and with an increase in unusual neurological symptoms.

Developmental toxicity

Epidemiological studies have not associated prenatal exposure to phenol with birth defects in human infants. There is some suggestion of increased spontaneous abortion and alterations in the sex ratio of offspring of phenol-exposed mothers, but this is not well documented in the secondary sources used for prioritization. Use of phenol as a disinfectant or in topical medications postnatally has caused death or grave illness in human newborns. Neonates are thought to be particularly sensitive to phenol-induced toxicity due to the susceptibility of fetal hemoglobin to methemoglobinemia; prenatal exposure to phenol is likely to result in a similar effect.

The most consistent findings of developmental toxicity studies conducted in animals have been decreases in fetal weights and viability. The significant decrease in fetal weights observed in rats has been used by US EPA to set the oral RfDs for chronic and subchronic exposure to phenol. Malformations have been reported in some studies, but not consistently. One study evaluated post-natal effects of phenol given prenatally, by gavage, on a single day. Exposed rat pups appeared to be morphologically normal at birth, but later developed a distinctive paralysis and palsy of the hind-limbs.

Female reproductive toxicity

One report was identified stating that women and men working with pheno-formaldehyde resins were prone to diseases of the uro-genital tract. A multi-generation reproductive toxicity study conducted by the drinking-water route in rats was not reported in enough detail to draw conclusions. Other reports have claimed associations between inhalation exposure to phenol and disruptions of the estrous cycle, or increases in preimplantation embryonic death or postnatal death.

Male reproductive toxicity

One report was identified stating that men and women working with pheno-formaldehyde resins were prone to diseases of the uro-genital tract. There is a case report of impotence following acute phenol poisoning, but this may have been due to generalized CNS effect. A multi-generation reproductive toxicity study conducted by the drinking-water route in rats was not reported in enough detail to draw conclusions.

Overview of Exposure Concern

OEHHA staff have found that there is a DRAFT **HIGH** level of concern over the extent of exposure to phenol. Total US production of phenol in 1993 was reported to be 3.72 billion pounds (HSDB). The housing and construction industries are considered to account for about half of the phenol used in the US, with an additional 10-15% attributed to automotive applications. Manufacture of phenolic resins is the largest single use of phenol,

reported to be 1.182 billion pounds in 1987 (HSDB). Exposures to phenol can occur in the workplace, from environmental media, from contaminated drinking water or foodstuffs, or from use of consumer products containing phenol (ATSDR). Phenol is well absorbed by the oral, inhalation, and dermal routes (Reprotox™).

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. Heinonen *et al.* (1977), as cited in Schardein.
   Data from the Collaborative Perinatal Project gave no evidence for an association between malformations and exposure to topical antimicrobial agents (including phenol) during early pregnancy.
2. Hernberg *et al.* (1983), as cited in Reprotext®.
   "In a Swedish reproductive epidemiological study on occupational exposure to disinfectants which included phenol and other substances, there was no clear association with risk for birth defects."
3. Malysheva (1976), as cited in Reprotext®.
   "One study concluded that phenol altered the sex ratio in rats at 30 mg/m^3 and also implied the same effect in humans."
4. NIOSH (1976), as cited in HSDB.
   Reports of abortion and other toxic symptoms (in humans) after phenol exposure.

Developmental toxicity in animals

1. Chapman *et al.* (1994), as cited in Shepard's Catalog of Teratogenic Agents.
   "Chapman et al ('94) found that at a concentration of 100 micromoles cultured rat embryos had reduced protein content and at 10 and 50 micromolar concentrations the prosencephalic measures were significantly reduced. The effect was seen only when rat hepatic microsomes were used in conjunction with the phenol."
2. Jones-Price *et al.* (1983A), as cited in TERIS, Reprotext®, ATSDR, RTECS.
   Phenol was given to pregnant mice by gavage on gds 6-15 at doses of 0, 70, 140, and 280 mg/kg/day. Decreased maternal weight gain, tremors, and increased maternal mortality occurred at 280 mg/kg/day. In the fetuses: growth retardation, decreased viability, abnormal structural development, and an increased incidence of cleft palate were observed at the 280 mg/kg/day dose level.
3. Jones-Price *et al.* (1983B), as cited in TERIS, Reprotext®, IRIS, ATSDR, RTECS.
   Developmental effects of phenol in rats were evaluated by gavage at 0, 30, 60, and 120 mg/kg/day in distilled water on gds 6-15. No dose-related signs of maternal toxicity or any clinical symptoms of toxicity related to phenol treatment. The most important finding was a highly significant reduction in fetal body weights in the high-dose group. The highest fetal NOAEL was 60 mg/kg/day.
4. Kavlock (1987), as cited in IRIS.
   Pregnant SD rats were given phenol by gavage at doses of 0, 667, and 1000 mg/kg on gd 11. Pups were delivered and postnatal weight, viability, and function were evaluated. Pup weaning weights were decreased in the high dose group. Kidney weights at weaning were decreased in female pups at both doses. The most striking finding was paralysis & palsy in the limbs of pups, which did not become evident until 10-14 days following birth. 667 mg/kg was the LOAEL in this study.
5. Kavlock *et al.* (1987), as cited in IARC.
   "Phenol was one of a series of chemicals used in a structure-activity developmental toxicology study reported in an abstract. The chemicals were administered [route unspecified]to groups of Sprague-Dawley rats on day 11 of gestation at four dose levels between 0 and 1000 mg/kg or added to embryos of the same developmental age in whole embryo culture in vitro. *In vivo*, phenol induced hind-limb and tail defects. *In vitro*, phenol was the least potent of seven congeners tested; the activity, however, was increased following co-culture with primary hepatocytes.".
6. Korshunov (1974), as cited in Reprotext®, Schardein.
   ". . . rats inhaling phenol at 0.5 or 5 mg/m^3 for 3 months . . . caused preimplantation deaths and early postnatal

deaths . . ." Phenol is listed as negative in a table in Schardein's book.

7. Malysheva (1976), as cited in Reprotext®.
   "One study concluded that phenol altered the sex ratio in rats at 30 mg/m^3 and also implied the same effect in humans."
8. Minor and Becker (1971), as cited in Reprotox™, TERIS, Shepard's Catalog of Teratogenic Agents, Reprotext®, RTECS.
   Pregnant rats were given phenol by ip injection on gds 8-10 or 11-13. No adverse fetal effects were reported with doses of up to 200 mg per kg.
9. Price *et al.* (1986), as cited in IARC, TERIS, RTECS. [abstract]
   ". . . groups of 23 CD rats were exposed by oral intubation to 0, 30, 60, or 120 mg/kg bw phenol per day on days 6-15 of gestation and the fetuses examined at term for growth, viability and malformations. There was no evidence of maternal toxicity or teratogenicity, but fetal growth was retarded at the highest dose."
   ". . . groups of CD-1 mice were exposed by oral intubation to 0, 70, 140 and 280 mg/kg bw phenol per day on days 6-15 of gestation. Fetuses were examined for growth, viability and malformations. Maternal and fetal toxicity but no significant evidence of teratogenicity were observed. Greater maternal toxicity as well as cleft palates in the fetus were reported at the high dose."

Female reproductive toxicity in humans

1. Ishchenko *et al.* (1978), as cited in Reprotext®.
   "Women and men working with phenol-formaldehyde resins were reported to suffer from uro-genital diseases."

Female reproductive toxicity in animals

1. Heller (1938), as cited in IRIS, ATSDR.
   Reported normal growth and reproduction with phenol given in drinking water in a multi-generation rat reproduction study. Concentrations used were: 5000 ppm (estimated to equal 686 mg/kg/day) for 3 generations; and 1000 ppm (estimated to equal 137 mg/kg/day) for 5 generations. Not reported in enough detail to be sufficient to setting reliable LOAELs and NOAELs.
2. Kolesnikova (1972), as cited in Reprotext®.
   "Phenol disrupted the estrous cycles in rats inhaling phenol at 0.5 or 5 mg/m^3 for 3 months"
3. Korshunov (1974), as cited in Reprotext®.
   ". . . rats inhaling phenol at 0.5 or 5 mg/m^3 for 3 months . . . caused preimplantation deaths and early postnatal deaths . . ."

Male reproductive toxicity in humans

1. Ishchenko and Pushkina (1978), as cited in Reprotext®.
   "Women and men working with phenol-formaldehyde resins were reported to suffer from uro-genital diseases."
2. O'Donaghue (1985), as cited in Reprotext®.
   Impotence has been reported following acute phenol poisoning in one man. This may have been due to a general CNS effect rather than to a specific effect on the sex organs.

Male reproductive toxicity in animals

1. Heller (1938), as cited in IRIS, ATSDR.
   Reported normal growth and reproduction with phenol given in drinking water in a multi-generation rat reproduction study. Concentrations used were: 5000 ppm (estimated to equal 686 mg/kg/day) for 3 generations; and 1000 ppm (estimated to equal 137 mg/kg/day) for 5 generations. Not reported in enough detail to be sufficient to setting reliable LOAELs and NOAELs.

Other relevant data

Use of phenol as a disinfectant or in topical medications has caused death or grave illness in human newborns

(postnatally). Neonates are thought to be particularly sensitive to phenol-induced toxicity due to their susceptibility to methemoglobinemia.

1. Deichman (1969), as cited in RTECS.
   Toxic effects in infants. LDLo, oral dose 10 mg/kg. Behavioral effects, muscle weakness, cyanosis.
2. Goodman and Gilman's The Pharmacological Basis of Therapeutics (1985), as cited in HSDB.
   Fatal neonatal hyperbilirubinemia from inhalation of phenolic vapors has occurred in poorly ventilated nurseries in which phenol was used to disinfect mattresses and bassinets.
3. Gray and Kavlock (1990), as cited in Shepard's Catalog of Teratogenic Agents, Reprotox™.
   "Gray and Kavlock (1990) fed C14^n-1labeled phenol to rats and determined that the levels in placenta and embryo were equivalent to maternal serum." [Abstract].
4. Hinkel (1968), as cited in HSDB.
   Information taken from citation of this paper in NIOSH, Criteria Document: Phenol, p. 41, 1976; DHEW Pub., NIOSH 76-196. A newborn baby died 11 hours after application of a bandage containing 2% phenol to the umbilicus. Another baby was exposed to phenol when treated for a skin ulcer with a 30% phenol-60% camphor ointment. The baby experienced circulatory failure, cerebral intoxication, and methemoglobinemia. The infant recovered following a blood transfusion.

Secondary Sources

ATSDR. (1989) Agency for Toxic Substances and Disease Registry. Toxicological Profile for Phenol.

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES JANUARY 31, 1997)

IARC. International Agency for Research on Cancer (IARC, 1989). *Monographs On The Evaluation Of Carcinogenic Risk To Humans, Volume 47.* World Health Organization.

IRIS®. Integrated Risk Information System. US Environmental Protection Agency. (TOMES JANUARY 31, 1997)

Reprotox™. Dr. Anthony M. Scialli. (TOMES JANUARY 31, 1997)

Reprotext®. Micromedex, Inc. (TOMES JANUARY 31, 1997)

RTECS®. Registry of Toxic Effects of Chemical Substances. National Institute of Occupational Safety And Health. (TOMES JANUARY 31, 1997)

Schardein J. L. (1993) *Chemically Induced Birth Defects*. Second Edition, Marcel Dekker.

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TERIS. Teratogen Information System. University of Washington. (TOMES JANUARY 31, 1997)

PROGESTERONE: DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

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. Use of progesterone, along with estrogen, for premenstrual and postmenopausal therapy is a recent development. It is also used as a veterinary drug. Progesterone is on the Proposition 65 list as a carcinogen.

Overview of Developmental/Reproductive Toxicity Concern

OEHHA staff have found that there is a DRAFT **HIGH** level of developmental/reproductive toxicity concern over progesterone due to effects on male and female reproductive toxicity endpoints. Progesterone has been reported to cause effects on female fertility that are consistent with therapeutic use as a contraceptive. Other studies report 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.

Female reproductive toxicity

Progesterone has a contraceptive effect that can be used therapeutically for birth control. When exposures occur outside of the context of contraceptive therapy, these effects are equivalent to female reproductive toxicity. RTECS cites 40 studies in animals in which progesterone was administered prior to mating; in 28 of these adverse effects on fertility were reported, and in the other 12 adverse effects on reproductive organs or the menstrual cycle were reported. In 15 studies progesterone was administered during pregnancy and adverse effects on fertility, parturition, or postpartum effects were reported. Test species include mice, rats, rabbits, monkeys, pigs, dogs, horses, and sheep/goats. RTECS also cites 7 human studies in which progesterone was administered prior to mating, and effects were reported on fertility, menstrual cycle and reproductive organs.

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 8 animal studies (including rats, mice, rabbits, guinea pigs, cattle and monkeys) progesterone administered by injection, oral, dermal, or inhalation routes was reported 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

OEHHA staff have found that there is a DRAFT **MEDIUM** level of concern over the extent of exposure to progesterone. Progesterone was formerly used therapeutically for bleeding during pregnancy, infertility, habitual abortion and birth control. Currently, birth control pills use synthetic progestins, rather than progesterone. A recent

PDR reported that one IUD uses progesterone. However, progesterone is available for purchase in numerous commercial products that are not sold or regulated as drugs, such as a dermal patch intended for use for menopausal symptoms. The medical literature also reports progesterone use for premenstrual symptoms. FDA allows use of progesterone in cosmetics in amounts not exceeding 5 mg/oz. There is considerable uncertainty concerning the extent of exposure from commercial products. No quantitative data on exposure were located. 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.
9. Reessiguie *et al*. (1985), as cited in Reprotox ™.
   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: - Delayed effects. 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®.
    Rats were exposed via subcutaneous injection to 1 mg/kg on gd 9. Toxic effects included: Effects On Newborn- Behavioral. Reference: Bulletin of Experimental Biology and Medicine 74:1255, 1972.
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.
15. Johnstone and Franklin (1964), as cited in Shepard's Catalog of Teratogenic Agents.
    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.
21. Suchowsky and Junkmann (1961), as cited in Shepard's Catalog of Teratogenic Agents.
    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: Contraception 13:559, 1976.
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- Uterus, cervix, vagina. Reference: Fertility and Sterility 16:158, 1965.
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 - Other measures of fertility. Reference: Vitamins and Hormones 17:307, 1959.
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 measures of fertility. Reference: Acta Endocrinologica, Supplementum 28:18, 1956.
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- Uterus, cervix, vagina. Reference: American Journal of Obstetrics and Gynecology 85:427, 1963.
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 Gynecology 76:626, 1958.

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 Fertility - Other measures of fertility. Reference: Fertility and Sterility 36:373, 1981.
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. Reference: Journal of Reproduction and Fertility 4:57, 1962.

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. Reference: Endocrinology 43:208, 1948.
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: Effects On Fertility - Mating Performance. Reference: Journal of Reproduction and Fertility 37:269, 1974.
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: Effects On Fertility - Other measures of fertility. Reference: Proceedings of the Society for Experimental Biology and Medicine 169:189, 1982.
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: Effects On Fertility - Female fertility index. Reference: Journal of Reproduction and Fertility 16:499, 1968.
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: Effects On Fertility - Other measures of fertility. Reference: Archives of Toxicology, Supplement 4:248, 1980.
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: Effects On Fertility - Other measures of fertility. Reference: Fertility and Sterility 39(Suppl):419, 1983.
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: Effects On Fertility - Other measures of fertility. Reference: Endocrinology 90:257, 1972.
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: Effects On Fertility - Other measures of fertility. Reference: Journal of Reproduction and Fertility 17:227, 1968.
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: Effects On Fertility - Female fertility index; Effects On Fertility - Pre-implantation mortality; Specific Developmental Abnormalities- Other developmental abnormalities. Reference: Biology of Reproduction 14:451, 1976.
16. Author not provided, as cited in RTECS®.
    Rabbits were exposed via intramuscular injection to 8 mg/kg on gd 2-9. Toxic effects included: Effects On Fertility - Pre-implantation mortality. Reference: Australian Journal of Biological Sciences 28:291, 1975.
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: Effects On Fertility - Female fertility index. Reference: Contraception 17:465, 1978.

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®.
    Rabbits were exposed via an intrauterine route to 684 µg /kg on 14D prior to mating and gd 1-10. Toxic effects included: Effects On Fertility - Pre-implantation mortality. Reference: American Journal of Obstetrics and Gynecology 109:536, 1971.
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 via dermal route 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 dermal route to 500 µg /kg on 1D prior to mating. Toxic effects included: Effects On Fertility - Pre-implantation mortality. Reference: Steroids 7:341, 1966.
24. 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.
25. Author not provided, as cited in RTECS®.
    Rabbits were exposed via subcutaneous injection to 150 µg /kg on 1D prior to mating. Toxic effects included: Effects On Fertility - Mating Performance. Reference: Acta Endocrinologica, Supplementum 73:3, 1963.
26. Author not provided, as cited in RTECS®.
    Rabbits were exposed via subcutaneous injection to 300 µg /kg on 2D prior to mating and gd 1. Toxic effects included: Effects On Fertility - Pre-implantation mortality. Reference: American Journal of Obstetrics and Gynecology 117:167, 1973.
27. 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.
28. Author not provided, as cited in RTECS®.
    Rats were exposed via subcutaneous injection to 500 µg /kg on 2D prior to mating. Toxic effects included: Effects On Fertility. Reference: Endocrinologica, Supplementum 105:7, 1966.
29. 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.
30. 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.
31. 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.
32. 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.
33. Author not provided, as cited in RTECS®.
    Rats were exposed via subcutaneous injection to 7 mg/kg on gd 10-16. Toxic effects included: Effects On Fertility - Abortion. Reference: Journal of Physiology 164:138, 1962.

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.
39. Author not provided, as cited in RTECS®.
Horses were exposed via a parenteral route to 16667 µg /kg on 45-47W of pregnancy. Toxic effects included: Maternal Effects- Parturition. Reference: Journal of Reproduction and Fertility, Supplement 23:637, 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: Maternal 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 - Prostate, seminal vesicle. Cowper's gland, accessory glands. Reference: Proceedings of the Society for Experimental Biology and Medicine 100:540, 1959.
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, seminal vesicle. Cowper's gland, accessory glands. Reference: Steroids 10:687, 1967.

Secondary Sources

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES JULY 31, 1995)

IARC. International Agency for Research on Cancer (IARC, 1979). *Monographs On The Evaluation Of Carcinogenic Risk To Humans, Volume 21*. World Health Organization.

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

RTECS®. Registry of Toxic Effects of Chemical Substances. National Institute of Occupational Safety And Health. (TOMES APRIL 30, 1995)

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

CARBAMAZEPINE: DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

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 $C_{15}H_{12}N_2O$. 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 $C_{15}H_{12}N_2O$ is also identified as carbamazepine in some sources.)

Overview of Developmental/Reproductive Toxicity Concern

OEHHA staff have found that 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

OEHHA staff have found that 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

1. Author not provided. (Eur. J. Pediat. 150:136. 1990), as cited in RTECS®.
   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.
2. Author not provided. (Neuropediatrics 16:167. 1985), as cited in RTECS®.
   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.
3. Author not provided. (Obstet. Gynecol. 82:705. 1993), as cited in RTECS®.
   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 anomalies in a case-control study.
6. Bertollini *et al*. (1987), as cited in Shepard's Catalog of Teratogenic Agents, Schardein.
   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 myleomeningocele. (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)).
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)).

25. Millar and Nevin (1973), as cited in Shepard's Catalog of Teratogenic Agents.
    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.
35. Vestermark and Vestermark (1991), as cited in Reprotox™, Schardein.
    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

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 85mg/kg/d). Fetal death and fetotoxicity (undefined) were reported. (Also cited under animal female reproductive 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, as well as fetotoxicity (undefined). (Also cited under animal female reproductive toxicity).
3. Author not provided. (Teratology 23:33A. 1981), as cited in RTECS®.
   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).
4. 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 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).
8. McElhatton and Sullivan (1977), as cited in Schardein.
   Reported to be teratogenic in mice (no information on dose, route, period or duration of exposure).
9. Paulson and Paulson (1981), as cited in Shepard's Catalog of Teratogenic Agents.
   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.
3. Levy and Yerby (1985), as cited in Reprotox™.
   Increased clearance of carbamazepine during pregnancy in humans.
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

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES JULY 31, 1995)

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

RTECS®. Registry of Toxic Effects of Chemical Substances. National Institute of Occupational Safety and Health. (TOMES JULY 31, 1995)

Schardein J. L. (1993) *Chemically Induced Birth Defects*. Second Edition, Marcel Dekker.

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

TERIS. Teratogen Information System. University of Washington. (TOMES JULY 31, 1995)

n-HEXANE:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

n-Hexane (CAS No. 110-54-3) is a colorless, volatile, flammable liquid present in natural gas and crude oil. It is a component of many petroleum products used as a solvent for glues, and has food uses in the extraction of oils from nuts and grains. It is present in ambient air.

Overview of Developmental/Reproductive Toxicity Concern

OEHHA staff have found that there is a DRAFT **MEDIUM-HIGH** level of developmental/reproductive toxicity concern over n-hexane, primarily for male reproductive toxicity. Several studies conducted in rats have described testicular damage following inhalation exposure to n-hexane. There is also evidence for developmental toxicity of this compound in two species, consisting of fetotoxicity and growth deficits following exposure of pregnant dams by the oral or inhalation route.

Developmental Toxicity

Fetotoxicity was observed in rats in one study following exposure during pregnancy to 5000 ppm n-hexane. Three animal studies have identified growth deficits following exposure to high levels of n-hexane by the inhalation or gavage route. A single negative study was conducted at much lower doses.

Male Reproductive Toxicity

Five studies conducted in rats found testicular toxicity following long-term exposure to high concentrations of n-hexane. Lesions ranged in nature from slight congestion of the testes to testicular degeneration and decreased testes weights. A metabolite of n-hexane, 2,5-hexanedione, is a potent testicular toxicant.

Of 6 studies giving negative results, only 1 seems to directly contradict the positive studies. The others were done in mice (which appear less sensitive than rats), at concentrations of less than 1000 ppm, and/or for a shorter period of exposure (3 of the negative studies used only a 5-day exposure period).

Overview of Exposure Concern

OEHHA staff have found that there is a DRAFT **HIGH** level of concern over exposure to n-hexane. n-Hexane is present in natural gas and crude oil, and is a component of many petroleum products. For 1987, total U.S. production was 773,000,000 lbs. It is used as a solvent for glues, and has food uses in the extraction of oils from nuts and grains. Exposed occupations include: leather workers, food oil extraction workers, gas station attendants, car repair workers, printers, and painters. Cottonseed products and hop extracts, modified for human consumption, may contain no more than 60 mg/kg and 25 mg/kg n-hexane, respectively. It is present in ambient 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 identified.

Developmental toxicity in animals

1. Bus *et al.* (1979), as cited in HSDB, IRIS®, Reprotext®, Shepard's Catalog of Teratogenic Agents.
   Deficits in postnatal growth in rats exposed on gd 8-16 to 1000 ppm by inhalation. Effects were significant for 3 weeks postnatally, but not by 7 weeks.
2. Marks *et al.* (1980), as cited in IRIS®, RTECS®, Reprotext®, Schardein.
   Dose-related reductions in fetal weights after pregnant mice were given 7.92 or 9.9 g n-hexane/kg/day by gavage.
3. Mast *et al.* (1987), as cited in IRIS®, RTECS®.
   There was a statistically significant reduction in the body weight of male fetuses gestationally exposed to n-hexane at concentrations of 1000 and 5000 ppm. 200 ppm was a NOAEL. Fetotoxicity was observed following exposure to 5000 ppm n-hexane.
4. Litton Bionetics (1979), as cited in IRIS®.
   No "teratologic results" of exposing pregnant female rats to concentrations of 0, 100, or 400 ppm 6 hrs/day for gd 6-15.

Female reproductive toxicity in humans

No studies identified.

Female reproductive toxicity in animals

No studies identified.

Male reproductive toxicity in humans

No studies identified.

Male reproductive toxicity in animals

1. API (1983), and DeGroot *et al.* (1984), as cited in IPCS.
   No testicular lesions were observed in Wistar or CD rats exposed for up to 6 months to 500 ppm or for 18 months to 900 ppm.
2. Cavender *et al.* (1984), as cited in IPCS.
   No testicular lesions in rats exposed to 3000, 6500, or 10,000 ppm 6 hrs/day, 5 days/wk for 13 weeks.
3. Demartino *et al.* (1987), as cited in IPCS.
   Sprague-Dawley rats exposed to 5000 ppm 16 hrs/day, 6 days/week. Clear testicular damage before symptoms of polyneuropathy set in.
4. Howd *et al.* (1983), as cited in IPCS.
   Decrease in relative testis weights in adult and weanling rats after 5 weeks of recovery following exposure to 1000 ppm 24 hrs/day, 7 days/week, for 4 weeks with 7 additional weeks of the same exposure 6 days/week.
5. Krasavage *et al.* (1980), as cited in Reprotext®.
   Degeneration of testes in rats exposed to n-hexane.
6. Kurita (1974), as cited in IPCS.
   Slight congestion of the testes of Wistar rats following 850 ppm 6 days/week, for 20 weeks.
7. Linder *et al.* (1992), as cited in Reprotext®.
   No spermatotoxicity observed in rats given multiple doses for up to 5 days; dose and route not stated.
8. Litton Bionetics (1980), as cited in HSDB; Mast *et al.* (1989 a & b), as cited in IRIS®.
   No clear evidence of male reproductive toxicity from dominant lethal assays in mice exposed to 100 or 400 ppm for 6 hrs/day, 5 days/week for 8 weeks., or to 200, 1000, or 5000 ppm for 20 hrs/day for 5 days.
9. Nylen *et al.* (1989), as cited in IRIS®, IPCS.
   Testicular lesions in adult male rats exposed to 1000 ppm for 61 days.

Other relevant data

2,5-hexanedione, a metabolite of n-hexane, was an even more potent testicular toxicant than n-hexane itself (Chapin, 1984), as cited in Reprotext®.

Secondary Sources

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES JULY 31, 1995)

IPCS. International Programme on Chemical Safety (1991) Environmental Health Criteria 122: N-Hexane. World Health Organization, Geneva, Switerland.

IRIS®. Integrated Risk Information System. US Environmental Protection Agency. (TOMES JULY 31, 1995)

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

RTECS®. Registry of Toxic Effects of Chemical Substances. National Institute of Occupational Safety and Health. (TOMES JULY 31, 1995)

Schardein J. L. (1993) *Chemically Induced Birth Defects*. Second Edition, Marcel Dekker.

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

STYRENE:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Styrene (CAS No. 100-42-5, chemical formula $C_6H_5CH=CH_2$) is one of the most important monomers worldwide, particularly in the reinforced plastics/composites industry. In addition to the secondary sources usually reviewed, documents submitted by an interested party (the Styrene Information and Research Center, SIRC) were also reviewed.

Overview of Developmental/Reproductive Toxicity Concern

OEHHA staff have found that there is a DRAFT **MEDIUM-HIGH** level of developmental/reproductive toxicity concern over styrene. The primary concerns are for developmental toxicity and female reproductive toxicity. Developmental toxicity manifested as impairments of viability, growth, and postnatal function has been described in at least three species of laboratory animals. Manifestations of female reproductive toxicity include disturbances of the reproductive cycle in humans and animals, as well as effects on offspring viability. Confidence in the data is weakened by the apparent poor quality of the individual studies as detailed by reviewers such as Barlow and Sullivan (1982), and Brown (1991, 1995). One study, conducted by the oral route in rats, reported testicular toxicity following styrene exposure. Inhalation studies of styrene in rats and mice, and a multigeneration study conducted by the oral route, have not reported clear evidence of treatment-related effects on the male reproductive system.

Developmental Toxicity

Developmental endpoints associated with styrene exposure of pregnant experimental animals consist of pre- and postnatal mortality, reduced or delayed growth, and effects on behavioral parameters. While most studies have been conducted in rats, there are also data on mice, hamsters, and rabbits. Effects have been observed in the first three species, less clearly in rabbits. There appears to be some, but not complete, overlap between developmentally and maternally toxic doses. The quality of individual studies has been questioned by reviewers such as Barlow and Sullivan (1982), and Brown (1991, 1995). Studies conducted in humans have not provided clear evidence of adverse effects of styrene on development. Behavioral parameters, which feature prominently in the animal data, have not been evaluated in humans.

Female reproductive toxicity

The increased mortality among preweaning pups can also be considered as an endpoint of female reproductive toxicity, and has been suggested to result from adverse effects of styrene on lactation. Lactational interference by styrene has also been suggested in a study on humans; support for this proposed mechanism is provided by human data indicating an effect of styrene on pituitary secretion of prolactin. There may also be a relationship between hyperprolactemia and menstrual dysfunction. Altered menstrual cycles in women, and altered estrus cycles in animals have been reported in many, but not all, studies of styrene exposure.

Male reproductive toxicity

Studies on humans have given evidence for abnormalities of sperm and/or semen parameters and effects on hormone excretion, but no fertility data were identified. One study, conducted by the oral route in rats, reported testicular toxicity following styrene exposure. Inhalation studies of styrene in rats and mice, and a multigeneration study conducted by the oral route, have not reported clear evidence of treatment-related effects on the male reproductive system.

Overview of Exposure Concern

OEHHA staff have found that there is a DRAFT **HIGH** level of concern over exposure to styrene due to its widespread production, industrial use, and release to the environment. Inhalation is the primary route of exposure, but dermal and oral contact may also occur. The highest exposure levels are found in occupationally exposed workers of the reinforced plastics/composites industry.

Billions of pounds of styrene are produced each year in the U.S., and large quantities are released to the air, water, and soil. Styrene breaks down quickly in air, usually within 1 - 2 days (ATSDR, 1992). Styrene biodegrades readily in most aerobic environments, with the rate of degradation dependent upon the concentration of styrene and the environmental pH (Fu and Alexander, 1992). While styrene is rapidly lost from surface waters by volatilization, it is expected to degrade more slowly in groundwater (Wilson et al., as cited in CEPA). Ambient levels in air, food, and drinking water are generally low.

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. Ahlborg (1987), as cited in ATSDR, Schardein, Brown (1991).
   Case-control studies performed in Sweden and Norway did not detect an increase in the odds ratio for developmental effects for women who worked in the plastics industry. The actual levels of exposure were not known for either group.
2. Harkonen *et al.* (1984), as cited in Reprotext®, Schardein, Brown (1991).
   No increase in birth defects for 2,209 workers (1,698 men and 511 women) in reinforced plastics industry.
3. Harkonen *et al.* (1982), as cited in ATSDR, Schardein, Brown (1991).
   No increase in spontaneous abortion for 67 Finnish lamination workers as compared to 67 age-matched controls.
4. Hemminki *et al*. (1984), as cited in ATSDR.
   Follow-up study to Hemminki *et al*. (1980), did not confirm the results of the prior report (see below).
5. Hemminki *et al.* (1980), as cited in ATSDR, Reprotext®, Schardein, Brown (1991).
   The frequency of spontaneous abortion among 9,000 Finnish chemical workers between 1973 and 1976 was compared to the Finnish population as a whole. The rate was significantly higher in women employed in styrene production.
6. Holmberg (1977), as cited in CEPA, Reprotext®, Barlow and Sullivan, Brown (1991).
   A possible cluster of CNS defects occurred among mothers working in the plastics industry in Finland. There were no exposure estimates or other details.
7. Holmberg (1979), as cited in Barlow and Sullivan, Brown (1991).
   A continuation of the 1977 study (see above). There was a significant increase in birth defects with 1st trimester exposure to solvents, but the specifics of styrene exposure are unknown.
8. Holmberg (1980), as cited in Brown (1991).
   Same data as Holmberg 1979.
9. Holmberg (1982), as cited in Brown (1991).
   No association was found between styrene exposure and the frequency of facial clefting among the Finnish chemical workers.
10. Holmberg (1978), as cited in Schardein, Brown (1991).
    Two cases of CNS defects in children of women working with styrene and other chemicals (same cases as Holmberg 1979, 1980)
11. Kurppa *et al.* (1983), as cited in Reprotext®, Brown (1991).
    Reanalysis of Finnish data did not support association with CNS defects.
12. Lemasters *et al*. (1989), as cited in ATSDR, IRIS®, Schardein, Brown (1991).
    Data from 819 unexposed pregnancies, 154 “low-exposed” pregnancies (2-29 ppm), and 75 “high-exposed” pregnancies (30-82 ppm). There was no statistically-significant concentration-response relationship with

decreasing birth weight. In women who worked at the most highly exposed jobs (estimated 82 ppm), there was a 4% reduction in average birth weight which was not statistically significant.

13. Lindbohm *et al.* (1985), as cited in ATSDR, Reprotext®, Schardein, Brown (1991).
    Did not confirm increase in spontaneous abortion for Finnish workers.

Developmental toxicity in animals

1. Beliles, et al. (1985), as cited in CEPA.
   Pup survival or weight was slightly reduced at some times in each of three generations of rats exposed to 250 mg/L styrene in drinking water over the lifespan (providing doses of 14 or 21 mg/kg/day to males and females, respectively). No adverse effects were described with exposure to 125 mg/L styrene in drinking water.
2. Efremenko, (1976), as cited in Schardein.
   Postnatal functional changes in rats.
3. Kankaanpaa *et al.* (1980), as cited in ATSDR, IRIS®, RTECS®, Reprotext®, Barlow and Sullivan, Brown (1991).
   a. mice: increased resorptions at 250 ppm by inhalation, but significance level only $p<0.10$. There were no maternal deaths at this dose, and the frequency of fetal death was not significantly increased.
   b. hamsters: up to 1000 ppm - increased dead or resorbed fetuses at this dose. Maternal toxicity not considered to have been a problem.
4. Khanna *et al.* (1991), as cited in Brown (1995).
   100 mg/kg styrene given orally to rats from gd 6 had no effect when animals were on a normal diet. Styrene enhanced the adverse effects of a low protein diet: reduced post-natal weight gain, and physical and behavioral developmental delays. Increased motor activity and decreases in biochemical measures.
5. Kishi (1992), as cited in CEPA, Reprotext®, Brown (1995).
   50 or 300 ppm styrene to rats on gd 7 - 21 led to decreased body weights and decreased brain serotonin levels.
6. Kishi *et al.* (1995a), as cited in Brown (1995).
   Continuation of Kishi 1992 - describes postnatal growth and behavioral parameters. Effects were found at the higher dose of 300 ppm on: weight-gain, physical maturation (incisor eruption, etc.), reflex development, and postweaning behavioral tests.
7. Kishi *et al.* (1995b) [original paper]
   Pregnant rats were exposed to 0, 50, or 300 ppm styrene for 6 hrs/day during gestation days 7-21. Dose-dependent effects on behavioral parameters were found.
8. Murray *et al.* (1978), as cited in ATSDR, HSDB, IRIS®, RTECS®, Shepard's Catalog of Teratogenic Agents, Barlow and Sullivan, Brown (1991).
   a. rats: 300 or 600 ppm by inhalation or 180 or 300 mg/kg/day by gavage. Significant decreases in maternal weight gain at both doses by either route. No clearly dose-related effects on offspring.
   b. rabbits: 300 or 600 ppm by inhalation. No clear fetal effects; possible increase in skeletal variations.
9. Ponomarkov (1978), as cited in ATSDR, Barlow and Sullivan, IARC, Brown (1991).
   a. mice: single gavage dose of 1.35 g/kg on gd 17 led to increased neonatal mortality.
   b. rats: increased pre-weaning mortality.
10. Ragule (1974), as cited in Barlow and Sullivan, Schardein, Brown (1991).
    a. Rats exposed to 0, 1.2 or 11.6 ppm styrene by inhalation throughout gestation. Significant increases in preimplantation death and total embryomortality at 11.6 ppm.
    b. animals exposed to 0, 0.35, or 1.2 ppm either throughout gestation, or during 1st trimester only. Preimplantation loss increased at both doses and both exposure groups; postimplantation loss increased at both doses for group exposed throughout gestation. Reductions in offspring size and weight stated to be reduced after exposure to high dose throughout gestation, but data not presented [Barlow and Sullivan, 1982, and Brown, 1991 expressed concern about the methods/reporting in this study].
11. Shigeta *et al.* (1989), as cited in CEPA.
    THA rats exposed to 50 ppm styrene, 7 hours/day, 6 days/week from birth to 48 days of age, experienced delayed development of exploratory and avoidance behavior. Developmental milestones (pinna detachment, incisor eruption) were retarded. The same developmental milestones were also affected at a concentration of 25 ppm. Neonates may not have been at a comparable stage of development at the start of the experiment.

12. Srivastava *et al.* (1990), as cited in Brown (1995).
    Rats were given 250 or 400 mg/kg styrene orally on gd 6-15. Low dose had no effect. High dose led to reduced maternal weight gain, fetal deaths, and reduced fetal weights.
13. Srivastava *et al.* (1992), as cited in Brown (1995).
    Rats given 200 or 400 mg/kg styrene orally (same animals as Srivastava (1990)?). Reduced fetal body and liver weights. Dose-dependent effects on fetal hepatic enzymes.
14. Vergiyeva *et al*. (1979), as cited in Reprotex t®, Barlow and Sullivan, Brown (1991).
    No adverse effects on offspring of female rats exposed to 47 or 163 ppm styrene.
15. Zaidi *et al*. (1985), as cited in Schardein, Brown (1991).
    Rats given 200 mg styrene/kg bw/day throughout pregnancy [and lactation?]. Effects on brain chemistry and protein content.

Female reproductive toxicity in humans

1. Alborg (1987), as cited in ATSDR, Schardein, Brown (1991).
   Case-control studies performed in Sweden and Norway did not detect an increase in the odds ratio for developmental effects for women who worked in the plastics industry. The actual levels of exposure were not known for either group.
2. Bobrova (1977), as cited in Brown (1991).
   Report of increased menstrual disorders among Russian women occupationally exposed to styrene.
3. Bondarevskaya (1961), as cited in Brown (1991).
   21% of women working in styrene concentrations of 4.7 to 30 ppm 1 yr or less reported some menstrual dysfunction. This decreased to 5.5% within 6 years of employment.
4. Gorobets (1984), as cited in Brown (1991).
   Increased menstrual disturbances in Russian women working with styrene.
5. Harkonen *et al*. (1982), as cited in ATSDR, CEPA, Schardein, Brown (1991).
   No increase in the frequency of spontaneous abortion for 67 Finnish lamination workers as compared to 67 age-matched controls.
6. Hemminki *et al*. (1984), as cited in ATSDR.
   Follow-up study to Hemminki et al., (1980). Did not confirm results of the prior report (see below).
7. Hemminki *et al.* (1980), as cited in ATSDR, Reprotext®, Schardein, Brown 1991.
   The frequency of spontaneous abortion among 9,000 Finnish chemical workers between 1973 and 1976 was compared to Finnish population as a whole. The rate was significantly higher in women employed in styrene production.
8. Izmerov (1984), as cited in Reprotext®.
   Occupational exposure to styrene associated with inhibition of lactation in women who worked at a glass-reinforced plastics factory.
9. Lemasters *et al.* (1985), as cited in CEPA, IRIS®, Reprotox™, Reprotext®, Brown (1991).
   Did not find increased menstrual disorders in U.S. plastics workers exposed to either 13 or 52 ppm styrene.
10. Lemasters (1989), as cited in ATSDR, IRIS®, Schardein, Brown (1991).
    Data from 819 unexposed pregnancies, 154 “low-exposed” pregnancies (2-29 ppm), and 75 “high-exposed” pregnancies (30-82 ppm). There was no statistically-significant concentration-response relationship with decreasing birth weight. In women who worked at the most highly exposed jobs (estimated 82 ppm), there was a 4% reduction in average birth weight which was not statistically significant.
11. Lindbohm *et al*. (1989), as cited in ATSDR, Reprotext®, Schardein, Brown (1991).
    Case-controlled study did not confirm increased spontaneous abortion for Finnish plastics workers.
12. Lindbohm *et al.* (1990), as cited in Brown (1995).
    Finnish occupational health group. No association between styrene and increased risk for spontaneous abortion.
13. Loseva *et al.* (1983), as cited in Brown (1991).
    Russian women occupationally exposed to styrene and other chemicals. Increased frequency of spontaneous abortion, premature rupture of membranes, and premature birth.
14. Mutti *et al.* (1988), as cited in Brown (1995).
    Reproductive histories of 43 women occupationally exposed to styrene in Italy. Mean exposure 25 ppm 8 hr

TWA; range 10 - 105 ppm. Shortened and irregular menstrual cycles in exposed women. Type of contraception not accounted for.

15. Pokrovskii (1967), as cited in Reprotext®, Barlow and Sullivan, Brown (1991).
    Menstrual disorders reported to be increased among 200 female Russian workers exposed to 5-30 ppm styrene.
16. Zlobina *et al*. (1975), as cited in Reprotext®, Barlow and Sullivan, Brown (1991).
    110 women working in polystyrene processing at approx. 50 ppm reported menstrual disorders and inflammatory diseases of the female sex organs. Women exposed to 0.5 - 3 ppm reported "toxicosis" during pregnancy, and "abnormal deliveries" [terms not defined]. Some women showed signs of styrene neurotoxicity [exposures underestimated?].

Female reproductive toxicity in animals

1. Bakhtizina *et al.* (1981, 1982, 1983), as cited in Reprotext®, Brown (1991).
   In 2 studies found effects on ovaries of rats exposed to 200 mg/kg by gavage, or to inhalation of an unknown concentration.
2. Beliles (1985), as cited in ATSDR, HSDB, IRIS®, RTECS®, Brown (1991).
   3-generation study in rats at doses of 8 to 21 mg/kg/day in drinking water. Decreased gestation length for F2 litters and reduced pup survival at the high dose.
3. Bondarevskaya (1957), as cited in Brown (1991).
   Changes in reproductive cycles of rats exposed to styrene [by inhalation?] at concentrations of 3500 and 7000 ppm (subacute), and 465 ppm (chronic).
4. Izyumova *et al.* (1971), as cited in Barlow and Sullivan, Brown (1991).
   Effects on estrus cycle length in rats exposed to 1.18 or 11.8 ppm styrene by inhalation.
5. Ponomarkov (1978), as cited in ATSDR, Barlow and Sullivan, IARC, Brown (1991).
   a. mice: 1.35 g/kg single gavage dose on day 17 caused increased preweaning mortality, possibly due to effects on lactation. 300 mg/kg was a no effect level.
   b. rats: similar effect in increasing preweaning mortality.
6. SIRC (1995a, 1995b), as cited in Brown (1995).
   13-weeks inhalation, 6 hrs/day, 5 days/wk.
   a. rat: 0, 200, 500, 1000, & 1500 ppm. uterine parameters not reported; no effects on ovarian weight or pathology. Adrenal weights slightly increased at 2 highest doses.
   b. mice: 0, 50, 100, & 200 ppm. No effects on adrenal, ovarian, or uterine weights or pathology.
7. Zlobina *et al.* (1975), as cited in Reprotext®, Barlow and Sullivan, Brown (1991).
   Female rats exposed to 0.23 or 1.18 ppm styrene by inhalation for 4 months. Estrus cycles lengthened at both doses; symptoms of general toxicity at high dose.

Male reproductive toxicity in humans

1. Jelnes (1988), as cited in CEPA, Reprotox™, Brown (1991).
   Abnormal sperm morphology in Danish windmill fabricators. Workplace air concentrations of 68, 84, 128 ppm styrene; peaks 2x higher.
2. Neshkov and Nosko (1976), as cited in Brown (1991).
   Workers in reinforced plastics industry complained of sexual problems. Reduced sperm counts, and other adverse effects on semen parameters. Increased urinary excretion of 17-ketosteroids. Exposure to several chemicals, including styrene, at levels above US OELs.
3. Taskinen *et al.* (1989), as cited in CEPA, Brown (1991).
   No increase in spontaneous abortion among wives of men occupationally exposed to styrene.
4. Wink (1972), as cited in Barlow and Sullivan.
   Urinary levels of steroid hormones were reduced, but not significantly, in men occupationally exposed to low levels of styrene.

Male reproductive toxicity in animals

1. Beliles (1985), as cited in ATSDR, CEPA, HSDB, IRIS®, RTECS®, Brown (1991).
   3-generation reproductive toxicity study conducted in rats. No clear evidence for male reproductive effects with styrene in drinking water giving doses of 8 to 21 mg/kg/day.
2. Jersey *et al.* (1978), as cited in Brown (1991).
   Inhalation exposure of male rats to styrene 6 hrs/day, 5 days/wk, 18 months, with observation to 24 months. 600 or 1200/1000 ppm. Body weights reduced at both doses, focal testicular lesions at both doses [unclear relationship to treatment].
3. Salomaa *et al*. (1985), as cited in ATSDR, Brown (1991).
   No sperm abnormalities in mice exposed to 150 or 300 ppm styrene by inhalation for 5 days.
4. SIRC (1995a, 1995b), as cited in Brown (1995).
   13-weeks inhalation, 6 hrs/day, 5 days/wk.
   a. rats: 0, 200, 500, 1000, 1500 ppm had no effects on testes.
   b. mice: 0, 50, 100, 150, 200 ppm. no effects mentioned.
5. Srivastava *et al.* (1989), as cited in ATSDR, Reprotox™, Brown (1991).
   400 mg/kg/day orally for 60 days produced testicular toxicity in male rats.

Other relevant data

Styrene is lipophilic, low molecular weight, easily absorbed, and presumed to cross the placenta. Blood levels in the fetus and umbilical cord are proportional to those in maternal blood. Styrene is neurotoxic in adult animals. Effects of styrene on the endocrine system, particularly on pituitary secretion of prolactin, are reviewed by Brown (1991).

Secondary Sources:

ATSDR. (1992) Agency For Toxic Substances And Disease Registry. Toxicological Profile for Styrene.

Barlow S.M. and Sullivan F.M. (1982) *Reproductive Hazards Of Industrial Chemicals*, Academic Press.

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES JULY 31, 1995)

IARC. International Agency for Research on Cancer (IARC, 1979). *Monographs On The Evaluation Of Carcinogenic Risk To Humans, Volume 19.* World Health Organization.

IRIS®. Integrated Risk Information System. US Environmental Protection Agency. (TOMES JULY 31, 1995)

Kishi, R. et al., (1995) Neurotoxicol. and Teratol. 17: 121-130.

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

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

RTECS®. Registry of Toxic Effects of Chemical Substances. National Institute Of Occupational Safety And Health. (TOMES JULY 31, 1995)

Schardein J. L. (1993) *Chemically Induced Birth Defects*. Second Edition, Marcel Dekker.

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

Other Sources (submitted by SIRC, the Styrene Information and Research Center)

Brown, N. A. (1991) Reproductive Toxicology. 5: 3-29.

Brown, N. A. et al., (1995). Unpublished review prepared for SIRC

CEPA. (1993) Canadian Environmental Protection Act. *Priority Substances List Assessment Report*. Canada Communication Group.

XYLENES (MIXTURES): DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Mixed xylene (CAS No. 1330-20-7) is a solvent composed of the ortho, meta, and para forms of xylene plus ethylbenzene (CAS Nos. 95-47-6, 108-38-3, 106-42-3, and 100-41-4, respectively).

Overview of Developmental/Reproductive Toxicity Concern

OEHHA staff have found that there is a DRAFT **MEDIUM-HIGH** level of developmental/reproductive toxicity concern over xylenes, due to concern for developmental toxicity. Adverse effects have been reported in three mammalian species for at least one route of exposure, and in two species following either oral or inhalation exposure. In different studies, under various protocols for prenatal exposure to xylenes, all four manifestations of developmental toxicity have been reported (death, malformations, growth deficits and functional abnormalities). There is also very limited evidence for male reproductive toxicity of xylenes, and insufficient evidence for an adverse effect of xylenes on female reproduction.

Developmental Toxicity

Caudal regression and CNS defects have been reported to occur at increased frequencies in offspring of women occupationally exposed to mixtures of solvents, including xylenes. Subsequent investigations of these apparently affected populations, however, did not confirm earlier findings. Adverse effects reported in animal studies include fetal death, growth deficits, malformations, retarded ossification, and behavioral alterations. Developmental toxicity following xylene exposure has been described in three mammalian species , as well as in chicks, and by the oral and inhalation routes. Death of the developing organism was coincident in many, but not all, cases with evidence of maternal toxicity.

Female reproductive toxicity

One study of women occupationally exposed to white spirit, a mixture including xylenes, found an association with menstrual disorders. No studies were identified on the female reproductive toxicity of xylenes in animals.

Male reproductive toxicity

One study was identified which evaluated the frequency of spontaneous abortion and congenital malformation among the wives of men occupationally exposed to organic solvents. The results were considered to be confounded by small sample size, mixed exposures, and unknown route of exposure. Two studies in rats describe adverse effects of mixed xylenes or one of the isomers of xylene on spermatogenesis, and on testicular and prostate weights.

Overview of Exposure Concern

OEHHA staff have found that there is a DRAFT **HIGH** level of concern over exposure to xylenes, as they are one of the top 30 chemicals produced in the U.S. by volume. Exposure to xylenes may occur in the workplace, through consumer products, or via environmental contamination.

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. Holmberg (1979), as cited in Reprotext®. Holmberg & Nurminen (1980), as cited in HSDB. Kurppa *et al*. (1983), as cited in Reprotext®.
   CNS defects including hydrocephalus more common in children of mothers exposed to a mix of solvents including xylenes, toluene, & white spirit.
2. Kucera (1968), as cited in Shepard's Catalog of Teratogenic Agents.
   Among 9 infants having caudal regression syndrome, 5 mothers had been exposed to fat solvents, including xylenes, during pregnancy. According to a cited personal communication with TH Shepard, later observations by the author did not support such a strong association.
3. Taskinen *et al*. (1994), as cited in Reprotext®.
   Risk for spontaneous abortion increased 3.1 fold in women exposed to xylenes in laboratory work for at least 3 days/wk during the 1st trimester of pregnancy.
4. Windham *et al.* (1991), as cited in ATSDR.
   Epidemiological study involving workers exposed to multiple solvents including xylenes.

Developmental toxicity in animals

1. Balogh *et al.* (1982), as cited in ATSDR, HSDB.
   Rat, inhalation for 24 hrs/day on gd 7-14. Reduced ossification at 53 ppm. Increased resorptions at 775 ppm. Possible maternal tox at 775 ppm.
2. Bio/dynamics (1983) as cited in ATSDR
   Rat, inhalation, 6 hrs/day/7 days/week, 166 days total exposure. NOEL = 250 ppm. At 500 ppm, 7% decrease in body weight of female fetuses.
3. Hass and Jakobsen (1993), as cited in RTECS®.
   Rat, inhalation, 200 ppm for 6 hrs/day during days 4-20 of gestation. "Musculoskeletal" and behavioral effects.
4. Hudak and Ungvary (1978), as cited in ATSDR, HSDB, Reprotox™, Barlow and Sullivan, Schardein, IARC.
   Rat, inhalation 24 hrs/day during gd 9-14. At 230 ppm, increased skeletal variations, 2 cases of agnathia; no effect on number of implantations, resorption frequency, or fetal weight. No maternal toxicity noted.
5. Krotov and Chebotar (1972), as cited in Barlow and Sullivan, Schardein.
   [Russian language] Rat, inhalation, 24 hrs/day on days 1-20 of pregnancy at 115 ppm. Significant increases in pre- and postimplantation loss.
6. Kucera (1968), as cited in ATSDR, Reprotox™, Reprotext®, Shepard's Catalog of Teratogenic Agents, Barlow and Sullivan, Schardein.
   Exposure of chick embryos to a xylene atmosphere caused "rumplessness", a defect resembling caudal regression.
7. Litton Bionetics (1978), as cited in ATSDR.
   Noted developmental toxicity without maternal toxicity. No details available. Study performed for the American Petroleum Institute.
8. Marks *et al.* (1982) as cited in ATSDR, HSDB, IRIS®, RTECS®, Shepard's Catalog of Teratogenic Agents, Schardein, IARC.
   Mouse, gavage; doses of 2.4, 3.0, and 3.6 ml xylene/kg bw/day decreased fetal weights at low dose. Significant and dose-related increases in the frequencies of malformations at the 2 higher doses (primarily cleft palate). 31.5% maternal toxicity at the highest dose.
9. Mirkova *et al.* (1979), as cited in ATSDR.
   Rats, dermal, 200 mg/kg/day throughout gestation decreased enzyme activity in fetal and maternal brain tissue. Impaired motor activity in pregnant dams.
10. Mirkova *et al*. (1983) as cited in ATSDR, HSDB, RTECS®, IARC.
    Rats, inhalation, 50 and 500 mg/ m^3. Increases in postimplantation loss and the frequency of skeletal anomalies.
11. Rosen *et al.* (1986), as cited in ATSDR, Reprotox™, Shepard's Catalog of Teratogenic Agents, IARC.
    Rat, inhalation 6 hrs/day, gd 7-16. p-xylene. NOAEL of 1612 ppm for postnatal growth and acoustic startle response.
12. Rumsey *et al*. (1969), as cited in ATSDR, Barlow and Sullivan.
    Rat, dermal exposure of pregnant dams to a 1% solution gave no evidence of fetal toxicity.

13. Seidenberg *et al*. (1986), as cited in ATSDR, IARC.
    Mouse, gavage, gd 8 - 12, screening protocol (details unknown), m-xylene, NOAEL = 2000 mg/kg/day.
14. Tatrai *et al*. (1979), as cited in Schardein, IARC.
    Rats exposed by inhalation to m-xylene at 0, 150, 1,100 or 3,000 mg/m^3 . At the highest concentration, maternal food consumption and weight gain were reduced, and 4 out of 30 animals died. Fetal weights were reduced, and the frequency of extra ribs was increased.
15. Teslina (1974), as cited in Barlow and Sullivan.
    Rats, subcut. injection 150 or 400 mg/kg on days 1 - 10 or 1 - 18 of pregnancy. Maternal toxicity in all groups. Preimplantation loss, postimplantation loss, and reduced fetal weights in survivors.
16. Ungvary and Tatrai (1985), as cited in ATSDR, HSDB, RTECS®, Shepard's Catalog of Teratogenic Agents, IARC.
    a. Rat, inhalation. 24 hrs/day, gd 7 - 15. Reduced ossification at 58 ppm. Increased fetal death and resorptions at 784 ppm. May have been coincident maternal toxicity.
    b. Mouse, inhalation 1,000 mg/m^3/12 hr/day on days 6 - 15 of pregnancy. Fetal toxicity and musculoskeletal effects.
    Rabbit, inhalation - 500 mg/ m^3/ 24 hrs/day on gd 7 - 20. Fetotoxicity. 1000 mg/ m^3/ 24 hrs/day caused abortion (presumably of entire litters).
17. Ungvary *et al*. (1979), as cited in Barlow and Sullivan.
    Rat, inhalation, p-xylene, 24 hrs/day on days 7 - 14 of gestation. Concentrations of 0, 35, 350, or 700 ppm. No maternal toxicity noted. Increased frequency on non-pregnancy in treated animals, unlikely to be related to treatment (which began on gd 7). At 700 ppm: increased frequency of total litter resorption, increased post-implantation loss, significant decrease in fetal and placental weights, significant increase in supernumerary ribs, and delayed enzyme development in fetal kidneys. The frequency of retarded ossification was significantly increased at all doses, in a dose-related manner.
18. Ungvary *et al.* (1980) as cited in ATSDR, RTECS®,Reprotox™, IARC.
    Rat, inhalation, 24 hrs/day, gd 7 - 14.
    a. m-xylene, NOAEL = 700 ppm,
    b. o-xylene, decreased fetal weight at 350 ppm.
    c. p-xylene, retarded skeletal development at 35 ppm.
19. Ungvary *et al*. (1981), as cited in ATSDR, RTECS®.
    Rat, inhalation, 24 hrs/day, on gd 9, or on gd 9 and 10. At 691 ppm, 27% decrease in fetal weight.

Female reproductive toxicity in humans

1. Syrovadko *et al*. (1973), as cited in Barlow and Sullivan.
   Occupational exposure to white spirit - mixture including xylenes - associated with menstrual disorders.

Female reproductive toxicity in animals

No studies identified.

Male reproductive toxicity in humans

1. Taskinen *et al*. (1989), as cited in ATSDR.
   Epidemiological study of pregnancy outcomes for wives of men occupationally exposed to solvents including xylenes. No male reproductive effects were reported.

Male reproductive toxicity in animals

1. Washington, *et al*. (1983), as cited in RTECS®.
   Rat, ip, 500 mg/kg of o-xylene, 2 days prior to mating caused toxic effects on spermatogenesis.
2. Yamada (1993), as cited in Reprotext®.
   Rat, unknown dose and route. Reduced testicular and prostate weights, reduced numbers of spermatozoa.

Other relevant data

While there is some indication that para-xylene is the most toxic isomer, the para, ortho and meta isomers have similar effects to the technical mixture.
Xylenes have been shown to cross the placenta in mice.
Most xylene is eliminated by 18 hrs post exposure. Alcohol consumption significantly slows metabolism.
Irritation of the eye, nose, and throat reported at concentrations as low as 200 ppm for 3-5 minutes. Neurological symptoms have been reported for exposures as low as 200 ppm for 4 hrs.

Secondary Sources

ATSDR. (1993) Agency for Toxic Substances and Disease Registry. Toxicological Profile for Xylenes (update).

Barlow S.M. and Sullivan F.M. (1982) *Reproductive Hazards Of Industrial Chemicals*, Academic Press.

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES JULY 31, 1995)

IARC. International Agency for Research on Cancer (IARC, 1989). *Monographs On The Evaluation Of Carcinogenic Risk To Humans, Volume 47.* World Health Organization.

IRIS®. Integrated Risk Information System. US Environmental Protection Agency. (TOMES JULY 31, 1995)

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

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

RTECS®. Registry of Toxic Effects of Chemical Substances. National Institute of Occupational Safety and Health. (TOMES JULY 31, 1995)

Schardein J. L. (1993) *Chemically Induced Birth Defects*. Second Edition, Marcel Dekker.

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

1,1-DICHLOROETHYLENE: DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

1,1-Dichloroethylene, or vinylidene chloride (CAS No. 75-35-4), is an intermediate in production of polyvinylidene copolymers (e.g. plastic food wrap). It is U.S. EPA class C (possible human) carcinogen.

Overview of Developmental/Reproductive Toxicity Concern

OEHHA staff have found that there is a DRAFT **MEDIUM-HIGH** level of developmental/reproductive toxicity concern over 1,1-dichloroethylene, primarily for developmental toxicity. Adverse effects have been observed in multiple studies, in multiple species, and by at least one relevant route of exposure (inhalation). All four manifestations of developmental toxicity have been reported following prenatal exposure to 1,1-dichloroethylene: death, malformations, growth deficits, and functional abnormalities. There is also limited evidence from animal studies for adverse effects on fertility, particularly male fertility.

Developmental Toxicity

There is very limited evidence suggesting increased neural tube defects in children of women consuming drinking water contaminated with 1,1-dichloroethylene.
Fetal death was reported in rats, mice, and rabbits following prenatal exposure to 1,1-dichloroethylene. Malformations have been reported in 2 species; in particular, hydrocephalus in rats increased in a dose-dependent manner. Rat pups followed postnatally after prenatal exposure showed delays in measures of growth and behavioral development. One study raised the possibility of transplacental carcinogenesis, but exposure was continued postnatally. There is some, but not complete, overlap between developmentally and maternally toxic doses.

Female Reproductive Toxicity

Two multigeneration reproductive toxicity studies conducted in rats used similar concentrations of 1,1-dichloroethylene in drinking water. One study reported no adverse effects, while the other reported reductions in fertility in all groups. The relationship of this effect to treatment is not clear at this level of review. No studies pertaining to female reproductive toxicity in humans were identified.

Male Reproductive Toxicity

Two dominant-lethal studies report evidence of reduced male fertility in rats and mice. Two multigeneration reproductive toxicity studies have been described above. One study reported no adverse effects, while the other reported reductions in fertility in all groups. The relationship of this effect to treatment is not clear at this level of review. No studies pertaining to male reproductive toxicity were identified.

Overview of Exposure Concern

OEHHA staff have found that there is a DRAFT **MEDIUM** level of concern over exposure to 1,1-dichloroethylene**.** Workplace exposures are expected to be by inhalation or dermal routes, while public exposures are expected to be by inhalation or drinking water (ATSDR, 1994). 1,1-Dicloroethylene is used in the manufacture of food packaging films, adhesives, flame-retardant coatings for fiber and carpet backing, piping, and coating for steel pipes. Quantitative data on environmental exposures are limited, but individuals residing near contaminated hazardous waste sites, especially those obtaining their drinking water from underground sources, may potentially be exposed. There are 44-51 National Priorities List (NPL) hazardous waste sites in California that contain 1,1-dichloroethylene. 1,1-Dichloroethylene volatilizes readily from surface water to the atmosphere, and atmospheric degradation by hydroxyl radicals is expected to occur with a half-life of 4-20 hours. U.S. FDA permits no more than 10 ppm 1,1-

dichloroethylene in food packaging films. 1,1-Dichloroethylene monomer has been detected in liver pate, cookies, potato chips, and cheese at levels less than 0.005 mg/kg.

Data on Developmental and Reproductive Toxicity

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

Developmental toxicity in humans

1. New Jersey Dept. of Health (1992), as cited in ATSDR.
   One human study was identified which suggested increased neural tube defects for children of women consuming drinking water contaminated with 1,1-dichloroethylene. Data were considered to provide only suggestive evidence.

Developmental toxicity in animals

1. Alumot *et al*. (1976), as cited in Shepard's Catalog of Teratogenic Agents.
   Pregnant rats given feed containing up to 500 ppm of 1,1-dichloroethylene showed no alteration in fetal mortality or weight. Maternal feed consumption was reduced to 60-70% of ad lib levels.
2. Cotti *et al*. (1988), as cited in HSDB.
   Male and female rats were exposed to 100 ppm vinylidene chloride by inhalation for 104 weeks. Offspring were exposed throughout gestation (transplacentally) and then by inhalation for 15 or 104 weeks postnatally. Survival was not affected. Exposed offspring showed an increased incidence of leukemias, related to the length of treatment.
3. Murray *et al*. (1979), as cited in ATSDR, IRIS®, RTECS®, Shepard's Catalog of Teratogenic Agents, Barlow and Sullivan, IARC.
   a. rats: effects reported differ somewhat between secondary sources. At 200 mg/ml drinking water, skeletal variations, fetotoxicity, or no effect have been variously reported. Inhalation: concentrations of 20, 80, or 160 ppm during organogenesis. Maternal toxicity at 80 ppm, and skeletal variations at 80 and 160 ppm.
   b. rabbits: inhalation: 80 or 160 ppm. Evidence of maternal toxicity at 160 ppm, also increased resorptions, increased skeletal variations, and reduced viability.
4. Norris (1977), as cited in Barlow and Sullivan, IARC.
   a: Rats exposed by inhalation to 20-160 ppm 1,1-dichloroethylene 7 hrs/day, on gd 6-15. Exposure resulted in embryo- and fetotoxicity, concurrent with maternal toxicity.
   b: Rabbits exposed as above during gd 6-18 showed the same effects as seen in rats.
5. Short *et al*. (1977), as cited in ATSDR, Barlow and Sullivan.
   a. Mice exposed by inhalation to 15, 30, 57, 144, or 300 ppm for 23 hrs /day on gd 6-16. Maternal weight gain was significantly decreased at 30, but not 15 or 57 ppm. At 144 and 300 ppm, all dams died or lost their litters. At 30 and 57 ppm, there were too few litters surviving for statistical analysis. Malformations and delayed ossification were observed at the 15 ppm level.
   b. Mice were exposed as above to concentrations of 0, 41, 54, or 74 ppm 1,1-dichloroethylene. Defects observed consisted of hydrocephalus, occluded nasal passages, micropthalmia, small liver, and hydronephrosis.
   c. Pregnant rats were exposed to 15, 57, 300, or 449 ppm 1,1-dichloroethylene by inhalation for 23 hrs/day on gd 6-16. Effects were similar to those observed in mice: in particular, hydrocephalus increased in a dose-dependent manner.
   d. Pregnant rats were exposed to 1,1-dichloroethylene at concentrations of 0, 56, or 283 ppm for 23 hrs/day on gd 8-20. Pups were delivered and followed postnatally. In both exposed groups there was significant retardation of development of the surface righting reflex, reduced weight gain, and delayed incisor eruption.

Female reproductive toxicity in humans

No studies identified

Female reproductive toxicity in animals

1. Nitschke *et al*. (1983), as cited in ATSDR, IARC.
   A 3-generation reproductive toxicity study was conducted in Sprague-Dawley rats given 50, 100, or 200 mg/l of drinking water. No adverse effects on reproduction were identified. ATSDR used this study to derive a NOAEL of 30 mg/kg/day.
2. Norris (1977), as cited in Barlow and Sullivan, IARC.
   In a 3-generation reproductive toxicity study male and female rats were given drinking water containing 0, 60, 100, or 200 ppm 1,1-dichloroethylene. Treatment commenced at 6-7 weeks of age, 1st mating at 90 days of age. Fertility was so reduced in all groups, that a second mating was done to obtain F1b animals. Pup survival was reduced in F3a litters, but not in other groups.

Male reproductive toxicity in humans

No studies identified.

Male reproductive toxicity in animals

1. Anderson *et al*. (1977), as cited in ATSDR, Shepard's Catalog of Teratogenic Agents, Barlow and Sullivan.
   Under a dominant lethal protocol in mice, males were exposed to 0, 10, 30, 50, or 75 ppm 1,1-dichloroethylene by inhalation. Survival decreased in a dose-dependent fashion, with no effect at 10 ppm, and almost total lethality at 75 ppm. There was no significant effect on preimplantation loss, but females mated to males surviving the 50 ppm dose were significantly less likely to be pregnant than females mated to control males. Suggests effects on male fertility.
2. Nitschke *et al*. (1983), as cited in ATSDR, IARC.
   A 3-generation reproductive toxicity study was conducted in Sprague-Dawley rats given 50, 100, or 200 mg/l of drinking water. No adverse effects on reproduction were identified. ATSDR used this study to derive a NOAEL of 30 mg/kg/day.
3. Norris (1977), as cited in Barlow and Sullivan, IARC.
   In a 3-generation reproductive toxicity study male and female rats were given drinking water containing 0, 60, 100, or 200 ppm 1,1-dichloroethylene. Treatment commenced at 6-7 weeks of age, 1st mating at 90 days of age. Fertility was so reduced in all groups, that a second mating was done to obtain F1b animals. Pup survival was reduced in F3a litters, but not in other groups.
4 Short *et al*. (1977), as cited in ATSDR, IRIS®, Shepard's Catalog of Teratogenic Agents, Barlow and Sullivan.
   Dominant lethal protocol in the rat. Males exposed to 1,1-vinylidene chloride by inhalation at a concentration of 55 ppm, 6 hrs/day, 5 days/week, for 11 weeks. Mated during the 11th week. All treated males fathered at least 1 litter with viable implants, but there was a significant increase in infertile matings - evidence for reduced male fertility.

Secondary Sources

ATSDR. (1994) Agency for Toxic Substances and Disease Registry. Toxicological Profile for 1,1-Dichloroethene (update).

Barlow S.M. and Sullivan F.M. (1982) *Reproductive Hazards Of Industrial Chemicals*, Academic Press.

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES JULY 31, 1995)

IARC. International Agency for Research on Cancer (IARC, 1986). *Monographs On The Evaluation Of Carcinogenic Risk To Humans, Volume 39.* World Health Organization.

IRIS®. Integrated Risk Information System. US Environmental Protection Agency. (TOMES JULY 31, 1995)

RTECS®. Registry of Toxic Effects of Chemical Substances. National Institute of Occupational Safety and Health. (TOMES JULY 31, 1995)

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

FOLPET:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Folpet (CAS No. 133-07-3) is a fungicide with molecular formula $C_9H_4C_{l3}NO_2S$. It is used on fruits, vegetables, ornamentals, and turf. It is actively registered for use in CA, but, in 1993, was not used on food crops. Folpet is on the Proposition 65 list as a carcinogen.

Overview of Developmental/Reproductive Toxicity Concern

OEHHA staff have found that there is a DRAFT **MEDIUM-HIGH** level of developmental/reproductive toxicity concern. This is due to reports of developmental and male reproductive toxicity in animals. Developmental toxicity includes several reports of post-implantation mortality and two reports of malformations. However, several reports have not found malformations. Reports of male reproductive toxicity include dominant lethal and/or fertility effects in rodents. Concern for both developmental and male reproductive toxicity is somewhat tempered by the high dosages used, less relevant routes, and/or possibly contradictory reports.

Developmental Toxicity

Folpet has structural similarity to thalidomide, a human teratogen. No studies of human teratogenicity with folpet have been identified. Folpet has been studied extensively in animals for teratogenicity. It has been found to be teratogenic in 1 study each in mouse, rabbit, and hamsters. However, the malformations observed were different from the malformations observed in these species with thalidomide. Several studies in mice, rats, rabbits, and non-human primates have not found malformations. Post-implant mortality has been observed in studies in mice, rabbits, and hamsters.

Female reproductive toxicity

A single animal study did not provide any evidence of female reproductive toxicity.

Male reproductive toxicity

Dominant lethal and/or fertility effects have been found in rats and mice. These studies were not well described in the sources consulted.

Overview of Exposure Concern

OEHHA staff have found that there is a DRAFT **LOW** level of concern over the extent of exposure. Folpet is used in the U.S. as a fungicide on fruits, vegetables, ornamentals, and turf (1980s). California use is minimal. While folpet is actively registered for use in California, it was not used on food crops in 1993. In 1993, 3.02 lbs. were used for cut flowers, 0.0065 lbs. for landscape maintenance, and 0.10 lbs. for structural pest control in California. FDA food residue tolerances are: 50 ppm for vegetables and 25 ppm for fruits. Low levels (usually less than 2 ppm) on fruits and vegetables were found with low frequency (about 3%) at the Los Angeles FDA testing station from 1981-86. Folpet degrades rapidly in air and in alkaline waters (but more slowly in neutral water). Bioconcentration is not significant.

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 located.

Developmental toxicity in animals

1. Author not provided (NTIS PB223-160), as cited in RTECS®.
   Mice were treated with folpet by injection (sc) at 100 mg/kg/d on gd 6-14. Effects on litter size, extraembryonic structures, fetotoxicity, and developmental abnormalities (eye, ear, craniofacial [including nose and tongue], and urogenital system) were observed. In this source, variations and malformations are reported together as abnormalities.
2. Chevron Chemical Co. (1983), as cited in IRIS.
   Rats were treated with folpet in a teratology study. Incomplete ossification was observed at 360 mg/kg/d, with a NOEL of 60 mg/kg/d. Reduced maternal weight gain was observed at 60 mg/kg/d.
3. Chevron Chemical Co. (1984), as cited in IRIS.
   Rabbits (NZ white) were treated with folpet in a teratology study. Hydrocephalus and skull bone defects were observed at 20 mg/kg/d, with a NOEL of 10 mg/kg/d. Reduced maternal food consumption and weight gain were observed at 20 mg/kg/d.
4. Chevron Chemical Co. (1985c), as cited in IRIS.
   Rabbits (HY/CR) were treated with folpet in a teratology study. Delayed ossification was observed at 40 mg/kg/d, with a NOEL of 10 mg/kg/d. No evidence of hydrocephalus or other skull defects was noted. Reduced maternal weight gain and clinical signs of toxicity were observed at 160 mg/kg/d, with a NOEL of 40 mg/kg/d.
5. Courtney *et al.* (1978), as cited in HSDB, Schardein.
   Mice were treated with folpet orally (gavage) at 100 mg/kg/d for gd 6-15, injection (sc) at 100 mg/kg/d for gd 6-15, or inhalation at 830 mg/m^3 for 4 hr/d for gd 6-13. No malformations were observed.
6. Courtney *et al.* (1983), as cited in HSDB, RTECS®.
   Mice were treated with folpet orally (gavage) at 100 mg/kg/d for gd 6-15, injection (sc) at 100 mg/kg/d for gd 6-15, or inhalation at 491 or 624 mg/m^3 for 4 hr/d for gd 6-13. No teratogenicity was observed by any route. Fetal death was increased by inhalation at 491 mg/m^3. Maternal death (10%) was observed by inhalation at 624 mg/m^3. Maternal death was not observed by other routes.
7. Fabro *et al.* (1966), as cited in Reprotox™, Shepard's Catalog of Teratogenic Agents, Schardein.
   Rabbits were treated with folpet at 80 mg/kg/d for gd 7-12. No malformations were observed.
8. Kennedy *et al.* (1968), as cited in RTECS®, Reprotox™, Shepard's Catalog of Teratogenic Agents.
   a. Rats were treated at 500 mg/kg (not clear if this is total dosage or dose per day) during organogenesis. No teratogenesis was observed.
   b. Rabbits were treated orally with folpet at 37.5 or 75 mg/g/d for gd 6-18. Post-implantation mortality was observed at 37.5 mg/kg/d. No teratogenicity was observed.
9. Kennedy *et al.* (1972), as cited in Reprotox™, Schardein.
   Mammalian species (mouse, rat, rabbit, hamster, or monkey: unclear which) was treated with folpet. No teratogenicity was observed.
10. Robens (1970), as cited in RTECS®, Reprotox™, Schardein.
    Hamsters were treated with folpet orally at various dosages on various days during gestation. At 500 mg/kg on gd 8, increased fetal death was observed. At 600 mg/kg on gd 7, abnormalities of the central nervous system were observed. At 900 mg/kg on gd 7, abnormalities of the tail and ribs were observed.
11. Vondruska *et al.* (1971), as cited in Reprotox™, Schardein.
    Nonhuman primates were treated with folpet (dosage etc. not known). No teratogenicity was observed.

Female reproductive toxicity in humans

No studies were located.

Female reproductive toxicity in animals

1. Chevron Chemical Co. (1985a), as cited in IRIS®
   Rats were treated with folpet, presumably orally, in a 2 generation reproduction study. No effects on female reproductive parameters were noted.

Male reproductive toxicity in humans

No studies were located.

Male reproductive toxicity in animals

1. Author not provided (Food Cosm Toxicol 10:363, 1972), as cited in RTECS®.
   Rats (male) were treated with folpet orally or by injection (ip) at 500 mg/kg (total) 5 days prior to mating. Dominant lethal effects were observed.
2. Bridges (1975), as cited in HSDB.
   Rats and mice (males) were treated with folpet (dosages etc. not known). Dominant lethal effects were observed, to the 2nd generation in mice.
3. Chevron Chemical Co. (1985a), as cited in IRIS®.
   Rats were treated with folpet, presumably orally, in a 2 generation reproduction study. Reduced male fertility was observed at 3200 ppm (160 mg/kg/d), with a NOEL at 690 ppm (34.5 mg/kg/d).
4. Jorgensen *et al.* (1976), as cited in HSDB.
   Mice (males) were treated with folpet orally (food) for 7 weeks. No dominant lethal effects were observed.

Other relevant data

Folpet has been extensively tested for malformations due to structural similarity to thalidomide (Manson, 1986). However, the structure of folpet is only partly similar (Budavari *et al.* eds, 1989), and observed limb malformations from thalidomide in humans and rabbits (Manson, 1986) were different from hydrocephaly and skull bone defects from folpet in rabbits reported above.

Secondary Sources

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES JULY 31, 1995)

IRIS®. Integrated Risk Information System. US Environmental Protection Agency. (TOMES JULY 31, 1995)

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

RTECS®. Registry of Toxic Effects of Chemical Substances. National Institute of Occupational Safety and Health. (TOMES JULY 31, 1995)

Schardein J. L. (1993) *Chemically Induced Birth Defects*. Second Edition, Marcel Dekker.

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

Manson J. M. (1986) Teratogens (Ch. 7) in Casarett and Doull's Toxicology, Klaassen *et al.* eds., 3rd Ed. Macmillan Pub. Co. NY

Budavari *et al.* eds (1989) The Merck Index. 11th Ed. Merck & Co. NJ. Entries 4142 and 9182

CHROMIUM (includes tri and hexavalent forms): DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Uses for chromium include: pigments (inks, paints, dyes, ceramics, colored glass), metal finishing (corrosion inhibitor), electroplating, leather tanning, alloys, fertilizers, and wood preservative. Chromium is an essential nutrient, and chromium picolinate is currently popular as a nutritional supplement. Cr^{+6} is a Proposition 65 carcinogen. ("Chromium trioxide" and "chromium" were individual candidates in the master list; a decision to combine them was made at the time of prioritization).

Overview of Developmental/Reproductive Toxicity Concern

OEHHA staff have found that there is a DRAFT **MEDIUM** level of concern for developmental/reproductive toxicity over chromium (includes tri and hexavalent forms) due to reports of teratogenic effects in animals and male reproductive effects in humans and animals. Most of the studies were conducted in the 1970's and used the injection route. However, in one 1989 study using administration via drinking water to mice, growth retardation, developmental delay and embryolethality were reported at doses below those producing maternal toxicity. Also, one 1990 study with dietary administration found decreased sperm count and testicular pathology in mice. Direct examination of these and possibly more recent information would be valuable.

Developmental toxicity

Malformations have been reported in mouse and hamster studies using parenteral administration. In a single study using administration via drinking water, growth retardation, developmental delay and embryolethality were reported in mice at doses below those producing maternal toxicity; however, a single generation study with diet administration in rats failed to report developmental toxicity. Effects are likely to depend on the route, dose and form (Cr^{+3}, Cr^{+6}) of chromium, but more thorough review will be necessary to determine this. In a study reported as an abstract, no association was found between chromium concentrations in drinking water and CNS malformations in humans.

Female reproductive toxicity

A Russian-language study with a small sample size was described as finding an increased incidence of toxicosis and postnatal hemorrhage in female workers exposed to dichromate. Studies in mice and rats using administration in feed and drinking water reported reduced fertility and embryotoxicity; however, inhalation studies have not demonstrated such effects and the role of general toxicity needs to be clarified.

Male reproductive toxicity

Dominant lethal effects and testicular and sperm pathology have been reported in mice, rabbits and rats using i.p. administration. One study with dietary administration found decreased sperm count and testicular pathology in mice; however, rodent multigeneration studies using inhalation and oral exposure have reported no effects on fertility.

Overview of Exposure Concern

OEHHA staff have found that there is a DRAFT **HIGH** level of concern over the extent of exposure. The U.S. imported 270,001 metric tons of Cr_2O_3 in 1988. There are 130 facilities in California that manufacture or process chromium. Moss Landing, CA is a major producer and Occidental Petroleum is a major manufacturer of CrO_3 in Los Angeles. The 1994 TRI reports releases of 1,491,183 lbs of chromium, which included 6,204 lbs to environmental media, and 1,250,395 lbs of chromium compounds, which included 14,496 lbs to environmental media. Uses include: pigments (inks, paints, dyes, ceramics, colored glass), metal finishing (corrosion inhibitor), electroplating, leather tanning, alloys, fertilizers, and wood preservative. CrO_3 is used to manufacture magnetic

tapes. It was also formerly used as a topical antiseptic, but is now used only in veterinary medicine. The daily intake from diet for chromium is 5-115 microg/day. The daily intake from air and water is 0.4 microg/day. Cr^{+3} is the predominant form in biosystems, Cr^{+6} predominates in anthropogenic sources. The bioconcentration factor is low (1-100).

Recently, chromium picolinate has been advertised as dietary supplement for weight control to improve utilization of energy. The advertisements state that adequate evidence exists to demonstrate the safety of chromium picolinate, but developmental and reproductive toxicity studies are not mentioned.

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. Morton and Elwood (1974), as cited in IPCS.
   No relationship was found between Cr in drinking water and CNS malformations in this study which was reported as an abstract.

Developmental toxicity in animals

1. Gale (1978), Gale and Bunch (1979), Gale (1982), as cited in ATSDR, RTECS®, USEPA HAD.
   In several studies by the same group using i.v. administration of CrO_3 to hamsters, cleft palate, hydrocephalus, skeletal and kidney defects were produced with an ED50=0.5LD75. At the 8 mg/kg dose, which was effective in producing malformations, maternal toxicity in the form of weight loss and kidney tubular necrosis was noted.
2. Iijima *et al.* (1975), as cited in ATSDR, Schardein, USEPA HAD.
   In mice, i.p. administration of $CrCl_3$ 10 or 20 mg Cr/kg on gd 7, 8, 9, 10, or 11 led to exencephaly and rib defects. In a second study, where the highest dose, 20 mg/kg, was equal to the LD30, cleft palate was produced (Iijima *et al.* (1979), as cited in ATSDR).
3. Ivankovic and Preussman (1975), as cited in ATSDR
   Rats were given Cr_2O_3 in feed for a single generation at a dose of 1806 mg Cr/kg/day. No developmental toxicity effects were reported.
4. Mason *et al.* (1989), as cited in ATSDR
   Rats were given i.p. $Na_2Cr_20_7$ at a dose of 2 mg Cr/kg on gd 8. No developmental toxicity effects were reported.
5. Matsumoto *et al.* (1976), as cited in ATSDR, USEPA HAD.
   In mice, i.p. exposure to $CrCl_3$, 2 mg/kg on gd 7, 8, or 9 led to increased fetal and embryonic death (gd 8 and 9) and external malformations (gd 8) including exencephaly, open eyelids, and skeletal. In a second experiment, 10, 15, 20 or 24 mg Cr/kg were given i.p. on gd 8. Fetal weights were decreased in all groups, and there was an increase in external malformations (exencephaly, open eyelids, acephalia) at doses greater than or equal to 15 mg/kg.
6. Trivedi *et al.* (1989), as cited in ATSDR.
   In mice oral exposure to $K_2Cr_20_7$ in drinking water at a dose of 57 mgCr/kg/day led to increased resorptions and post implantation loss, decreased fetal weight, and decreased ossification. Maternal toxicity was recorded at >120 mg/kg/day.

Female reproductive toxicity in humans

1. Shmitova (1978), as cited in ATSDR, USEPA HAD.
   Women exposed to dichromate in a manufacturing facility in Russia reportedly had an increased incidence of toxicosis and postnatal hemorrhage. This study had a small sample size.

Female reproductive toxicity in animals

1. Glaser *et al.* (1985), as cited in ATSDR
   A rat three generation study with inhalation exposure to $Na_2Cr_2O_7$ reported no reproductive toxicity.
2. Glaser *et al.* (1985), as cited in ATSDR.
   A rat inhalation study with Cr_2O_3 reported no ovarian pathology.
3. Gross and Heller (1946), as cited in HSDB, USEPA HAD.
   Sterility and impaired reproductive function were reported in rats given Cr^{+6} (zinc chromate and potassium chromate) in feed at concentrations greater than 0.125%.
4. Ivankovic & Preussman (1975), as cited in ATSDR.
   A rat single generation study using oral Cr_2O_3 at a dose of 1806 mg Cr/kg/day reported no reproductive toxicity.
5. Trivedi *et al.* (1989), as cited in ATSDR.
   Increased pre and post implantatation loss, and decreased litter size were reported in mice exposed to $K_2Cr_2O_7$, in drinking water at 57 mg Cr/kg. No implantations were found at 234 mg Cr/kg.

Male reproductive toxicity in humans

No studies were identified.

Male reproductive toxicity in animals

1. Behari *et al.* (1978), as cited in ATSDR, USEPA HAD.
   Rabbits treated i.p. with $K_2Cr_2O_7$ 2 mg/kg for 3 or 6 weeks had edema of the testes, biochemical changes and absence of spermatocytes.
2. Glaser *et al.* (1985), as cited in ATSDR, USEPA HAD.
   No testicular pathology or reproductive effects were found in rats exposed by inhalation to chronic Cr_20_2 over three generations.
3. Ivankovic and Preussman (1975) as cited in ATSDR.
   No effects were reported in rats exposed orally to Cr_2O_3 at a dose of 1806 mg/kg/day over three generations.
4. Lee *et al.* (1989), as cited in ATSDR.
   No testicular pathology was found in rats exposed by inhalation to chronic Cr_20_2,
5. Murthy *et al.* (1991), as cited in ATSDR.
   Rats given $K_2Cr_2O_7$, by the i.p. route (2 mgCr/kg/day, 15 days) showed no effect on sperm but demonstrated spermatid morphology changes and leakage of Sertoli cell tight junctions.
6. Pashin *et al.* (1982), as cited in IPCS.
   In a dominant lethal study, mice received 0.5-20 mg/kg $K_2Cr_2O_7$ as a single i.p. injection or 1 or 2 mg/kg $K_2Cr_2O_7$ daily i.p. for 21 days. The daily injections, or the single injection at doses above 2 mg/kg, produced dominant lethal effects manifested as decreased embryo survival.
7. Zahid *et al.* (1990), as cited in ATSDR.
   Mice fed $Cr_2(SO_4)_3$, 14 mg Cr/kg/day and $K_2Cr_2O_7$, 9.1 mg Cr/kg/day in diet had decreased sperm count and testicular pathology.

Other relevant data

1. ATSDR (1993).
   Placental transfer has been demonstrated for chromium in humans.
2. Daniellson *et al.* (1982), as cited in ATSDR.
   In mice, 19% of an i.v. dose of $Na_2Cr_2O_7$ administered on gd 8-18, was found in the fetal skeleton and yolk sac.
3. HSDB (1995).
   The human fetus showed an accumulation factor of 10 for total chromium. Chromium is an essential trace element. Deficiency affects glucose tolerance; the RDA is 50-200 µg/day. In rats, <1% of Cr^{+6} is absorbed. There is greater absorption of Cr^{+3} than Cr^{+6}. Cr^{+3} salts are not corrosive, but are poorly soluble, and have low membrane permeability.
4. Iijima *et al.* (1975), as cited in ATSDR.
   In mice, $CrCl_3$, administered i.p. on gd 8, produced pyknotic cells in the neuroepithelium. This was considered a possible mechanism for neural tube defect.

Secondary Sources

ATSDR. (1993) Agency for Toxic Substances and Disease Registry. Toxicological Profile for Chromium.

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES JULY 31, 1995)

IPCS. International Programme on Chemical Safety (1988) Environmental Health Criteria 61. Chromium. World Health Organization, Geneva, Switzerland.

RTECS®. Registry of Toxic Effects of Chemical Substances. National Institute of Occupational Safety and Health. (TOMES JULY 31, 1995)

Schardein J. L. (1993) *Chemically Induced Birth Defects*. Second Edition, Marcel Dekker.

USEPA HAD. US Environmental Protection Agency. Health Assessment Document for Chromium. (EPA-600/8-83-014F, 1984).

COPPER SULFATE:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Copper sulfate (CAS No. 7758-98-7) is used in agriculture, industrial metal finishing, wood preservatives, and water treatment. Copper salts that release Cu^{+2} in solution were also reviewed if mentioned in secondary sources.

Overview of Developmental/Reproductive Toxicity Concern

OEHHA staff have found that there is a DRAFT **MEDIUM** level of developmental/reproductive toxicity concern over copper sulfate due to reports of cardiac and neural tube defects in animal studies. With the exception of intrauterine death in mink, and one mouse study reported intrauterine death and developmental abnormalities (not further characterized in the the secondary sources) after dietary administration of copper sulfate, developmental effects have been demonstrated by the injection route only. There are no relevant human studies of birth defects.

Developmental toxicity

Copper sulfate and citrate apparently induce a reproducible malformation syndrome including cardiac and neural tube defects when injected in pregnant mice and hamsters. These effects have not been demonstrated by the oral route of administration. A study in mice reported intrauterine death and other unspecified developmental abnormalities after ingestion of copper sulfate at the highest of several doses before and during pregnancy. No information on maternal toxicity was provided.

Female reproductive toxicity

Decreased fertility and increased postimplantation loss has been reported in rats after administration of copper sulfate by injection. A single study with dietary administration in mink reported no effect on fertility but increased postnatal mortality. Studies of copper-containing intrauterine devices were not included in the review.

Male reproductive toxicity

Effects on male reproductive organs have been reported after injection exposure of rats, but general toxicity and effects on fertility at these doses are not known.

Overview of Exposure Concern

OEHHA staff have found that there is a DRAFT **MEDIUM** level of concern over the extent of exposure. Its use breakdown is as follows: 65% agriculture, 28% industrial metal finishing and wood preservatives, and 7% water treatment. In 1992, 3,146,844 lbs of copper sulfate were used as a pesticide in California. Copper sulfate is widely used for home gardening, and is added to surface water as an algicide. However, it has been classified as exempt SB950 which requires submission of complete set of developmental toxicity studies. It is the most commonly used copper compound in US. There are no mines or smelters in CA. There are, however, two manufacturers in CA according to 1987 data. Other releases result from mining, sewage plants, fungicidal/algicidal use, copper pipes, etc. According to the 1994 TRI, total releases for “copper” were: 63,600 lbs to air, 1,224 lbs to water, 79,659 lbs to land. Copper is an essential trace element with an RDA of 2-3 mg/day. It has a low BCF (10-100) and it does not bioaccumulate. Some poisoning has occurred from drinking acidic beverages stored in copper containers. Copper sulfate is on the FDA Generally Recognized As Safe (GRAS) list.

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. Aulerich *et al.* (1982), as cited in ATSDR, Reprotox™.
   Increased intrauterine mortality was reported in mink fed copper in diet at doses of 3 mg Cu/kg/day or greater.
2. DiCarlo (1979), (1980), as cited in Schardein.
   In a series of experiments, heart malformation were described in offspring of hamsters given i.v. administration of copper citrate.
3. Ferm and Hanlon (1974), as cited in HSDB, RTECS®, Reprotox™, Schardein.
   Hamsters administered copper sulfate (2 mg/kg) or copper citrate i.v. on gd 8, were reported to demonstrate resorptions, and heart and CNS defects in offspring.
4. James *et al*. (1966), as cited in Schardein
   No teratogenic effects were reported in a study with a small number of sheep using oral administration.
5. Lecyk (1980), as cited in ATSDR, HSDB, Reprotox™, Schardein.
   Pregnant mice were fed Cu as copper sulfate in diet at 7 concentrations for 1 mo prior to pregnancy and on gd 0-19. These concentrations were described as being equivalent to 26, 52, 104, 155 and 208 mg/kg/day. At 26 and 52 mg/kg/day increased fetal weights and litter size were reported. At 104 mg Cu/kg/d increased intrauterine mortality was reported. At 155 mg/kg/d, "developmental abnormalities", as cited in ATSDR, "multiple defects", as cited in Schardein, "skeletal and other malformations", as cited in HSDB, were reported.
6. Mason *et al*. (1989), as cited in Reprotext™.
   No teratogenic effects were found in rats.
7. O'Shea and Kaufman (1979), (1980), as cited in RTECS®, Reprotext®.
   Neural tube defects were demonstrated in mice after i.v. (13 mg/kg, gd 7) or in vitro exposures to copper sulfate.

Female reproductive toxicity in humans

No studies were identified

Female reproductive toxicity in animals

1. Aulerich *et al.* (1982), as cited in ATSDR, Reprotox™.
   This study found no effect on female reproduction in mink fed copper sulfate in the diet (3 and 13 mg Cu/kg/day) except an increase in newborn mortality.
2. Giavini *et al.* (1980), as cited in RTECS®.
   Female fertility was reduced in rats treated i.p. on gd 3 at a dose of 7.5 mg/kg, and in rats treated s.c. on gd 7-10 with copper acetate at 40 mg/kg.
3. James *et al.* (1966), as cited in Reprotox™.
   Copper sulfate caused abortion in a small study using oral administration to sheep.
4. O'Shea and Kaufman (1979), (1980), as cited in ATSDR, RTECS®.
   Rats treated i.v. with 3.2 mg Cu/kg as copper sulfate on gd 7 were reported to have increased postimplantation loss.
5. Suzuki *et al.* (1970), (1972), as cited in Reprotext™.
   Copper sulfate stimulated ovulation and caused false pregnancy in rabbits and rats (route not given).

Male reproductive toxicity in humans

No studies were identified.

Male reproductive toxicity in animals

1. Aulerich (1982), as cited in ATSDR.
   No effect on male mink fertility from dietary exposure to copper sulfate (3 and 13 mg Cu/kg/day) was reported.
2. Kamboj and Kar (1964), as cited in RTECS®.
   Effects on testes, epididymis and sperm ducts were reported when copper sulfate, 13 mg/kg, was administered s.c. to male mice 30 days prior to mating or to male rats 1 day prior to mating. Intratesticular injection of 3 mg/kg 1 day prior to mating had a similar effect on rats.

Other relevant data

Copper is an essential trace element with a daily requirement of 2-3 mg/day. Copper is known to cross the placenta of various species and to be stored in the fetal liver. In vineyard workers exposed to copper sulfate, milk copper was 6.2 times greater than in controls, as cited in HSDB. Copper can induce methemoglobinemia and the fetus is thought to be more sensitive than the adult, as cited in Reprotox™. Infants (< 1 year old) are more sensitive to copper toxicity than adults due to poor elimination, as cited in ATSDR. There are apparent species differences in sensitivity to copper sulfate; mink are 50 times more sensitive than mice. Copper, inserted as a metal wire into the uterus or vas deferens, is used as a human contraceptive. Adverse pregnancy outcome is not noted in Wilson's disease, a hereditary disease with excess copper levels. In vitro inhibition of human sperm motility has been demonstrated (Rosada *et al.* (1970), as cited in Reprotext®).

Secondary Sources

ATSDR. (1990) Agency for Toxic Substances and Disease Registry. Toxicological Profile for Copper.

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES JULY 31, 1995)

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

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

RTECS®. Registry of Toxic Effects of Chemical Substances. National Institute of Occupational Safety and Health. (TOMES JULY 31, 1995)

Schardein J. L. (1993) *Chemically Induced Birth Defects*. Second Edition, Marcel Dekker.

FORMAMIDE:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Formamide (CAS No. 75-12-7) is an organic compound with formula $HCONH_2$. It appears to be used mainly in the pharmaceutical industry as a chemical intermediate or a solvent. It has some use in molecular biology laboratories. It is also used in some glues, and has been used in water soluble inks (including felt-tipped pens).

Overview of Developmental/Reproductive Toxicity Concern

OEHHA staff have found that there is a DRAFT **MEDIUM** level of developmental/reproductive toxicity concern. This is due to reports of developmental toxicity in animals, including resorptions, malformations, and reduced fetal weight. However, the very high dosages used, and other weaknesses in the data, temper the level of concern.

Developmental toxicity

There are several reports in animals, including mice, rats, and rabbits, of developmental toxicity. Increased resorptions and malformations, and reduced fetal weight have been observed. However, most of these effects occurred at high dosages (in the grams/kg/d range). Also, most of the studies are old, in foreign languages and are not readily available in English translation, and/or are available only in abstract.

Female reproductive toxicity

One report in rats observed reduced fertility and litter size in the continuous breeding protocol. However, the dosage was high (750 ppm in water) and the report was available only in abstract.

Male reproductive toxicity

There is one report in rats of testicular lesions from injection (ip) at grams/kg dosages. These effects were seen only in animals which died, but not in animals which survived for 1 month after treatment (if testicular lesions occurred, they were reversed in this time).

Overview of Exposure Concern

OEHHA staff have found that there is a DRAFT **LOW** level of concern over the extent of exposure. Formamide appears to be used mainly in the pharmaceutical industry as a chemical intermediate or a solvent. It is used in molecular biology laboratories in denaturing gel electrophoresis. It is also used in some glues, and has been used in water soluble inks (including felt-tipped pens). It is miscible in water and has low volatility. Formamide is biodegraded and degraded by hydroxyl radicals in the atmosphere. It is not expected to bioconcentrate or biomagnify.

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 ot provided here.

Developmental toxicity in humans

No studies were identified.

Developmental toxicity in animals

1. Fail *et al.* (1993), as cited in Reprotox™.
   Mice (male and female) were treated orally (water) at 750 ppm in a continuous breeding protocol. Reduced fertility and litter size were observed. Effects were female mediated. (Note: abstract only.) (Also cited in the female repro section.)
2. Gleich (1974), as cited in Barlow and Sullivan.
   a. Mice (female) were treated by injection (ip) at 0.076 or 0.19 ml/kg/d on gd 6-15. Fetal losses (13% or 27%) and malformations (4% or 25% of survivors) were observed.
   b. Mice (female) were treated dermally at 0.008 or 0.076 ml/d [if 35 g mice, about 0.26 or 2.4 g/kg/d, respectively] on gd 10 and 11. Increased resorptions (8% or 61%) and malformations (0% or 36%) were observed. LD50 is 0.4 ml(/d?). (Note: abstract only.)
   Kreybig (1968), as cited in Schardein.
   Rats were treated by injection (no details). Various malformations were observed. (NOTE: probably redundant to von Kreybig (1968)).
3. Merkle and Zeller (1980), as cited in HSDB, RTECS®, Reprotox™, Schardein.
   Rabbits were treated orally (gavage) at 70 mg/kg/d for gd 6-18. No maternal toxicity was observed. Increased post-implantation mortality, malformations, and other fetotoxicity were observed.
4. Oettel and Frohberg (1964), as cited in Barlow and Sullivan, Schardein.
   Mice (female) were treated dermally with 0.1 ml or 2x0.1 ml [if 35 gram mice, about 3.2 or 6.4 g/kg, respectively] on gd 11. Increased resorptions (50% or 80%) and malformations (>50% or unreported %) were observed. These doses correspond to 1/4 and 1/2 of the LD50.
5. Stula and Kraus (1977), as cited in HSDB, RTECS®, Shepard's Catalog Of Teratogenic Agents, Barlow and Sullivan.
   Rats (female) were treated dermally at 0.6 g/kg on 1 or 2 days between gd 9-13. Increased embryonic death (control: 2%, treated gd 9, 10, or 13: 5%; gd 11, or 12: 13%; stat sig not addressed) was observed. Fetal weight was reduced (2.4g in controls, 2.1g in "some treated groups"; stat sig not addressed). Malformations were similar in treated groups to historical controls, although increased subcutaneous hemorrhages (4/60) may have been observed. LD50 reported to be about 17 g/kg on gd 11.
6. Thiersch (1962), as cited in Barlow and Sullivan.
   a. Rats (female) were treated orally at 2 g/kg on gd 7. Resorption (50%) and stunting (26% of survivors) was observed. No malformations were observed.
   b. Rats (female) were treated orally at 3x2 g/kg after gd 7 (days not specified). Complete resorption of litters was observed.
   c. Rats were treated orally: the LD50 was found to be 6 g/kg (not specified if this is male or female, pregnant or non-pregnant). Note: abstract only. See also Thiersch (1971).
7. Thiersch (1971), as cited in RTECS®, Reprotox™, Shepard's Catalog of Teratogenic Agents.
   a. Rats (female) were treated by injection (ip) at 1 ml/d [if 300 g rat, about 3.8 g/kg/d] on gd 11-16. Increased resorptions (36%), stunting (46% of survivors) and increased malformations (palate and extremities) were observed.
   b. Rats (female) were treated orally at 2 g/kg, on gd 7. Increased post-implantation mortality and "fetotoxicity" were observed. (NOTE: reads like Thiersch (1962).)
   c. Rats (female) were treated orally at 1.6 g/kg/d for gd 7-12. Increased developmental abnormalities - musculoskeletal system were observed. (Note: malformations and variations are combined under the category "abnormalities".)
8. Von Kreybig (1968), as cited in Barlow and Sullivan.
   Rats were treated by injection (sc) at above 3 g/kg on gd 13. The LD50 was over 4 g/kg. Teratogenic effects at over 3 g/kg were observed. (Note: probably redundant to Kreybig (1968)).

Female reproductive toxicity in humans

No studies were identified.

Female reproductive toxicity in animals

1. Fail *et al.* (1993), as cited in Reprotox™.
   Mice (male and female) were treated orally (water) at 750 ppm in the continuous breeding protocol. Reduced fertility and litter size were observed. Effects were female mediated. (Note: abstract only.) (Also cited in the developmental section.)

Male reproductive toxicity in humans

No studies were identified.

Male reproductive toxicity in animals

Chanh *et al.* (1971), as cited in HSDB, Barlow and Sullivan.
Rats (male) were treated by a single injection (ip) at 5.0-5.4 g/kg. Some rats died. In the dead rats, testicular atrophy with complete disruption of seminiferous epithelium and hyperplasia of interstitial tissue was observed. These lesions were not observed in animals which survived the treatment for 1 month.

Other relevant data

Formamide is absorbed directly through guinea pig skin (as cited in HSDB). It is probably hydrolyzed in liver to formic acid and ammonia.

Secondary Sources

Barlow S.M. and Sullivan F.M. (1982) *Reproductive Hazards Of Industrial Chemicals*, Academic Press.

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES JULY 31, 1995)

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

RTECS®. Registry of Toxic Effects of Chemical Substances. National Institute of Occupational Safety and Health. (TOMES JULY 31, 1995)

Schardein J. L. (1993) *Chemically Induced Birth Defects*. Second Edition, Marcel Dekker.

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

METHYL BUTYL KETONE: DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Methyl butyl ketone (MBK), (CAS No. 591-78-6), synonym 2-hexanone, has the molecular formula $C_6H_{12}O$. It was previously used as a solvent in lacquers, varnishes, inks, and as a chemical intermediate (1970s and 1980s). It is not currently produced, processed, or used in the U.S.

Overview of Developmental/Reproductive Toxicity Concern

OEHHA staff have found that there is a DRAFT **MEDIUM** level of toxicological concern. This is due to reports of male reproductive toxicity in rats, specifically reduced testicular weight and atrophy of the germinal epithelium. Concern is tempered by the high dosages used, and the lack of fertility studies.

Developmental Toxicity

There is one study in rats, by inhalation, which found reduced litter size, birth weight, postnatal growth, and behavioral effects at high, maternally toxic, levels of exposure.

Female Reproductive Toxicity

Same as developmental toxicity.

Male Reproductive Toxicity

There are 3 studies in rats, by inhalation, drinking water, and gavage, all at high levels, which showed testicular effects (reduced weight, atrophy of germinal epithelium). No studies of reproduction were found.

Overview of Exposure Concern

OEHHA staff have found that there is a DRAFT **LOW** level of concern over the extent of exposure. MBK was previously used as a solvent in lacquers, varnishes, inks etc., and as a chemical intermediate (1970s and 1980s). It is not currently produced, processed, or used in the U.S. The reason for the current lack of use in U.S. may be related to a well-reported occupational poisoning (neurotoxicity) from the early 1970s, and numerous subsequent supporting animal studies. It is photooxidized in air with a half-life of approximately 36 hours. It is probably biodegraded in soil and water. It is not expected to bioconcentrate or biomagnify.

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. Peters *et al*. (1981), as cited in ATSDR, HSDB, RTECS.
   Rats were treated with MBK by inhalation at 1,000 or 2,000 ppm for 6 hr/d on gd 1-21. Reduced maternal weight gain (by 10% at 1,000 ppm and 14% at 2,000 ppm) was observed. Reduced litter size, birth weight and postnatal growth at 2,000 ppm were observed. Behavioral alterations (increased activity, reduced learning) at

1,000 and 2,000 ppm were observed. RTECS reports gastrointestinal and urogenital abnormalities at 1,000 ppm. (Note: RTECS combines variations and malformations under the category abnormalities.)

Female reproductive toxicity in humans

No studies were identified.

Female reproductive toxicity in animals

1. Peters *et al*. (1981), as cited in ATSDR, HSDB, RTECS.
   Rats were treated with MBK by inhalation at 1,000 or 2,000 ppm for 6 hr/d for gd 1-21. Reduced maternal weight gain (by 10% at 1,000 ppm and 14% at 2,000 ppm) was observed. Reduced litter size, birth weight and postnatal growth at 2,000 ppm were observed (which could potentially have resulted from toxicity to the maternal reproductive system).

Male reproductive toxicity in humans

No studies were identified.

Male reproductive toxicity in animals

1. Boekelheide (1987), as cited in ATSDR.
   Rats (male) were treated with MBK orally (water) at 1% (est. 1,400 mg/kg/d) for 4 weeks. Reduced testicular weight and histopathologyical lesions of the testes were observed.
2. Katz *et al*. (1980), as cited in ATSDR, RTECS®.
   Rats (male) were treated with MBK by inhalation at 692 ppm for 18 hr/d, 72 hr/wk, 11 weeks. Reduced testicular weight and atrophy of the germinal epithelium were observed.
3. Krasavage (1980), as cited in ATSDR.
   Rats (male) were treated with MBK orally (gavage) at 660 mg/kg/d for 90 days. Atrophy of the germinal epithelium was observed (statistical significance not addressed).

Other relevant data

MBK appears to readily cross the placenta. Neurotoxicity was observed within 2 weeks in Katz *et al*. (1980), as cited in ATSDR, RTECS®, above. Neurotoxicity is a commonly observed endpoint in adult animals.

Secondary Sources

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

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES JULY 31, 1995)

RTECS®. Registry of Toxic Effects of Chemical Substances. National Institute of Occupational Safety and Health. (TOMES JULY 31, 1995)

TOXAPHENE:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY:

Toxaphene (CAS No. 8001-35-2) in an organochlorine pesticide with an approximate empirical formula of $C_{10}H_{10}Cl_8$. Toxaphene is a reproducible mixture of at least 177 compounds produced by the chlorination of camphene. It was previously used as insecticide on crops (mainly cotton, also food) and poultry and livestock. U.S. EPA restricted uses in 1982, and banned all registered uses 1990. Small amounts are still used in California for landscape maintenance and structural pest control. Toxaphene is on the Proposition 65 list as a carcinogen.

Overview of Developmental/Reproductive Toxicity Concern

OEHHA staff have found that there is a DRAFT **MEDIUM** level of developmental/reproductive toxicity concern. This is due to reports of developmental toxicity, including malformations, altered growth and behavioral and biochemical alterations in animals. Concern is tempered by several reports of no effect on embryonic or fetal death or malformations, and the sporadic observation of other adverse effects. No studies in humans were identified.

Developmental toxicity

There is one report of an acutely poisoned pig giving birth to a stillborn litter. There is a report of malformations in mice by gavage at a dosage at which "marked" maternal lethality was found. There is one report each of malformations in rat and hamster by unknown route, with no discussion of maternal toxicity. Most studies in animals have found no malformations or death of developing organism. There are reports in rat of reduced fetal body weight and sternal ossification, in mouse of reduced newborn pup weight, and in rat of reduced postnatal weight gain. There have also been reports in rat of behavioral changes, and of biochemical changes in kidney and neural elements. In mice, there is a single report of alteration in immune parameters.

Female reproductive toxicity

In rat, there is one report of vaginal bleeding at high dosages; hematuria and other toxic effects were also observed. Other studies have found no effect on fertility or litter size.

Male reproductive toxicity

In rat, there is a poorly documented report of effects on spermatogenesis. Other studies found no effects on fertility or litter size, or dominant lethal effects.

Overview of Exposure Concern

OEHHA staff have found that there is a DRAFT **LOW** level of concern over the extent of exposure. Toxaphene was previously used as an insecticide on crops (mainly cotton, but also food crops), poultry and livestock. US EPA restricted uses in 1982, and banned all registered uses in 1990. However, California DPR reported use of 228.6 lbs. in 1992 for landscape maintenance and 5.2 lbs. for structural pest control; "special, exempt, and experimental" uses for small quantities are outside of the US EPA ban on registered uses. There are 4-7 NPL hazardous waste sites in California which contain toxaphene. It is manufactured for export in Delaware and Texas. Toxaphene is widely used outside of the U.S. It volatilizes readily, and can be transported great distances in the atmosphere. It bioconcentrates at lower trophic levels, but does not appear to biomagnify. The latter is possibly due to metabolism in higher organisms. Toxaphene is often found at hazardous waste sites.

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. Allen *et al*. (1983), as cited in ATSDR.
   Mice were treated with toxaphene orally (food) at 1.3 (or 13? different on different pages of secondary source) mg/kg/d for 9.5 weeks including gestation and lactation. Alterations in immunological parameters (delayed hypersensitivity and humoral antibody response) were observed. No malformations were observed.
2. Badaeva (1979), as cited in Reprotox™, Shepard's Catalog of Teratogenic Agents.
   Rats were treated with toxaphene orally at 12 mg/kg/d for 2 weeks during pregnancy. Reduced cholinesterase activity of fetal neural structures and hampered differentiation of cardiac neural elements was observed.
3. Chernoff and Carver (1976), as cited in ATSDR, RTECS®, Reprotox™, Reprotext®, Schardein, IARC.
   a. Rats were treated with toxaphene orally (gavage) at 0, 15, 25, or 35 mg/kg/d for gd 7-16. Increased maternal mortality (31%) at 35 mg/kg/d and reduced maternal weight gain at 15 mg/kg/d was observed. Reduced fetal body weight at 25 mg/kg/d was observed. Reduced fetal sternal ossification was observed at 15 mg/kg/d. No malformations were observed.
   b. Mice were treated with toxaphene orally (gavage) at 0, 15, 25, or 35 mg/kg/d for gd 7-16. "Marked" maternal mortality, reduced weight gain, and increased liver weight at 35 mg/kg/d were observed. Exencephaly and/or encephalocele in fetuses were observed at 35 mg/kg/d. No increase in resorptions or reduced fetal weight were observed.
4. Chernoff and Kavlock (1982), as cited in ATSDR, RTECS®.
   Mice were treated with toxaphene orally at 75 mg/kg/d for gd 8-12. Reduced pup weight on postnatal day 1 was observed. No malformations were observed.
5. Chu *et al*. (1988), as cited in ATSDR, Reprotox™, Reprotext®, Shepard's Catalog of Teratogenic Agents.
   Rats (male and female) were treated with toxaphene orally (food) at 4.0 to 500 ppm for 48 weeks (1 generation, 2 litters). Reduced postnatal weight gain was observed. No effects on fertility or postnatal viability were observed. (Also cited in the male and female reproductive sections.)
6. Crowder *et al*. (1980), as cited in ATSDR.
   Rats were treated with toxaphene (dosage etc. unknown). No malformations were observed.
7. Kavlock *et al*. (1982), as cited in ATSDR.
   Rats were treated with toxaphene at 12.5 mg/kg/d for gd 7-16. Reduced fetal renal protein and alkaline phosphatase activity were observed. No malformations were observed.
8. Kavlock *et al*. (1985), as cited in RTECS®, Reprotox™, Reprotext®.
   Mice were treated with toxaphene orally at 12.5 mg/kg/d for 8 days of pregnancy. Maternal toxicity and increased fetal supernumerary ribs were observed.
9. Kennedy *et al*. (1973), as cited in ATSDR, Reprotext®, IARC.
   Rats (male and female) were treated with toxaphene orally (food) at 25 or 100 ppm for 3 generations. Slight cytoplasmic vacuolization in livers of parental animals, but no effects on survival, growth, or organ weight were observed. No effect on litter sizes, pup survival, malformations, or weanling body weights were observed. (Also cited in the female and male reproductive toxicity in animals sections.)
10. Keplinger *et al*. (1968), as cited in ATSDR, IARC.
    Mice were treated with toxaphene orally (food) at 25 ppm for 5 generations. Fatty changes in parental animals livers were observed. No effects on litter size or postnatal viability or growth were observed. (Also cited in the female and male reproductive toxicity in animals sections.)
11. Martson and Shepelskaya (1980), as cited in Shepard's Catalog of Teratogenic Agents, Schardein.
    a. Rats were treated with toxaphene (by unknown route) at 40 mg/kg/d for gd 6-15 or 4 mg/kg/d for gd 1-20.

Teratogenic effects were observed.
b. Hamsters were treated with toxaphene (by unknown route) at 40 mg/kg/d for gd 7-11 or 4 mg/kg/d for gd 1-15. Teratogenic effects were observed.

12. Mount *et al*. (1980), as cited in Reprotext®.
A litter of stillborn pigs was born to an acutely poisoned sow.
13. Olson *et al*. (1980) , as cited in ATSDR, RTECS®.
Rats were treated with toxaphene orally (food) at 0.05 mg/kg/d for gd 5-22. Reduced swimming ability in developing pups was observed. Mature swimming ability was achieved in all groups by postnatal day 16. No malformations were observed.

Female reproductive toxicity in humans

No studies were identified.

Female reproductive toxicity in animals

1. Chu *et al*. (1988), as cited in ATSDR, Reprotox™, Reprotext®, Shepard's Catalog of Teratogenic Agents.
Rats (males and females) were treated with toxaphene orally (food) at 4.0 to 500 ppm for 48 weeks (1 generation, 2 litters). Reduced postnatal weight gain was observed. No effects on fertility or postnatal viability were observed. (Also cited in the developmental and male reproductive toxicity in animals sections.)
2. Kennedy *et al*. (1973), as cited in ATSDR, Reprotext®, IARC.
Rats (male and female) were treated with toxaphene orally (food) at 25 or 100 ppm for 3 generations. Slight cytoplasmic vacuolization in livers of parental animals, but no effects on survival, growth, or organ weight were observed. No effect on litter sizes, pup survival, malformations, or weanling body weights were observed. (Also cited in the developmental and male reproductive toxicity in animals sections.)
3. Keplinger *et al*. (1968), as cited in ATSDR, IARC.
Mice (male and female) were treated with toxaphene orally (food) at 25 ppm for 5 generations. Fatty changes in parental animals livers were observed. No effects on litter size or postnatal viability or growth were observed. (Also cited in the developmental and male reproductive toxicity in animals sections.)
4. National Cancer Institute (NCI) (1977), as cited in ATSDR, HSDB.
Rats (female) were treated with toxaphene orally (food) at 540 ppm for 80 weeks. Vaginal bleeding was observed. Also, hematuria, ataxia, and other neurotoxicity was observed.

Male reproductive toxicity in humans

No studies were identified.

Male reproductive toxicity in animals

1. Author not provided (1980) Gigiena I Sanitarya 45(5):14, as cited in RTECS®.
Rats were treated with toxaphene orally at 280 mg/kg (total) 10 weeks prior to mating (duration of treatment not clear). Toxic effects on spermatogenesis were observed.
2. Chu *et al*. (1988), as cited in ATSDR, Reprotox™, Reprotext®, Shepard's Catalog of Teratogenic Agents.
Rats (males and females) were treated with toxaphene orally (food) at 4.0 to 500 ppm for 48 weeks (1 generation, 2 litters). Reduced postnatal weight gain was observed. No effects on fertility or postnatal viability were observed. (Also cited in the developmental and female reproductive toxicity in animals sections.)
3. Epstein *et al*. (1972), as cited in ATSDR.
Mice (male) were treated with toxaphene orally (gavage) at 80 mg/kg/d for 5 days or by injection (ip) at 180 mg/kg (1x). Death by gavage at 80 mg/kg/d (9/12) and by injection at 180 mg/kg (2/9) were observed. When males were mated to untreated females, no reduction in live implants or increase in dead implants was observed.
4. Kennedy *et al*. (1973), as cited in ATSDR, Reprotext®, IARC.
Rats (male and female) were treated with toxaphene orally (food) at 25 or 100 ppm for 3 generations. Slight

cytoplasmic vacuolization in livers of parental animals, but no effects on survival, growth, or organ weight were observed. No effect on litter sizes, pup survival, malformations, or weanling body weights were observed. (Also cited in the developmental and female reproductive toxicity in animals sections.)

5. Keplinger *et al*. (1968), as cited in ATSDR, IARC.
   Mice (male and female) were treated with toxaphene orally (food) at 25 ppm for 5 generations. Fatty changes in parental animals livers were observed. No effects on litter size or postnatal viability or growth were observed. (Also cited in the developmental and female reproductive toxicity in animals sections.)
6. Peakull (1976), as cited in ATSDR.
   Rats (male) were treated with toxaphene orally at 120 mg/kg (1x, capsule) or at 2.4 mg/kg/d (food) for 1, 3, or 6 months. No effect on testosterone levels in the blood was observed.

Other relevant data

Toxaphene is highly lipophilic, and has been reported to distribute mainly to maternal fat. Very low levels are found in the fetus. It is rapidly metabolized in adult animals. Toxaphene and metabolites are excreted over a period of several days in urine and feces. If it behaves similarly to other organochlorine pesticides, there is potential for excretion in milk. Toxaphene has been found in cow's milk. It has also detected in human breast milk from Sweden at 0.1 mg/kg (milk fat basis).

Secondary Sources

ATSDR. (1994) Agency for Toxic Substances and Disease Registry. Toxicological Profile for Toxaphene.

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES JULY 31, 1995)

IARC. International Agency for Research on Cancer (IARC, 1979). *Monographs On The Evaluation Of Carcinogenic Risk To Humans, Volume 20, pp. 327-348*. World Health Organization.

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

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

RTECS®. Registry of Toxic Effects of Chemical Substances. National Institute of Occupational Safety and Health. (TOMES JULY 31, 1995)

Schardein J. L. (1993) *Chemically Induced Birth Defects*. Second Edition, Marcel Dekker.

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

1,2-DICHLOROPROPANE: DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

1,2-Dichloropropane (synonym: propylene dichloride) (CAS No. 78-87-5) is an organochlorine compound with the formula $C_3H_6Cl_2$. It is used as a chemical intermediate, and in pesticides, industrial and commercial solvents, and as a lead scavenger in anti-knock compounds. 1,2-Dichloropropane is on the Proposition 65 list as a carcinogen.

Overview of Developmental/Reproductive Toxicity Concern

OEHHA staff have found that there is a DRAFT **LOW** level of developmental/reproductive toxicity concern. This is due to the existence of several studies in animals which show lack of major effects, lack of consistent effects, and/or lack of effects at dosages not substantially toxic to the adult.

Developmental toxicity

There are 3 relevant industry studies in animals. There are 2 developmental studies, in rat and rabbit by gavage, which found delayed fetal ossification, but no other effects, at dosages where reduced maternal weight gain was observed in rats and rabbits and maternal anemia was observed in rabbits. A 2-generation study in rats by water found reduced neonatal survival and weight gain in the F1 generation, but no other effects, at a dosage where adult weight gain was reduced, and anemia was observed in adult females. No reduced neonatal survival was observed in the F2 generation.

Female reproductive toxicity

There is 1 case report in humans of a 20 year old female who sniffed a stain remover containing 60-100% 1,2-dichloropropane “every night”. She was admitted to the hospital with uterine bleeding, hematuria, acute kidney and liver failure, and other signs. Following blood transfusions and dialysis, she recovered.

In animals, a 2-generation study in rats by water found reduced neonatal survival and weight gain in the F1 generation, but no other effects (including fertility or litter size), at a dosage where adult weight gain was reduced, and anemia was observed in adult females. No reduced neonatal survival was observed in the F2 generation. A 13 week study by inhalation found no effect on female reproductive organs in mice, rats, or rabbits.

Male reproductive toxicity

In animals there is one study in rats by gavage in which testicular degeneration and reduced sperm production was observed. Reduced body weight gain and anemia were observed at lower dosages than testicular and sperm effects. Also, long-term exposure to the dosages at which testes and sperm effects were observed produced death in the animals. Short-term and sub-chronic studies in rat, mouse, and rabbit by inhalation found no effects on testes. A 2-year NTP study by gavage in rats and mice also found no effects on testes. A dominant lethal study in rats by water found no effects on fertility or litter size. A 2-generation study in rats exposed via water provided no evidence of male reproductive effects.

Overview of Exposure Concern

OEHHA staff have found that there is a DRAFT **MEDIUM** level of concern over the extent of exposure. 1,2-dichloropropane is used as a chemical intermediate, pesticide, industrial and commercial solvent, and as a lead scavenger in anti-knock compounds. Annual U.S. production was 60 million lbs. in 1984. Annual releases to the environment in the U.S. were 1.1 million lbs. in 1986. Most information on use and exposure is from the 1980’s; information from 1990’s is sparse. It is a component of a mixture of 3-carbon compounds used as a pesticide; 319 lbs. were reported to have been used in California in 1993. Use patterns are reported to be changing, but recent

information is lacking. It was found in groundwater in 75 wells in 9 counties in California in the early 1980s (12 wells over 10 ppb, peak level 1200 ppb), probably from use in pesticides. Degradation in water has a half life of 25-200 weeks.

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. Hanley *et al*. (1989a), as cited in IRIS®.
   Rabbits were treated orally (gavage) at 0, 15, 50, or 150 mg/kg/d for gd 7-19. Maternal anemia, and reduced maternal body weight gain at 150 mg/kg/d were observed. Delayed ossification of skull bones of fetuses at 150 mg/kg/d was observed.
2. Hanley *et al*. (1990), as cited in Schardein.
   Rats and rabbits were treated (no details given). No teratogenicity was observed. (Probably abstract, redundant to Hanley et al. (1989a) and Kirk et al. (1989).)
3. Kirk *et al*. (1989), as cited in ATSDR, IRIS®.
   Rats were treated orally (gavage) at 0, 10, 30 or 125 mg/kg/d for gd 6-21 (or possibly 6-15). Reduced maternal weight gain at 125 mg/kg/d on gd 8-16 was observed. Delayed fetal ossification was observed at 125 mg/kg/d. No adverse developmental effects were observed at 30 mg/kg/d or less. No effect on number of pregnancies, implantation sites, litter size, resorptions, malformations, or gravid uterine weight was observed.
4. Kirk *et al*. (1990), as cited in IRIS®.
   Rats (males and females) were treated orally (water) at 0, 0.024, 0.10, or 0.24% (w/v) (approx. 24, 100, or 200 mg/kg/d) for 2 generations. In the F0 generation, a statistically significant reduction in body weight gain before mating, during gestation and lactation at 0.24% was observed. Anemia in F0 females at 0.24% was observed. No effects on F0 reproductive organs, fertility, mating index, conception index, viable litters, gestation length, litter size, live pups, or sex ratio were observed. In F1 neonates reduced neonatal survival and body weight at 0.24% were observed. In F1 parental animals reduced weight gain at 0.24% was observed. In F1 parental animals no histopathological changes in reproductive organs were observed. In F2 neonates no reduced neonatal survival was observed. (Also cited in the female and male reproductive toxicity in animals sections.)

Female reproductive toxicity in humans

1. Pozzi *et al*. (1985), as cited in ATSDR, HSDB, IRIS®.
   Trielina is a stain remover sold in Italy which contains 60-100% 1,2-dichloropropane. A 20 year old female was admitted to the hospital with vomiting, abdominal pain, widespread ecchymoses (bluish spots on skin), hematuria, and uterine bleeding. Symptoms regressed. Nine months later, the patient was readmitted with oliguria, epistaxis, hematuria, uterine bleeding, and periorbital and conjunctival hemorrhages. Clinical tests found severe renal failure, acute liver damage, hemolytic anemia, and disseminated intravascular coagulation. She admitted to sniffing Treilina every night. No information on concentration was given. Following transfusion with fresh blood, and dialysis, she was discharged with recovery of renal and liver function.

Female reproductive toxicity in animals

1. Kirk *et al*. (1990), as cited in IRIS®.
   Rats (males and females) were treated orally (water) at 0, 0.024, 0.10, or 0.24% (w/v) (approx. 24, 100, or 200 mg/kg/d) for 2 generations. In the F0 generation, a statistically significant reduction in body weight gain before mating, during gestation and lactation at 0.24% was observed. Anemia in F0 females at 0.24% was observed. No effects on F0 reproductive organs, fertility, mating index, conception index, viable litters, gestation length, litter size, live pups, or sex ratio were observed. In F1 neonates reduced neonatal survival and body weight at 0.24% were observed. In F1 parental animals reduced weight gain at 0.24% was observed. In F1 parental animals no histopathological changes in reproductive organs were observed. In F2 neonates no reduced neonatal survival was observed. (Also cited in the developmental and male reproductive toxicity in animals sections.)
2. Nitschke *et al*. (1988), as cited in ATSDR, IRIS®.
   a. Rats (males and females) were treated by inhalation at 0, 15, 50, or 150 ppm for 6 hr/d, 5 d/wk, for 13 weeks. No effects on reproductive organs (female: ovaries, oviduct, uterus, cervix, mammary glands; male: testes, epididymus, or prostate) were found. A statistically significant reduction in body weights were reported at 150 ppm.
   b. Mice (males and females) were treated by inhalation at 0, 15, 50, or 150 ppm for 6 hr/d, 5 d/wk, for 13 weeks. No effects on reproductive organs (female: ovaries, oviduct, uterus, cervix, mammary glands; male: testes, epididymus, or prostate) were found. No treatment related pathological effects were observed.
   c. Rabbits (males and females) were treated by inhalation at 0, 150, 500, or 1,000 ppm for 6 hr/d, 5 d/wk, for 13 weeks. No effects on reproductive organs (female: ovaries, oviduct, uterus, cervix, mammary glands; male: testes, epididymus, or prostate) were found. Anemia was observed at 150 ppm and up. (Also cited in the male reproductive toxicity in animals section.)
3. National Toxicology Program (NTP) (1986), as cited in ATSDR, IRIS®.
   a. Mice (male and female) were treated orally (gavage) at 0, 125 or 250 mg/kg/d for 5 d/wk for 103 weeks. In females, increased infections of ovary, uterus, or other organs were observed, but it is not clear if this was treatment related, since controls also had infections. No histopathology of male reproductive organs was observed. No reduced body weight was observed.
   b. Rats (female) were treated orally (gavage) at 0, 125, or 250 mg/kg/d for 5 d/wk for 103 wks. Rats (male) were treated at 0, 62, or 125 mg/kg/d. No histopathology of male reproductive organs was observed. No reduced body weight was observed. (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. Bruckner *et al*. (1989), as cited in ATSDR, IRIS®, Reprotext®.
   a. Rats were treated orally (gavage) at 100, 250, 500, or 1,000 mg/kg/d for 1, 5, or 10 consecutive days. Testicular degeneration, with reduced sperm production, increased numbers of degenerate sperm, and reduced numbers of sperm in the epididymus, was observed at 500 mg/kg/d. No testicular effects were observed at 250 mg/kg/d. Reduced body weight gain and slight anemia at 250 mg/kg/d, and pronounced anemia at 500 mg/kg/d were also observed.
   b. Rats were treated orally (gavage) at 100, 250, 500, or 750 mg/kg/d for 5d/wk for 13 weeks. Increased mortality and testicular degeneration, with reduced sperm production, increased numbers of degenerate sperm, and reduced numbers of sperm in the epididymus, was observed at 500 and 750 mg/kg/d. No testicular effects were observed at 250 mg/kg/d. Reduced body weight gain and slight anemia at 100 mg/kg/d, and pronounced anemia at 250 mg/kg/d were also observed.
2. Hanley *et al*. (1989b) as cited in ATSDR.
   Rats (male) were treated orally (water) at 162 mg/kg/d for at least 10 weeks prior to breeding. Two days after

exposure was ended, males were bred with untreated females. No effect on mating performance, fertility, number of implantations, resorptions, or liter sizes were observed.

3. Kirk *et al*. (1990), as cited in IRIS®.
   Rats (males and females) were treated orally (water) at 0, 0.024, 0.10, or 0.24% (w/v) (approx. 24, 100, or 200 mg/kg/d) for 2 generations. In the F0 generation, a statistically significant reduction in body weight gain before mating, during gestation and lactation at 0.24% was observed. Anemia in F0 females at 0.24% was observed. No effects on F0 reproductive organs, fertility, mating index, conception index, viable litters, gestation length, litter size, live pups, or sex ratio were observed. In F1 neonates reduced neonatal survival and body weight at 0.24% were observed. In F1 parental animals reduced weight gain at 0.24% was observed. In F1 parental animals no histopathological changes in reproductive organs were observed. In F2 neonates no reduced neonatal survival was observed. (Also cited in the developmental and female reproductive toxicity in animals sections).
4. National Toxicology Program (NTP) (1986), as cited in ATSDR, IRIS®.
   a. Mice (male and female) were treated orally (gavage) at 0, 125 or 250 mg/kg/d for 5 d/wk for 103 weeks. Females had increased infections of ovary, uterus, or other organs, but it is not clear if this was treatment related, since controls also had them. No histopathology of male reproductive organs was observed. No reduced body weight was observed.
   b. Rats (female) were treated orally (gavage) at 0, 125, or 250 mg/kg/d for 5 d/wk for 103 wks. Rats (male) were treated at 0, 62, or 125 mg/kg/d. No histopathological changes of male reproductive organs were observed. No reduced body weight was observed. (Also cited in the female reproductive toxicity in animals section.)
5. Nitschke and Johnson (1983), as cited in ATSDR, IRIS®.
   a. Rats (male and female) were treated by inhalation at 0, 100, 300, or 1,000 ppm for 6 hr/d, 4-5d/wk, for 2 weeks (9 exposures). No histopathological changes in testes were observed. There was a statistically significant reduction in body weight (male and female) at 100 ppm exposure and upwards.
   b. Rabbits were treated by inhalation at 0, 100, 300, or 1,000 ppm for 6 hr/d, 4-5d/wk, for 2 weeks (9 exposures). No histopathological changes in testes were observed.
   c. Mice were treated by inhalation at 0, 30, 100 or 300 ppm for 6 hr/d, 4-5d/wk, for 2 weeks (9 exposures). No histopathological changes in testes were observed. No effect on body weight was observed.
6. Nitschke *et al*. (1988), as cited in ATSDR, IRIS®.
   a. Rats (males and females) were treated by inhalation at 0, 15, 50, or 150 ppm for 6 hr/d, 5 d/wk, for 13 weeks. No effects on reproductive organs (female: ovaries, oviduct, uterus, cervix, mammary glands; male: testes, epididymus, or prostate) were found. A statistically significant reduction in body weights were reported at 150 ppm.
   b. Mice (males and females) were treated by inhalation at 0, 15, 50, or 150 ppm for 6 hr/d, 5 d/wk, for 13 weeks. No effects on reproductive organs (female: ovaries, oviduct, uterus, cervix, mammary glands; male: testes, epididymus, or prostate) were found. No treatment related pathological effects were observed.
   c. Rabbits (males and females) were treated by inhalation at 0, 150, 500, or 1,000 ppm for 6 hr/d, 5 d/wk, for 13 weeks. No effects on reproductive organs (female: ovaries, oviduct, uterus, cervix, mammary glands; male: testes, epididymus, or prostate) were found. Anemia was observed at 150 ppm and up. (Also cited in the female reproductive toxicity in animals section.)

Other relevant data

1. ATSDR
   Following oral ingestion or inhalation, 1,2-dichloropropane is relatively rapidly exhaled, metabolized, and/or excreted in the urine.

Secondary Sources

ATSDR. (1989) Agency for Toxic Substances and Disease Registry. Toxicological Profile for 1,2-dichloropropane.

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES JULY 31, 1995)

IRIS®. Integrated Risk Information System. US Environmental Protection Agency. (TOMES JULY 31, 1995)

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

Schardein J. L. (1993) *Chemically Induced Birth Defects.* Second Edition, Marcel Dekker.

BERYLLIUM:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Beryllium (CAS No. 7440-41-7) is used in the defense, semiconductor, and computer industries as an alloy, in ceramics, and in the mantels of gas lanterns. The review includes beryllium (Be) and Be salts. Beryllium and beryllium compounds are on the Proposition 65 list as carcinogens.

Overview Developmental/Reproductive Toxicity Concern

There are **INSUFFICIENT DATA** to determine a level of developmental/reproductive toxicity concern for beryllium. There are fewer than five relevant animal studies, and these studies are limited by the use of nonstandard study designs and methodologies.

Developmental toxicity

Two studies reported effects after intratracheal administration during pregnancy in rats. One study is complicated by methodological issues, and the other is a Russian language report which was minimally described in the secondary sources.

Female reproductive toxicity

A study in female workers reported no reproductive toxicity. A single rat study using intratracheal administration reported no effects on reproduction, and chronic toxicity studies reported no reproductive organ pathology.

Male reproductive toxicity

A study in male workers reported no reproductive toxicity. Chronic toxicity studies with dietary administration in rats found decreased testes/body weight but no reproductive tract pathology.

Overview of Exposure Concern

OEHHA staff have found that there is a DRAFT **MEDIUM** level of concern over the extent of exposure. The US is a leading producer and user of beryllium (although there do not appear to be any manufacturers or processors in California). According to 1986-88 data, 490,000 lbs. were produced in the US per year and 375,000 lbs were released. It is used in the defense, semiconductor, and computer industries as an alloy and is used in ceramics. Occupational exposures occur primarily via inhalation. Air sources include manufacturing, fuel combustion, and municipal waste incinerators. There are increased concentrations in urban air due to coal burning. Potential consumer exposures could occur from the mantels of gas lanterns. It is present in food but poorly (<1%) absorbed. The average daily intake for beryllium is estimated at 12 micrograms, mostly from drinking water and food. It has a low BCF (19-100).

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. ATSDR (1993).
   This recent review reported no human studies. No studies were identified in other secondary sources

Developmental toxicity in animals

1. Mathur *et al.* (1987), as cited in IPCS.
   Rats were given Be nitrate intravenously at 0.316 mg/kg (0.1LD50). When administered on gd 1 or gd 2,13,15 or 17, postnatal death resulted, and when administered on gd 11 intrauterine death resulted. No malformations were noted. This study is complicated by anesthesia and surgery involved in two laparoscopies conducted during pregnancy (gd 11 and 20).
2. Selinova *et al.* (1986), as cited in ATSDR, Shepard's Catalog of Teratogenic Agents.
   Rats were given an intratracheal administration of 50 mg/kg Be oxide suspension and chloride solution on gd 3, 5, 8 or 20. Effects reported in this Russian language paper were increased death, decreased fetal weight (no effect on fetal length) and edema of internal organs.
3. Tsuji *et al.* (1979), as cited in IPCS.
   This Japanese language report described postnatal neurobehavioral effects of Be sulfate administered by i.p. injection to mice.

Female reproductive toxicity in humans

1. ATSDR (1993)
   This recent review reported no human studies by the oral or inhalation routes.
2. Kline *et al.* (1951), as cited in IARC.
   In one case report of a pregnant woman with occupational exposure, newborn hypoglycemia was found.
3. Savitz *et al.* (1989), as cited in TERIS.
   No effects on stillbirth, low birthweight, or small for gestational age were reported with maternal occupational exposure.

Female reproductive toxicity in animals

1. ATSDR (1993).
   This recent review reported no animal studies with DART endpoints by the oral or inhalation routes.
2. Clary *et al.* (1975), as cited in ATSDR.
   In a single generation study in rats, a single intratracheal administration of Be oxide (0.6 mg/kg prior to mating) had no effect on pregnancy outcome. The purpose was to study the effect of pregnancy on the onset of chronic symptoms of Be toxicity.
3. Morgareidge *et al.* (1975), as cited in ATSDR.
   A chronic diet study in rats using <31 mg Be/kg/day as Be sulfate tetrahydrate showed no reproductive tract pathology.

Male reproductive toxicity in humans

1. Savitz *et al.* (1989), as cited in Shepard's Catalog of Teratogenic Agents.
   No effects were reported on stillbirth, low birthweight, or small for gestational age, with paternal occupational exposure.

Male reproductive toxicity in animals

1. ATSDR (1993)
   This recent review reported no animal studies by the oral or inhalation routes and no dominant lethal study.
2. Morgareidge *et al.* (1975), as cited in IPCS.
   No reproductive tract pathology was found in a chronic diet study in rats using Be sulfate tetrahydrate, <31 mg Be/kg/day. However decreased testes/body weights were reported in this study as cited in ATSDR.

Other relevant data

Absence of teratologic effects was reported in chicks using Be chloride by Ridgway *et al.* (1952) (as cited in Reprotox™), but malformations were described in chicks using Be sulfate (Puzanova *et al.* (1978), as cited in IPCS).

Be is poorly absorbed orally and dermally, and transplacental transport is "relatively poor" in mice (Bencko *et al.* (1979), as cited in IPCS) and rats (Clary *et al.* (1975), Schulert *et al.* (1969), as cited in Barlow and Sullivan). <1% of the oral dose is excreted in milk in cows (Mullen *et al.* (1972), as cited in IARC).

Secondary Sources

ATSDR. (1993) Toxicological Profile for Beryllium. Agency for Toxic Substances and Disease Registry.

Barlow S.M. and Sullivan F.M. (1982) *Reproductive Hazards Of Industrial Chemicals*, Academic Press.

IARC. International Agency for Research on Cancer (IARC, 1993). *Monographs On The Evaluation Of Carcinogenic Risk To Humans, Volume 58.* World Health Organization.

IPCS. (1990) International Programme on Chemical Safety. Environmental Health Criteria 160. Beryllium. World Health Organization, Geneva, Switzerland.

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

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

TOLUENE-2,4-DIISOCYANATE: DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Toluene-2,4-diisocyanate (CAS No. 584-84-9) is a clear-to-yellow volatile liquid with the formula $C_9H_6N_2O_2$. It is used in the manufacture of polyurethane foams, paints, varnishes, sealers, spandex and nylon. Toluene-2,4-diisocyanate is usually (>95%) sold as a 80:20 mixture with toluene-2,6- diisocyanate. The commercial toluene diisocyanate mixture (CAS No. 26471-62-5) is on the Proposition 65 list as a carcinogen.

Overview of Developmental/Reproductive Toxicity Concern

There are **INSUFFICIENT DATA** to prioritize toluene-2,4-diisocyanate with regard to its developmental/reproductive toxicity.

Developmental toxicity

No studies were identified.

Female reproductive toxicity

No studies were identified.

Male reproductive toxicity

One study, citing an incident involving an industrial fire, reported impotence in 2 out of 35 firefighters. The two men affected also showed signs of neurological problems (including memory problems and depression). The impotence was most likely secondary to the neurological effects. No animal studies were identified for the 2,4 isomer.

Overview of Exposure Concern

OEHHA staff have found that there is a DRAFT **MEDIUM** level of concern over exposure due to toluene-2,4-diisocyanate. Toluene diisocyanate is used as an industrial chemical for the production of polyurethane foams, paints, varnishes, sealers, spandex and in nylon. Polyurethane foams are commonly used in furniture, automobile seats and home insulation. Toluene-2,4- diisocyanate is usually (>95%) sold as a 80:20 mixture with toluene-2,6-diisocyanate. The CAS number for the mixture is 26471-62-5. None of the major manufacturing sites appear to be located in California. According to the 1994 California TRI, 2,000 lb. were released to the air and 5,000 lb. were disposed of offsite. TDI is released primarily through stack and fugitive emissions (0.005% of TDI used in flexible foam slabstock is released in vent stack exhaust). It rapidly hydrolyzes in water and has an atmospheric half-life of 3.3 hours.

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 identified.

Developmental toxicity in animals

No studies identified.

Female reproductive toxicity in humans

No studies identified.

Female reproductive toxicity in animals

No studies identified.

Male reproductive toxicity in humans

1. Le Quesne *et al.* (1976) as cited in Reprotext®, Barlow and Sullivan.
   Thirty-five firefighters were exposed to high levels of toluene-2,4-diisocyanate while fighting a fire in a polyurethane foam factory. They were exposed over an 8 hour period via inhalation and possibly dermal routes. The exposure resulted in neurological problems for 23 of the firefighters (two of which complained of impotence lasting 2 weeks). Of the two reporting impotence, one lost consciousness during the fire and the other reported confusion for 3 weeks following the fire. Both showed signs of ataxia and abnormal EEG three weeks after the fire as well as persistent neurological effects 4 years later.

Male reproductive toxicity in animals

No studies identified.

Other relevant data

1. Le Quesne *et al.* (1976) as cited in Barlow and Sullivan.
   Non-reproductive effects include respiratory sensitization (and the accompanying asthma), gastrointestinal problems and neurological problems, which in some cases persisted for months to years after the exposure.
2. Tyl (1988), as cited in IRIS®.
   Rats were exposed via inhalation to 0, 0.021, 0.120 and 0.480 ppm of an unspecified TDI mixture for 6 hr/day on gd 6-15 for 23 h/day. No embryotoxicity or teratogenicity was noted. Maternal toxicity was noted at 0.480 ppm.
3. Tyl and Neeper-Bradley (1989), as cited in IRIS®.
   Male and female rats were exposed via inhalation to 0, 0.020, 0.079 and 0.290 ppm of an unspecified TDI mixture for 6 hr/day, 5 days/week for 10 weeks in a 2 generation reproduction study. The study reported no effects on any of the reproduction parameters evaluated (no specifics given).

Secondary Sources

Barlow S.M. and Sullivan F.M. (1982) *Reproductive Hazards Of Industrial Chemicals*, Academic Press.

IRIS®. Integrated Risk Information System. US Environmental Protection Agency. (TOMES JULY 31, 1995)

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

BORIC ACID:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Note: Further consideration of this chemical has been postponed pending resolution of its potential status with regard to listing through an administrative mechanism.

This data summary covers boric acid (H_3BO_3, CAS No. 10043-35-3) and sodium tetraborate or borax ($Na_2B_4O_7$, CAS No. 1303-96-4). In dilute aqueous solutions and at physiological pH the predominant form is boric acid, whether the initial material was borax (sodium tetraborate) or boric acid. Thus doses of borax and boric acid are often expressed as boron equivalents, and are considered to be toxicologically equivalent. This equivalency does not apply to all boron compounds. Boric acid and borax are used in numerous industrial and commercial settings and consumer products. In addition to the secondary sources normally reviewed during the prioritization process, documents submitted by an interested party (Murray and Associates) were also reviewed.

Overview of Developmental/Reproductive Toxicity Concern

OEHHA staff have found that there is a DRAFT **HIGH** level of developmental/reproductive toxicity concern over boric acid, due to concern for male reproductive toxicity and developmental toxicity. Reduced fertility and sperm abnormalities have been reported in boron-exposed men, but most of the evidence on the male reproductive toxicity of boric acid comes from studies in experimental animals. Effects reported in animal studies include reduced testes weights, testicular atrophy, histopathological changes in the testes, and impaired spermatogenesis and fertility. The evidence from experimental animals for developmental toxicity consists of growth deficits and reduced viability, as well as a consistent increase in the frequency of agenesis of the 13th rib. There is some evidence for an effect of boric acid on ovulation in rats and estrus cycle length in mice, but no effects on the female reproductive system were seen in 2-year dietary studies of dogs and rats.

Developmental Toxicity

Studies in rats, mice, and rabbits have consistently reported reduced fetal or birthweights following prenatal exposure to boric acid. Reduced viability has also been reported in offspring of exposed mice and rabbits. Minor skeletal variations, particularly agenesis or shortening of the 13th rib and reductions in the frequency of supernumerary lumbar ribs, have been a consistent finding in rats and mice prenatally exposed to boric acid.

There is one case report of death of a human fetus following maternal ingestion of boric acid. Case reports of infants poisoned by boric acid have suggested that neonates are relatively more sensitive to boron-induced lethality than their smaller body weights alone would indicate. It has been suggested that this sensitivity results from inability of the immature kidney to efficiently remove boron.

Female Reproductive Toxicity

A two-generation reproduction study was identified which reported decreased ovulation in female rats exposed to borax or boric acid. A three-generation, continuous breeding study performed in mice reported shortened estrus cycles in F_1 females. Implanted embryos were completely resorbed in pregnant mice given a high dose of boric acid during gestation days 8 - 14. Other studies have reported no effects on female reproduction in rats or dogs, but it is not clear if these studies can be directly compared in terms of dose or other experimental parameters.

Male Reproductive Toxicity

Reduced fertility and sperm abnormalities have been reported in men exposed to high concentrations of boron, but the vast majority of literature concerns effects in experimental animals. Nineteen references, some reporting on multiple studies, found adverse effects on the male reproductive system in rats, mice, and dogs exposed to borax or boric acid. Observed effects range from reduced fertility and reduced sperm counts, to abnormal testicular histology and testicular atrophy.

Overview of Exposure Concern

OEHHA staff have found that there is a DRAFT **HIGH** level of concern over exposure to boric acid/borax. The U.S. is the world's largest producer of boric acid and borates, producing greater than 550,000 metric tons per year (1987-88 data). Most of the world's borates are mined and processed in California. Boron is ubiquitous in the environment, it is often found in surface and ground waters and in soil. Boron is commonly found in food (1.2 mg/day average human intake) and drinking water (3.95 mg/liter, highest estimate)(reviewed by Murray 1995). There is some evidence that boron might be an essential micronutrient in humans. In a data submission from the private sector, several articles described the nutritional role of boron (Anderson et al. 1994; Hunt 1994; Hunt et al. 1994; Mertz 1993; Nielson 1988, 1990, 1991, 1992, 1994, 1995; Newnham 1994).

Uses of boric acid/borax include manufacture of: porcelain enamels, heat-resistant glass, glass fibers, food packaging materials, and flame retarding treatments for wood and textiles. The primary concern with these products is occupational exposures; however, in some cases, consumer exposures are also possible. Boric acid also has medicinal uses as an antiseptic/antibacterial/antifungal agent in topical preparations for humans and animals. It is used at low concentrations (less than 5%) in many cosmetics and personal care products. Pesticide uses include domestic applications (e.g., ant killers). There is little absorption of boron through intact skin, although absorption does occur through broken or abraded skin.

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. Anon (1970); Goldbloom *et al*. (1953); Gordon *et al*. (1973), Litovitz *et al*. (1988); Samuel, (1970); Skipworth *et al*. (1967); Wong *et al*. (1964); as cited in ATSDR, HSDB, Barlow and Sullivan.
   Neonates are particularly sensitive to the lethality of boron, possibly due to a lower capacity of immature kidneys to remove it from the body. Babies have died from the use of boric acid-containing talcum powders, formerly a common treatment for diaper rash. Infants have also been poisoned by accidental ingestion of boric acid
2. Grella *et al*. (1976), as cited in HSDB.
   Case study of neonatal death following delivery by caesarian section of a 34 week fetus whose mother had ingested 70 g of boric acid.
3. Heinonen *et al*. (1977), as cited in Reprotox™, Shepard's Catalog of Teratogenic Agents, Schardein.
   Collaborative perinatal project suggestive of an association between use of boric acid as an antimicrobial agent and increased risk for birth defects. In 253 exposed pregnancies, 7 major malformations were expected and 19 were found; this was within the 95% confidence interval. A "hospital standardized" relative risk of 7.9 for congenital cataract was reported.

Developmental toxicity in animals

1. Fail *et al*. (1991), as cited in ECETOC, Reprotox™, Reprotext®.
   Under a continuous-breeding protocol, offspring of Swiss (CD-1) mice given boric acid in the diet did not show an increased frequency of malformations, but litter size and body weights were reduced. 4,500 ppm in the diet (calculated to provide adult males with and average dose of 111 mg B/kg body weight) was an effective concentration for these endpoints.
2. Harris *et al*. (1992), as cited in ECETOC.
   Swiss CD-1 mice were given 21, 70 and 210 mg/kg boric acid by gavage on gestational days 8-14. Complete resorption of implants occurred in all females exposed to 210 mg B/kg bw. No effects on implantation, viability, or pup weights were seen at lower doses.
3. Heindel *et al.* (1992), as cited in ATSDR, ECETOC, RTECS®, Reprotox™, Reprotext®, Shepard's Catalog of Teratogenic Agents.
   a. Rats given boric acid in the diet throughout gestation: Boric acid doses of 78, 163, and 330 mg/kg, corresponded to 13.7, 28, and 58 mg B/kg bw, respectively. A high dose of 94 mg B/kg bw was given during days 6 - 15 of gestation only. Maternal weight gain was decreased at doses of 58 and 94 mg B/kg bw, and relative liver and kidney weights at doses of 28 mg B/kg bw and above. Increased resorptions and fetal deaths occurred at the 94 mg B/kg bw, and decreases in mean fetal body weights were seen at all doses. The incidence of litters containing at least one fetus with a skeletal anomaly was increased at 28 mg B/kg bw and above. At 13.7 and 28 mg B/kg bw the frequency of rudimentary or full ribs at L1 (a common variant among controls) was reduced.
   b. Mice given boric acid in the diet throughout gestation: Boric acid doses of 248, 452, and 1003 mg/kg corresponded to boron levels of 43, 79, and 175 mg B/kg bw, respectively. 43 mg B/kg was considered to be a no effect level; fetal body weights were significantly decreased at the 2 higher doses. At the highest dose, there was an increase in malformations, primarily skeletal effects including an increased incidence of shortened rib 13. The presence of full or rudimentary ribs at L1 (a normally common variant) was significantly reduced at 43 and 79 mg B/kg bw. Reduced maternal weight gain at the high dose; mild renal lesions at all dose levels.
4. NTP. (1991), as cited in ECETOC.
   New Zealand White rabbits were given 0, 62.5, 125 or 250 mg boric acid/kg bw by gavage on gestation days 6 - 19, corresponding to doses of 0, 10.9, 21.8 and 43.5 mg B/kg bw. Maternal food intake was decreased, and the frequency of vaginal bleeding increased in the high dose group. Offspring viability was reduced at the high dose. Malformation frequency was increased in the high dose group, particularly cardiovascular defects.
5. Price *et al*. (1994), as cited in ECETOC.
   Sprague-Dawley rats were given average daily doses of 19, 36, 55, 76, and 143 mg boric acid/kg bw in the diet (corresponding to 3.3, 6.3, 9.3, 13.3 or 25 mg B/kg bw, respectively) on gestational days 0-20. There was little evidence of maternal toxicity at any dose. Reduced fetal weights and an increase in the frequency of shortened rib 13 were seen at doses of 13.3 and 25 mg B/kg bw. The incidence of the skeletal variant of an extra rib at L1 was reduced, but this was not statistically significant at any dose. In a second part of this study, pregnant animals were similarly dosed, but were allowed to deliver their litters and raise them until weaning. When examined on pnd 21, there were no differences between groups in body weight, but there was an increased incidence of short rib 13 in the high dose group.

Female reproductive toxicity in humans

No studies identified.

Female reproductive toxicity in animals

1. Caujolle *et al.* (1962), as cited in ECETOC.
   Female rats given 200, 400, or 800 mg boric acid/kg bw (corresponding to 35, 70, and 140 mg B/kg bw, respectively) by gavage for 30 days. Reported no lesions of the female reproductive organs.
2. Fail *et al*, (1991), as cited in ECETOC, Reprotox™, and Reprotext®.

In a 3 generation reproductive study in Swiss CD-1 mice using a continuous breeding protocol, boric acid was added to the diet to approximate doses of 0, 27, 111, and 220 mg B/kg bw. F1 females were found to have shorter estrus cycles than controls at the 27 mg B/kg bw level. Slightly lower adjusted pup body weights were statistically significant in F2 pups.

3. Harris *et al.* (1992), as cited in ECETOC.
   Pregnant female Swiss CD-1 mice were given boric acid by gavage to doses of 0, 21, 70, or 210 mg B/kg bw on days 8-16 of gestation. Complete resorption of all implants occurred in all females exposed to the high dose. In another part of this study, groups of female animals were exposed to the same doses of boric acid as above, for 20 days. Animals were mated during days 8 to 12 of the treatment period. Three out of 10 females died in the high-dose group, but no significant effects on fertility parameters were noted.
4. Lee *et al*. (1978), as cited in ATSDR, Reprotox™.
   A multigeneration study in rats found decreased ovulation at 58.5 mg boron (as borax or boric acid) /kg/day.
5. Weir *et al*. (1972), as cited in ATSDR, ECETOC, HSDB, RTECS®, Reprotox™, Reprotext®, Shepard's Catalog of Teratogenic Agents, Barlow and Sullivan.
   A 2-year diet study of 350 ppm boron (approximately 17.5 mg B/kg bw, given as borax or boric acid) found no adverse effect on fertility, lactation, litter size, weight, or appearance of rats or dogs. There was evidence of decreased ovulation in females exposed to a higher dose of 58.5 mg B/kg bw, and no litters were produced by these females even when mated to control males.

Male reproductive toxicity in humans

1. Beyer *et al*. (1993); Lee (1983), as cited in Reprotox™.
   There have been reports that boron reproductive toxicity in humans consisted of oligospermia and decreased libido in exposed men. It has been difficult to examine the dose of boron associated with this form of intoxication
2. Krasovskii *et al*. (1976), as cited in Reprotox™, Reprotext®, Barlow and Sullivan, ECETOC.
   Men living in an area of high borates in drinking water had fertility problems. "Reduced function" reported in men in the highest boron-consumption group, 0.3 mg/kg.
3. Tarasenko *et al*. (1972), as cited in ATSDR, RTECS®, Reprotext®, Barlow and Sullivan, ECETOC.
   Men occupationally exposed to boric acid aerosols (22-80 mg/m^3) for 10 or more years experienced "weakened sexual activity and fertility". Semen analysis showed reduced volume, low sperm count, low sperm motility, and elevated fructose content.
4. Whorton *et al.* (1994), as cited in ECETOC
   Studied live births to wives of employees of the U.S. Borax mine and production facility in California Exposure to inorganic borates up to an estimated maximum of 24 mg B/day was not associated with a reduction in birth weight.

Male reproductive toxicity in animals

1. Bouissou and Castagnol (1965), as cited in Barlow and Sullivan, ECETOC.
   Partial testicular tubular atrophy was found from day 30 onward in rats given single gavage dose of boric acid by gavage, giving doses of 525, 700 or 875 mg B/kg bw. Lower doses of 175, 350 mg B/kg bw had no reported effect. Effects observed at 525 and 700 mg B/kg bw, but not at 875 mg B/kg bw, were partially reversed after 130 days. A second part of this study evaluated the effects of repeated exposures (daily, for 30 days) to boric acid at a dose of 800 mg boric acid/kg (corresponding to 140 mg B/kg bw). The incidence and severity of testicular atrophy increased during the treatment period until all animals were affected. Recovery began to be apparent in some animals from 45 days after the cessation of treatment, and only 1/5 animals showed partial atrophy at 79 days following the cessation of treatment. Comparison of the severity of boric acid's effects on males of different ages indicated that sensitivity was maximum at the time of puberty.
2. Caujolle *et al*. (1962), as cited in ECETOC.
   days following a single gavage exposure of male Wistar rats to 3, 4, or 5 g boric acid/kg bw (525, 700 and 875 mg B/kg bw, respectively), testicular lesions were observed at the two highest doses. Another part of this study involved exposure of multiple generations of males and females to doses of 200, 400, or 800 mg boric acid/kg bw by gavage (corresponding to doses of 35, 70 and 140 mg B/kg bw, respectively). Histopathological lesions of

male reproductive organs occurred at all doses, their frequency and severity increasing with dose. Fertility was reduced at the two highest doses.

3. Dixon, *et al*. (1976a), as cited in ATSDR, RTECS®, ECETOC.
   Single oral doses of borax giving doses of 45, 150, or 450 mg B/kg bw did not affect fertility of male Sprague-Dawley rats at up to 70 days post-dosing. Another part of this study evaluated the effects of repeated dosing; borax was added to drinking water to concentrations of 0.3, 1.0, or 6.0 mg B/liter. No effects on fertility were found after 30, 60, or 90 days. RTECS states that adverse effects on spermatogenesis were found in male rats given 52 mg/kg borax orally for 26 weeks prior to mating
4. Dixon *et al*. (1979), as cited in ATSDR.
   Reduced testicular and epididymal weights, germinal aplasia and biochemical changes were seen in rats fed 50 mg/kg boron (as borax) for up to 60 days.
5. Fail *et al*. (1991), as cited in ECETOC, Reprotox™, Reprotext®.
   Boric acid, given in the diet, partially inhibited fertility in male mice at 4500 ppm, total inhibition of fertility occurred at 9000 ppm. These concentrations corresponded to doses of approximately 111 and 220 mg B/kg bw, respectively. Fertility of mated pairs was similarly affected whether both males and females were treated, or treated males were mated with untreated females. This finding was taken to confirm the male as the predominantly affected sex. Significant abnormal testicular histopathology was seen at both doses, as were adverse effects on sperm parameters.
6. Harris *et al.* (1992), as cited in ECETOC.
   Swiss CD-1 mice were given boric acid by gavage to doses of 0, 21, 70, or 210 mg B/kg bw from study day 3 until necropsy on day 20. Reduced testes weights were observed at the two highest doses. There were abnormalities of testicular histopathology at the high dose.
7. Krasovskii *et al* (1976), as cited in Barlow and Sullivan, ECETOC, Reprotox™, Reprotext®.
   Boric acid was added to the diet of male rats for 6 months at concentrations of 0.3, 1, and 6 mg B/liter. Study doses were equivalent to 0.015, 0.05 and 0.3 mg B/kg bw. Adverse effects on sperm parameters were noted at the two highest doses, and there the testes weight/body weight ratio was decreased at the high dose.
8. Ku *et al*. (1993), as cited in ECETOC, Reprotox™, Reprotext®.
   3000 to 4500 ppm boric acid (approximate doses of 26 and 38 mg B/kg bw) in the diet of rats for 9 weeks inhibited sperm production. 6000 to 9000 ppm (approximate doses of 52 and 68 mg B/kg bw) produced testicular atrophy as well. Sperm production effects were reversible, atrophy was not.
9. Lee *et al*. (1978), as cited in ATSDR, ECETOC, Reprotox™.
   a. Male rats were given borax in the diet at levels of 500, 1,000, and 2,000 ppm boron for 30 or 60 days (corresponding to 50, 100, or 200 mg B/kg bw). Dose-dependent changes in seminiferous tubules and FSH levels were found at all doses; changes in sperm parameters and reduced testes weights were found at the two highest doses. Multi-generation rat study found a lack of viable sperm in atrophied testes at doses of 58.5 mg boron (as borax or boric acid).
   b. Dogs fed 29 mg boron/kg/day as borax or boric acid for 38 weeks had testicular atrophy and spermatogenic arrest. 8.8 mg boron/kg/day for 2 years was a no effect level in dogs.
10. Linder *et al*. (1990), as cited in ECETOC.
    Histopathological changes and altered sperm parameters were found at the two highest doses in Sprague-Dawley rats given single oral doses of 0, 250, 500, 1,000, or 2,000 mg boric acid/kg bw (corresponding to 0, 44, 88, 175, or 350 mg B/kg bw). A time-response segment of this study showed that altered sperm parameters caused by a dose of 350 mg B/kg bw had returned to normal by 57 days post dosing.
11. Linder *et al*. (1992), as cited in Reprotext®.
    Boric acid given to male rats for up to 5 days caused adverse reproductive effects as measured by a series of endpoints, including testicular and epididymal histology. Doses not stated.
12. NIEHS (1990), as cited in ATSDR.
    A 2-generation, continuous-breeding mouse study found degeneration of the seminiferous tubules and impaired spermatogenesis at doses of 111 mg boron/kg/day (636 mg boric acid/kg/day). 27 mg boron/kg/day (152 mg boric acid/kg/day) was a no effect level.
13. NTP (1987), as cited in ATSDR, ECETOC, HSDB.
    a. Mice were given 0, 1,200, 2,500, 5,000, 10,00, or 20,000 ppm boric acid in the diet (corresponding to doses of 0, 34, 71, 142, 284 and 568 mg B/kg bw) for 13 weeks. Mortality was over 60% at the high dose. Body weight gain was significantly reduced at the 3 highest doses. Degeneration or atrophy of the seminiferous tubules was observed at doses of 142 mg B/kg bw.

b. In a 2-yr bioassay in mice, a high dietary level of 5,000 ppm boric acid was associated with testicular atrophy and interstitial cell hyperplasia. Viability at this concentration was poor: 22/50 survived, as compared to 41/50 controls. Also, body weight gain was reduced by 13% of control values.

14. Seal *et al.* (1980), as cited in ATSDR.
    Impaired spermatogenesis was seen in rats given 300 mg borax (44.7 mg boron/kg/day) in drinking water for 70 days.
15. Silaev *et al*. (1977), as cited in Barlow and Sullivan.
    Testicular damage was evidenced at the ultrastructural level in male rats given 1 g/kg boric acid by gavage for 2 weeks.
16. Tarasenko *et al*. (1972), as cited in ATSDR, RTECS®, Reprotext®, Barlow and Sullivan.
    Damaged testes and effects on male fertility in rats occurred with inhalation of boron aerosols at 3-19 ppm.
17. Treinen *et al.* (1991), as cited in ECETOC and Reprotox™.
    Male rats were given 9,000 ppm in the diet for 4 weeks (corresponding to a dose of 61 mg B/kg bw). Effects became progressively more severe with time of exposure (between 4 and 28 days), and included reduced spermiation, epithelial disorganization, loss of spermatocytes and spermatids from the tubules, and decreased basal serum testosterone levels.
18. Truhaut *et al*. (1964), as cited in Reprotext®, Barlow and Sullivan.
    0.4 g boric acid/kg bw/day for 24 months by gavage, or doses of 125-250 mg/kg/day for 12 months in drinking water rendered male rats totally sterile. Boric acid in feed at concentrations of 350 or 525 ppm also affected testes or fertility.
19. Weir *et al.* (1972), as cited in ATSDR, HSDB, ECETOC, RTECS®, Reprotox™, Reprotext®, Shepard's Catalog of Teratogenic Agents, Barlow and Sullivan.
    a. dogs: Damage to testes or sperm production have occurred in rats from a single high dose of boron as boric acid or borax. Severe testicular atrophy was seen in dogs fed up to 44 mg boron/kg bw/day (1,750 ppm borax or boric acid) for 90 days. Testicular atrophy and spermatogenic arrest was found in beagle dogs fed 29.3 mg/kg boron (as borax or boric acid) for 38 weeks. Effects were more severe in the borax group. Some evidence suggested reversibility.
    b1. Rats, chronic: 2-year diet study of rats fed borax or boric acid at levels giving approximate doses of 5.9, 17.5, or 58.5 mg B/kg bw. Atrophic testes were observed in all high-dose group males at 6 months and later time points. Testes weights and testes/body weight ratios were significantly reduced in this group also. No gross or histopathologic effects were reported at the lower doses.
    b2. Rats, 3-generation: Borax or boric acid given in the diet to approximate doses of 0, 5.9, 17.5, 58.5 mg B/kg bw, respectively. Treated diets initiated 14 weeks before breeding. High-dose group males were sterile, and their atrophied testes were devoid of viable sperm. Adverse effects were not reported at lower doses.

Other relevant data

There is indirect evidence that boron can be absorbed via the oral and inhalation routes. There is little absorption through intact skin, but good absorption through broken skin. Boric acid complexes with riboflavin and enhances its excretion in the urine. Riboflavin depletion has been proposed as a mechanism of developmental toxicity. Boron is excreted in urine, with a half-life approx. 13.4 hr. It has been proposed that, compared to adults, the immature kidney is less able to remove boron from the body.

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BENZO[A]PYRENE: DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Note: Further consideration of this chemical has been postponed pending resolution of its potential status with regard to listing through an administrative mechanism.

Benzo[a]pyrene (B[a]P, CAS No. 50-32-8) is released into the environment as a combustion product of wood and coal (especially in coke manufacturing) and of other petroleum hydrocarbons. It is usually a minor component of mixtures of polycyclic aromatic hydrocarbons (PAHs). It is a fairly ubiquitous environmental contaminant. B[a]P is on the Proposition 65 list as a carcinogen.

Overview of Developmental/Reproductive Toxicity Concern

OEHHA staff have found that there is a DRAFT **HIGH** level of developmental/reproductive toxicity concern over B[a]P, because animal studies have demonstrated that it is toxic to oocytes and produces infertility in mouse offspring when administered by the oral route to their dams during gestation. Transplacental cancer has been reported by injection routes in mice, rats, and rabbits. Developmental immunotoxicity has been reported in mice and rats. Malformations and embryotoxicity have been reported by injection route in mice, and developmental delay and intrauterine death by gavage in rats. Apparently no studies have been conducted in humans that are directly relevant to oocyte toxicity. In addition to these developmental toxicity effects, oocyte toxicity and infertility have been reported in mice injected with B[a]P, and infertility has been reported in rats fed B[a]P in diet.

Developmental toxicity

No relevant studies in humans were identified. Numberous studies in mice have reported embryotoxicity, malformations and transplacental carcinogenesis after parenteral administration of B[a]P to pregnant dams. Transplacental carcinogenicity was also reported in rabbits injected i.v. with B[a]P on gestation day 25/26. Embryotoxicity, fetotoxicity, and malformations were reported in rats following gavage exposure of pregnant dams. Reports of transplacental cancer and postnatal immunosuppression after in utero exposure in animals are in accord with known carcinogenic and immunotoxic effects of PAHs in adults. Several studies report severe reproductive organ pathology and infertility in the offspring of mice treated by gavage with B[a]P during pregnancy at doses that produced no maternal toxicity. This finding is supported by studies reporting toxicity of B[a]P to germ cells, suggesting that destruction of germ cells in utero can seriously impact fertility.

Female reproductive toxicity

No relevant studies in humans were identified. In a series of studies in mice, Mattison and colleagues demonstrated that B[a]P reaches the ovary after intraperitoneal injection, that it is converted to an active metabolite, that the active metabolite is associated with ovarian toxicity, and that toxicity to the ovary results in destruction of oocytes, decreased follicular growth, decreased corpora lutea, ovarian atrophy and infertility. Although these mouse studies did not evaluate fertility, infertility has also been demonstrated in rats after dietary exposure to B[a]P.

Male reproductive toxicity

No relevant studies in humans were identified. In animal studies, little research has been done concerning male reproductive effects, but infertility in males has been reported in single generation studies in rats and mice using oral routes of administration, and decreased spermatogenesis was reported in hamsters after i.p. injection of B[a]P. These findings are consistent with germ cell effects reported in female laboratory animals.

Overview of Exposure Concern

OEHHA staff have found that there is a DRAFT **MEDIUM** level of concern over the extent of exposure to B[a]P. It is released into the environment as a combustion product of wood and coal (especially coke manufacture). 98% of these releases are to the air. Daily intakes range from: 0.04 µg/day for commuters, 0.02 ug/day for populations living near freeways, 0.4 µg/pack from cigarettes and 750 µg/day for coal tar pitch workers. ARB estimates that 890-4,600 lbs of B[a]P were emitted into ambient air in California in 1987 fromauto and diesel engines. California's highest exposure is mainly from coke ovens. ARB estimates that 460,625 tons of coke are burned per year in California, primarily in the manufacturing of cement; estimates of B[a]P emissions are not available. No TRI data was available for California releases, but US EPA estimates that 8.1 million lbs were released in the US in 1984. The following products contain benzo[a]pyrene: Coal tar (10 mg BaP/kg), creosote (<.01 mg BaP/kg), bitumen (a major constituent of asphalt) (0.1-2.7 mg/kg B[a]P). Occupational exposures are to a mixture of PAHs with the highest exposure from coke ovens. B[a]P's half-life in soil is 290 days.

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. Barbieri *et al*. (1986), as cited in ATSDR, HSDB, Shepard's Catalog of Teratogenic Agents, Reprotox®.
   Decreased fetal survival but no evidence of malformation was produced in mice by intraembryonal injection of B[a]P.
2. Beniashvili (1978), Dimant and Beniashvili (1978), as cited in HSDB, Shepard's Catalog of Teratogenic Agents, IARC, Barlow and Sullivan.
   Rabbits were injected i.v. with 30 mg/kg on gd 25/26. Transplacental cancer (tumors of the peripheral nerves and kidneys) was reported.
3. Borodin *et al*., (1989), as cited in Shepard's Catalog of Teratogenic Agents.
   Rats were exposed in utero. Suppression of the B cell system was reported postnatally.
4. Bulay and Wattenberg (1971), as cited in ATSDR, Schardein, IARC, Barlow and Sullivan.
   Mice were injected i.p. with 4 mg on gd 11,13, and 15. Transplacental cancer (lung adenoma) was reported. No teratologic effects were found in this study.
5. Csaba *et al*. (1993), as cited in RTECS®), Barlow and Sullivan.
   Rats were injected i.m. with 2.1 mg/kg (total dose) on gd 15-19. Postnatal behavioral effects were reported.
6. Erickson (1981), as cited in RTECS®.
   Effects on oogenesis (1280 mg/kg total dose) and germ cells (100 mg/kg total dose) were produced when mice were given B[a]P by the oral route 16 days prior to mating to 5 days after birth.
7. Herd and Greene (1980), as cited in RTECS®.
   Rats were injected i.p. with 60 mg/kg (total dose) on gd 16-18. Postnatal biochemical and metabolic effects were reported.
8. Hoshino *et al*. (1981), as cited in ATSDR, Shepard's Catalog of Teratogenic Agents, IARC.
   Malformation (increased cervical ribs) and resorptions were reported in AH-responsive mice after i.p. injection of B[a]P.
9. Legreverand *et al*. (1984), as cited in ATSDR, Reprotox®.
   "In utero toxicity" was reported in an AH nonresponsive strain of mice when B[a]P was administered in diet at approximately 120 mg/kg/day on gd 2-10.

10. Mackenzie and Angevine (1981), as cited in ATSDR, HSDB, Shepard's Catalog of Teratogenic Agents, Barlow and Sullivan, IARC.
    Mice were treated by gavage on gd 7-16 with 0, 10, 40, or 160 mg/kg/day B[a]P. Severe reproductive organ pathology and infertility in the F1 and F2 generation were reported with no maternal toxicity.
11. Nikonova (1977), as cited in Barlow and Sullivan.
    Mice were injected i.p. with 4-12 mg on gd 18-19. Transplacental cancer (lung, liver, mammary gland) was reported.
12. Sheveleva (1978), as cited in ATSDR, Barlow and Sullivan.
    Rats were given 0.05, 0.5 or 5 mg/kg/day B[a]P by gavage during gestation. Increased pre and post implantation loss, decreased live fetuses, hydronephrosis, bladder dilatation, and decreased fetal weights were reported.
13. Shum *et al*. (1979), as cited in Shepard's Catalog of Teratogenic Agents, ATSDR, HSDB, IARC.
    Malformations (club foot, hemangioma, cleft lip and cleft palate) and embryotoxicity were reported when B[a]P was administered by i.p. injection of 200 mg/kg on gd 7 to pregnant, AH-responsive mice.
14. Soyka (1980), as cited in RTECS®.
    Mice were injected s.c. with 160 mg/kg (total dose) on gd 12. Effects were reported on the live birth index and on metabolic and biochemical parameters in the postnatal period.
15. Turusov *et al*. (1990), as cited in RTECS®, Reprotox™.
    Mice were given s.c. injections of B[a]P at a total dose of 12 gm/kg in a multigeneration study. Transplacental lung cancers were reported.
16. Urso and Gengozian (1980), as cited in ATSDR, HSDB, IARC.
    Mice were injected i.p. with 100 mg/kg/day B[a]P on gd 16-18. Immunosuppression was reported in the postnatal period.

Female reproductive toxicity in humans

No studies were identified.

Female reproductive toxicity in animals

1. Bui *et al*. (1986), as cited in RTECS®, Reprotox™
   Rats were given B[a]P i.p. 50 mg/kg/day on gd 6-8. Decreased uterine weights, postimplantation loss, fetal death and fetotoxicity were reported.
2. Miller *et al*. (1992), as cited in Reprotox™.
   A series of studies by Mattison and colleagues has demonstrated primordial oocyte destruction and decreased fertility in mice treated with B[a]P. The ovary appears capable of metabolizing B[a]P to its toxic metabolite.
3. Payne, 1958, as cited in ATSDR, Barlow and Sullivan.
   Mice were injected i.p. with a single dose of 10 mg and killed 12 mo later. Decreased follicular growth and corpora lutea were also reported.
4. Raimondi and Pagani (1967), as cited in Barlow and Sullivan.
   Rats were given B[a]P in water-soluble 40% vitamin PP complexes or i.m. in oil from gd 15 onward. Premature delivery was noted in only in the dams given the water-soluble complexes
5. Rigdon and Rennels (1964), as cited in ATSDR, Reprotox®, Shepard's Catalogue of Teratogenic Agents, Schardein, Barlow and Sullivan.
   Rats fed a diet containing 1000 mg/kg B[a]P in a single generation study with a small sample size and demonstrated decreased fertility and increased fetal death. Vaginal bleeding during pregnancy was also reported in this study. In an evaluation of estrus cycles, 7/8 females had normal cycles.
6. Swartz and Mattison (1985), as cited in ATSDR, Reprotox®.
   Mice given i.p. injections of B[a]P had decreased follicular growth and corpora lutea.
7. Wolfe and Byron (1939) as cited in IRIS, Barlow and Sullivan.
   Rats were injected s.c. with 5 mg/day from gd 1 to sacrifice on gd 10 or gd 18. The study reported profuse vaginal bleeding, hemorrhage of the placenta and resorption of all fetuses.

Male reproductive toxicity in humans

No studies were identified.

Male reproductive toxicity in animals

1. Epstein *et al.* (1972), as cited in ATSDR, Barlow and Sullivan.
   Male mice were given a single i.p. injection of 500, 750 or 1000 mg/kg. A mixed positive/negative effect was noted in this dominant lethal study.
2. Payne (1958), as cited in ATSDR, Barlow and Sullivan.
   Mice were injected i.p. with a single dose of 10 mg and killed 12 mo later. Testicular atrophy was reported.
3. Rigdon and Neal (1965), as cited in ATSDR, Barlow and Sullivan.
   Male mice were fed 0.25 mg B[a]P /kg diet for 9 days, then placed with females who were fed the same diet during mating. A small N (5 females) prevented conclusions from this study which reported various pregnancy outcomes.
4. Singh and Tate (1981), as cited in RTECS®.
   Hamsters were given i.p. injection of 10 mg/kg for 5 days prior to mating. Decreased spermatogenesis and effects on testes, epididymis and sperm ducts were reported.
5. Wyrobeck and Bruce (1975) as cited in Barlow and Sullivan.
   Mice were given i.p. injections of 20 or 100 mg/kg for 5 days. At 100 mg/kg, 15-20% of sperm were abnormal 4 and 10 weeks after exposure. Mortality was also noted in this group.

Other relevant data

Placental transfer (as cited in ATSDR, p.47) and adduct formation in the fetus (Shugart (1985), Lu and Wang (1990), as cited in Reprotox™), have been reported in mice. B[a]P is found in milk; the amount varies with the species (West and Horton (1976), as cited in Barlow and Sullivan). B[a]P metabolites are embryotoxic (Barbieri *et al*. (1986), as cited in Reprotox™).

Secondary Sources

ARB. California Air Resources Board. (1994) Benzo(a)pyrene as a Toxic Air Contaminant, PartA Exposure Assessment. Stationary Source Division. Sacramento, California.

ATSDR. (1988) Toxicological Profile for Benzo(a)pyrene. Agency for Toxic Substances and Disease Registry.

Barlow S.M. and Sullivan F.M. (1982) *Reproductive Hazards of Industrial Chemicals*, Academic Press.

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES JULY 31, 1995)

IARC. International Agency for Research on Cancer (IARC, 1983). *Monographs On The Evaluation Of Carcinogenic Risk To Humans, Volume 32.* World Health Organization.

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

RTECS®. Registry of Toxic Effects of Chemical Substances. National Institute of Occupational Safety and Health. (TOMES JULY 31, 1995)

Schardein J.L. (1993) *Chemically Induced Birth Defects*. Second Edition, Marcel Dekker.

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

CARBON DIOXIDE BY INHALATION: DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Note: Further consideration of this chemical has been postponed pending resolution of its potential status with regard to listing through an administrative mechanism.

Carbon dioxide (CAS No. 124-38-9) has the chemical formula CO_2, and is a gas at room temperature. It is used as a commodity fumigant and in carbonated beverages, and is a normal metabolic product of respiration.

Overview of Developmental/Reproductive Toxicity Concern

OEHHA staff have found that there is a DRAFT **MEDIUM-HIGH** level of reproductive/developmental toxicity concern due to several studies in rats, mice and rabbits that showed various developmental effects associated with inhalation of relatively high levels of carbon dioxide. These effects include cardiac defects and ectrodactyly following single-day inhalation exposures to carbon dioxide, as well as effects on various indices of morphological development. No studies were identified which indicated any adverse developmental effects of carbon dioxide by the oral route of exposure.

Developmental toxicity

Studies in rats, mice and rabbits have shown various developmental effects associated with inhalation exposure, while a study in hamsters did not produce teratogenic effects. Three related studies in rats showed high incidence of cardiac defects at air concentrations of 3-10% carbon dioxide on single gestational days, and a study in mice demonstrated ectrodactyly in C57BL-6J, but not SWV, strain animals following single-day inhalation exposure to 25% carbon dioxide in air. Concentrations from 2-30% in air affected various indices of morphological development in rats, mice and rabbits. No studies were identified which indicated any adverse developmental effects by the oral route of exposure. No relevant studies in humans were identified.

Female reproductive toxicity

No studies were identified.

Male reproductive toxicity

Reduced fertility, changes in spermatogenesis or sperm parameters, premature release of sperm and alterations in testes have been reported in rats exposed to carbon dioxide in air. Where atmospheric concentrations were reported they ranged between 15% and 50%. Reduced fertility has also been reported in mice, and changes in sperm production reported in guinea pigs exposed to similar concentrations in air. No relevant studies in humans were identified.

Overview of Exposure Concern

OEHHA staff have found that there is a DRAFT **MEDIUM** level of concern over inhalation exposure to carbon dioxide. Ambient air in temperate zones shows 0.027-0.036% CO_2; this occurs primarily as result of volcanic activity and from burning of fossil fuels. Exposure to 0.5-1.5% CO_2 is generally well tolerated by normal individuals. Atmospheric CO_2 is reported by some sources to have increased at a rate of 0.05 ± 0.02 annually between 1974-85. Carbon dioxide is used as a commodity fumigant (pesticide) as well as an effervescent in carbonated beverages. Oral exposure via carbonated beverages is not thought to pose any risk - CO_2 is on the FDA Generally Recognized As Safe (GRAS) list. According to a 1983 National Occupational Exposure Survey, it was used in 286 industries (60,159 facilities), and 970,496 workers (192,988 of which were female) are exposed. In California, there were four applications in 1992, with a total of 14090 lbs used. In addition, there are seven production sites in California.

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 identified.

Developmental toxicity in animals

1. Author not provided (1984), as cited in RTECS.
   Mice were exposed via inhalation to 2% carbon dioxide for 8 hours on gd 10. Post-implantation mortality and effects on musculoskeletal development (undefined) were reported.
2. Grote (1965), as cited in RTECS®, Reprotox™, Shepard's Catalog of Teratogenic Agents, Schardein.
   Rabbits were exposed via inhalation to 10-13% carbon dioxide for 4 h/day on gd 7-12. 16 of 67 fetuses had defects of the vertebral column. Undefined effects on development of the musculoskeletal system were also reported. The possible role of O_2 deficiency is unclear.
3. Haring (1960), as cited in RTECS®, Reprotox™, Reprotext®, Shepard's Catalog of Teratogenic Agents, Schardein.
   Rats were exposed via inhalation to 3 or 6% concentrations at selected periods in gestation. Cardiac defects (undefined) were reported at maternal exposures of 3%. Exposure to 6% carbon dioxide for 24 h on a single gestational day caused 23% incidence of cardiac malformations (6.8% in controls). The highest incidence occurred on gd 10 (range of days exposed not given). The majority of defects were partial transpositions or ventricular outflow stenosis, with intraventricular septal defects also observed. Unspecified developmental abnormalities in musculoskeletal system and on growth statistics in newborn were also reported.
4. Haring (1966), as cited in Schardein.
   Rats were exposed via inhalation to 6 or 10% carbon dioxide during various periods of gestation, resulting in a 28% incidence of heart defects (unspecified).
5. Haring and Polli (1957), as cited in Reprotox™, Schardein.
   Reports the same information as Haring (1960).
6. King *et al.* (1962), as cited in Reprotox™, Schardein.
   Rats were exposed via inhalation to 30% carbon dioxide during 3 days of gestation. Defects in dentition (unspecified) were reported.
7. Nagai *et al.* (1987), as cited in Reprotox
   Rabbit were exposed via inhalation to 8% carbon dioxide during several days in late pregnancy. This was reported to result in increased maturation of fetal lungs, consistent with increase in fetal respiratory efforts induced by maternal hypercapnea.
8. Storch and Layton (1971), as cited in Shepard's Catalog of Teratogenic Agents.
   Hamsters were exposed via inhalation to 10% carbon dioxide in atmosphere (period and duration of exposure undefined). No teratogenic effects observed. (Unclear if this is an abstract only).
9. Weaver and Scott (1984), as cited in Shepard's Catalog of Teratogenic Agents.
   Mice were exposed via inhalation to 20% CO_2 on gd 10. Ectrodactyly was reported in C57BL-6J mice, while no such effect was seen in SWV mice. No information on the duration of exposure or the incidence of the defect was provided.

Female reproductive toxicity in humans

No studies identified.

Female reproductive toxicity in animals

No studies identified.

Male reproductive toxicity in humans

No studies identified.

Male reproductive toxicity in animals

1. Murkherjee and Singh (1967), as cited in RTECS®, Reprotext®.
   Rats were exposed via inhalation to 55% carbon dioxide for 2 hours 3 days prior to mating, or 55% for 4 hours 6 days prior to gestation. The first treatment regimen resulted in effects on spermatogenesis, while the second resulted in effects on male fertility index. (One secondary source reported this as a mouse study).
2. Schaefer *et al.* (1971), as cited in Reprotext®.
   a. Rats were exposed via inhalation to 15% carbon dioxide (no information provided on period or duration of exposure), resulting in changes (undefined) in sperm production.
   b. Guinea pigs were exposed via inhalation to 15% carbon dioxide (as for rats), and also had changes (undefined) in sperm production reported.
3. Schanbacker *et al.* (1974), as cited in Reprotext®.
   Rats were exposed to carbon dioxide, presumably via inhalation (No information on concentration, period or duration of exposure provided). Premature release of sperm was reported.
4. Vandenmark *et al.* (1972), as cited in Reprotext®.
   Rats were exposed to carbon dioxide, presumably via inhalation (No information on concentration, period or duration of exposure provided). Testes were reportedly altered (no information on the nature of the alteration was provided).

Other relevant data

Carbon dioxide exerts direct toxicity to heart muscle (decreased contractile force), is a vasodilator and the most potent cerebrovascular dilator known. It may cause neurotoxicity independent of anoxia - a possible mechanism is reaction with excitatory amino acids to form carbamates. Long-term exposure to fairly low levels (0.5-1%) may upset acid-base and calcium-phosphorus balance and cause calcium deposition in soft tissues. Developmental effects in animals occur at levels well above those in the environment. Usual atmospheric concentrations are in the range 0.03-0.6%. There are no apparent effects in humans of exposures to approximately 0.5% for 6 hours, while 3% is mildly narcotic and causes increased blood pressure and rapid pulse. 5% produces shortness of breath and headache, while 8-10% causes severe headache, tremors, dimness of vision and loss of consciousness after 5-10 minutes. 10% causes difficulty in breathing, vomiting and high blood pressure, while 20% for 1 minute causes convulsions and loss of consciousness. Concentration above 10% can be fatal. Fetal hemoglobin has higher affinity for O_2 and lower affinity for CO_2 than the adult form - fetus is also more sensitive to anoxia, though, so may balance reduced CO_2 affinity. Exposure of pregnant women to 5% CO_2 resulted in increase respiratory rate in both fetus and adult of approximately 3-fold.

Secondary Sources

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

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

RTECS®. Registry of Toxic Effects of Chemical Substances. National Institute of Occupational Safety and Health. (TOMES JULY 31, 1995)

Schardein J. L. (1993) *Chemically Induced Birth Defects*. Second Edition, Marcel Dekker.

DICHLOROPHENOXYACETIC ACID, 2,4 BUTYL ESTER (2,4-D butyl ester): DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Note: Further consideration of this chemical has been postponed pending resolution of its potential status with regard to listing through an administrative mechanism.

Dichlorophenoxyacetic acid, 2,4 butyl ester (2,4-D butyl ester; CAS No. 94-80-4) is a selective herbicide for broadleaf weeds and brush. Leaves readily absorb the ester forms of 2,4-D and rapidly convert them to the acid, which is the active herbicidal form.

Overview of Developmental/Reproductive Toxicity Concern

OEHHA staff have found that there is a DRAFT **HIGH** level of developmental/reproductive toxicity concern over dichlorophenoxyacetic acid, 2,4 butyl ester (2,4-D butyl ester) due to reports of developmental toxicity in animal studies. Malformations have been reported in rats, mice, and sheep. Growth deficits and fetal death have also been observed in treated animals.

Developmental Toxicity

Structural abnormalities have been reported in offspring of rats, mice, and sheep following oral exposure to 2,4-D butyl ester during pregnancy. Growth deficits and fetal death have also been reported in animal studies. No studies on exposure of humans to 2,4-D butyl ester were located.

Male Reproductive Toxicity

No studies were identified.

Female Reproductive Toxicity

No studies were identified.

Overview of Exposure Concern

OEHHA staff have found that there is a DRAFT **LOW** level of concern over exposure to 2,4-D Butyl ester, as it is not widely used. The “Pesticide Usage Report” of California’s Department of Pesticide Registration records that 2.1 pounds of 2,4-D butyl ester were used for landscape maintenance in California in 1992.

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 on 2,4-D butyl ester were identified. Exposure to 2,4-D (acid) during pregnancy has been associated with increased spontaneous abortion and premature birth (Carmelli *et al*., 1980 as cited in Schardein). In one case report "heavy" exposure to 2,4-D during pregnancy led to severe mental retardation and multiple congenital anomalies (Casey and Collie, 1984 as cited in Schardein).

Developmental toxicity in animals

1. Author not provided (Arch. Env. Cont. Tox., 1977), as cited in RTECS®.
   Oral doses of 277.25 mg/kg/day to mice on gd 12-15 led to fetotoxicity and craniofacial abnormalities.
2. Blakley *et al.* (1986), as cited in HSDB, RTECS®.
   n-Butyl ester was given to pregnant CD-1 mice by gavage on gd 11 at doses ranging from 0 - 200 mg/kg body weight. No clear effects on immune system of offspring.
3. Courtney *et al.* (1970), as cited in Schardein.
   Esters of 2,4-D were found to be of equal teratogenic potency to 2,4-D itself in 2 strains of mice. (details of doses and effects unknown).
4. Khera *et al*. (1971), as cited in Schardein.
   Butyl ester was found to be teratogenic in rats (details of dose and effects not known).
5. Khera *et al.* (1972), as cited in HSDB, RTECS®.
   Fetal death and increased incidence of skeletal abnormalities followed oral dosing of pregnant rats with 2,4-D butyl ester on gd 6-15. Doses were in the range of 100-150 mg/kg body weight.
6. NRC (1977), as cited in HSDB.
   155 mg 2,4-D butyl ester/kg/day given to mice in drinking water affected fetal weight, but not mortality or incidence of cleft palate.
7. National Toxicology Information Services (NTIS) (1968), as cited in RTECS®, IARC.
   Butyl ester given orally or subcutaneously to mice during gd 6-14 increased the incidence of fetal anomalies in 3 different strains, but not in 2 others.
8. Sadykov *et al.* (1972), as cited in Schardein.
   Butyl ester was found to be teratogenic in sheep.

Female reproductive toxicity in humans

No studies identified.

Female reproductive toxicity in animals

No studies identified.

Male reproductive toxicity in humans

No studies identified.

Male reproductive toxicity in animals

No studies identified.

Other relevant data

Courtney *et al*. (1970), as cited in Schardein; Khera *et al.* (1971) as cited in Schardein and (1972) as cited in HSDB, RTECS®; NRC, (1977) as cited in HSDB; NTIS (1968), as cited in RTECS®, IARC compared the potencies of various esters of 2,4-D for inducing developmental toxicity and found them to be similar. In rats, 2,4-D butyl ester is rapidly hydrolyzed to 2,4-D acid. 95% of an injected dose was excreted in the urine within 48 hours. No amino acid conjugates or parent ester could be detected in the urine. Plants also hydrolyze the ester to the acid, which is the active herbicidal form.

2,4-D butyl ester can be absorbed by all routes. For the general population, the principal route of exposure is presumed to be oral. For occupational exposure and exposure of bystanders during spraying operations, the principal route of concern is expected to be dermal.

Secondary Sources

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES JULY 31, 1995)

IARC. International Agency for Research on Cancer (IARC, 1977). *Monographs On The Evaluation Of Carcinogenic Risk To Humans, Volume 15.* World Health Organization.

RTECS®. Registry of Toxic Effects of Chemical Substances. National Institute of Occupational Safety and Health. (TOMES JULY 31, 1995)

Schardein J. L. (1993) *Chemically Induced Birth Defects*. Second Edition, Marcel Dekker.

ENDRIN:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Note: Further consideration of this chemical has been postponed pending resolution of its potential status with regard to listing through an administrative mechanism.

Endrin (CAS No. 72-20-8) is an organochlorine pesticide with the formula $C_{12}H_8Cl_6O$. It is atypical of organochlorines in that it has an epoxide group. It was previously used as agricultural insecticide. All uses were voluntarily canceled in 1986.

Overview of Developmental/Reproductive Toxicity Concern

OEHHA staff have found that there is a DRAFT **HIGH** level of Developmental/Reproductive toxicity concern. This is due to reports of developmental toxicity in animals, including embryonic or fetal death, malformations, and growth retardation. No studies of developmental or reproductive toxicity in humans were located.

Developmental toxicity

There are several studies in animals showing developmental toxicity. Malformations have been observed in studies in hamsters and mice. In some, but not all, cases there was concurrent maternal mortality. Embryonic or fetal death and fetal growth retardation have been observed in hamsters, mice, and rats. In some cases, concurrent maternal mortality and/or reduced weight gain were also observed. Reduced postnatal growth and behavioral changes have also been observed.

Female reproductive toxicity

In reproductive studies, reduced litter size in mice and rats has been observed, although parental death was increased in one of these reports. No effects on fertility have been reported.

Male reproductive toxicity

There is one report of effects on sperm morphology in rats from intratesticular injection. The relevance of this to other routes of exposure is not known. Although the data are weak, reproductive studies in rats and mice suggest lack of male mediated effects, at least at dosages where significant parental mortality is not also found.

Overview of Exposure Concern

OEHHA staff have found that there is a DRAFT **LOW** level of concern over the extent of exposure. Endrin was previously used as agricultural insecticide. All uses were voluntarily canceled in 1986. It is not currently manufactured in the U.S. Endrin is degraded in soil and water over days to months. There is currently probably little remaining in the environment. It is not expected to bioconcentrate or biomagnify.

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. Author not provided (Toxic Appl Pharm 48: A201, 1979), as cited in RTECS®.
   Hamsters (female) were treated orally at 5 mg/kg on gd 8. Toxic effects: Specific developmental abnormalities - central nervous system, musculoskeletal system. (Note: malformations and variations under the category "abnormalities" in this source.) (Note: abstract, probably redundant to Chernoff et al. (1979a)).
2. Author not provided (J Toxicol Env Health 10:541), as cited in RTECS®.
   Mice (female)were treated orally at 2 mg/kg/d on gd 8-12. Toxic effects: Effects on newborn - growth statistics.
3. Chernoff *et al*. (1979a), as cited in ATSDR, Reprotox™, Reprotext®.
   a. Hamsters (female) were treated orally (gavage) at 1.5 mg/kg/d for gd 5-14. Maternal death (37%) was observed. Increased fetal mortality (17%), malformations (irregular supraoccipitals, visceral abnormalities) and reduced fetal weight were observed.
   b. Hamsters (female) were treated orally (gavage) at 1.5, 5 or 10 mg/kg/d on gd 8. No effect on maternal mortality or maternal weight gain was observed. Reproductive NOAEL at 10 mg/kg/d. Fused fetal ribs, and increased incidence of meningioencephaloceles at 5 mg/kg/d were observed (NOAEL 1.5 mg/kg/d).
4. Eisenlord *et al*. (1968), as cited in ATSDR.
   Rats (male and female) were treated orally (food) at 0, 0.1, 1.0, or 2.0 ppm (0, 0.005, 0.05, or 0.1 mg/kg/d) for 3 generations. No effects on fertility, gestation, viability, or lactation were observed. Reproductive and developmental NOAEL at 0.1 mg/kg/d. Interpretation confounded by presence of infection in controls and possibly all animals in study. (Also cited in the female and male repro sections.)
5. Goldenthal (1978a), as cited in ATSDR.
   Rats (female) were treated orally (gavage) at 0.5 or 2 mg/kg/d for gd 6-15. Maternal death (2/25 on gd 13 and 14) and reduced maternal weight gain at 2 mg/kg/d was observed (NOAEL 0.5 mg/kg/d). Reduced fetal body weight and crown-rump length, and delayed ossification of sternbrae and skull at 2 mg/kg/d was observed (NOAEL 0.5 mg/kg/d).
6. Goldenthal (1978b), as cited in ATSDR.
   Hamsters (female) were treated orally (gavage) at 2.5 mg/kg/d on gd 4-13. Reduced maternal weight gain at 2.5 mg/kg/d was observed. No teratogenicity was observed. Developmental NOAEL at 2.5 mg/kg/d.
7. Good and Ware (1969), as cited in ATSDR.
   Mice (male and female) were treated orally (food) at 5 ppm (0.65 mg/kg/d) for 120 days beginning 30 days before mating. Mortality among 1/3 of treatment pairs during study was observed. Reduced litter size and increased fetal mortality was observed. No effect on fertility or fecundity was observed. (Also cited in female and male repro sections.)
8. Gray *et al*. (1979), as cited in RTECS®, Schardein.
   Hamsters were treated orally at 0.75 mg/kg/d for gd 5-14. Reduced postnatal survival and postnatal behavioral alterations were observed. (Note: Abstract)
9. Gray *et al*. (1981), as cited in ATSDR, HSDB, RTECS®, Reprotox™, Reprotext®.
   a. Hamsters (female) were treated orally (gavage) at 0.075 or 1.5 mg/kg/d for gd 5-14. Maternal death (57%) was observed. Reproductive NOAEL at 1.5 mg/kg/d. Increased activity in pups through 125 days of age at 1.5 mg/kg/d was observed (NOAEL 0.075 mg/kg/d).
   b. Rats (female) were treated orally (gavage) at 0.3 mg/kg/d for gd 7-15. No effect on pup growth or survival was observed. Reproductive NOAEL at 0.3 mg/kg/d. Increased locomotor activity, disappearing by 90 days of age, was observed.
10. Kavlock *et al*. (1981), as cited in ATSDR, HSDB, RTECS®, Reprotox™, Reprotext®.
    a. Rats (female) were treated orally (gavage) at 0.075, 0.15, 0.3 or 0.45 mg/kg/d for gd 7-20. Reduced maternal weight gain (decreased by 38%) at 0.3 mg/kg/d was observed. No teratogenicity was observed. Developmental NOAEL at 0.45 mg/kg/d.
    b. Mice (female) were treated orally (gavage) at 0.5, 1, or 1.5 mg/kg/d for gd 7-17. Reduced maternal weight gain (decreased by 24%) at 1 mg/kg/d was observed (NOAEL 0.5 mg/kg/d). Reduced fetal body weight,

number of caudal vertebra, and delayed ossification at 1 mg/kg/d were observed (NOAEL 0.5 mg/kg/d). No malformations were observed.

11. Kavlock *et al*. (1985), as cited in ATSDR, RTECS®, Reprotext®.
    Mice (female) were treated orally at 7 or 9 mg/kg/d on gd 8. Increased supernumerary ribs at 7 mg/kg/d were observedin offspring. (Exencephaly was observed in about equal numbers in control and endrin treated groups.)
12. Kettering Lab (1971), as cited in ATSDR.
    Dogs (female) were treated orally (food) at 0, 0.1, 0.5, 1.0, or 2.0 ppm (0, 0.003, 0.0.14, 0.027, or 0.059 mg/kg/d) for 64-156 weeks. Reproductive and developmental NOAEL 0.059 mg/kg/d. Interpretation is difficult because there were only 3 dogs/group, infection was present, and reproductive success of controls was low. (Also cited in the female repro section.)
13. Noda *et al*. (1972), as cited in RTECS®, Reprotox™, Reprotext®, Shepard's Catalog of Teratogenic Agents.
    Rats and mice (female) were treated at 0.58 mg/kg/d for 4d/wk for 1 month, then mated 1 week or more after the end of treatment. Reduced litter size in both species was observed. In mice fetuses, increased club foot was observed. (Also cited in the female repro section.)
14. Ottolenghi *et al*. (1974), as cited in ATSDR, RTECS®, Reprotox™, Reprotext®,Schardein.
    a. Mice (female) were treated orally (gavage) at 2.5 mg/kg on gd 9. Statistically significant increases in malformations (open eye 2.7% and cleft palate 2.2%) were observed.
    b. Hamsters were treated orally (gavage) at 5 mg/kg/d once on gd 7, 8, or 9. Increased malformations (gd 7, 8, or 9: cleft palate and fused ribs, gd 8: open eye and webbed foot) were observed. Reduced pup survival (38% mortality) for the gd 8 group was observed.

Female reproductive toxicity in humans

No studies were identified.

Female reproductive toxicity in animals

1. Eisenlord *et al*. (1968), as cited in ATSDR.
   Rats (male and female) were treated orally (food) at 0, 0.1, 1.0, or 2.0 ppm (0, 0.005, 0.05, or 0.1 mg/kg/d) for 3 generations. No effects on fertility, gestation, viability, or lactation were observed. Reproductive and developmental NOAEL at 0.1 mg/kg/d. Interpretation confounded presence of infection in controls and possibly all animals in study. (Also cited in the developmental and male repro sections.)
2. Good and Ware (1969), as cited in ATSDR.
   Mice (male and female) were treated orally (food) at 5 ppm (0.65 mg/kg/d) for 120 days beginning 30 days before mating. Mortality among 1/3 of treatment pairs during study was observed. Reduced litter size and increased fetal mortality was observed. No effect on fertility or fecundity was observed. (Also cited in developmental and male repro sections.)
3. Kettering Lab (1971), as cited in ATSDR.
   Dogs (female) were treated orally (food) at 0, 0.1, 0.5, 1.0, or 2.0 ppm (0, 0.003, 0.0.14, 0.027, or 0.059 mg/kg/d) for 64-156 weeks. Reproductive and developmental NOAEL 0.059 mg/kg/d. Interpretation is difficult because there were only 3 dogs/group, infection was present, and reproductive success of controls was low. (Also cited in the developmental section.)
4. Noda *et al*. (1972), as cited in RTECS®, Reprotox™, Reprotext®, Shepard's Catalog of Teratogenic Agents.
   Rats and mice (female) were treated at 0.58 mg/kg/d for 4d/wk for 1 month, then mated 1 week or more after the end of treatment. Reduced litter size in both species was observed. In mice fetuses, increased club foot was observed. (Also cited in the developmental section.)

Male reproductive toxicity in humans

No studies were identified.

Male reproductive toxicity in animals

1. Author not provided (Acta Pharm et Toxicol 31:1, 1972), as cited in RTECS®.
   Rat (male) were treated by injection (intratesticular) at 10 mg/kg 10 d prior to mating. Effects on spermatogenesis (sperm morphology) were observed.
2. Eisenlord *et al*. (1968), as cited in ATSDR.
   Rats (male and female) were treated orally (food) at 0, 0.1, 1.0, or 2.0 ppm (0, 0.005, 0.05, or 0.1 mg/kg/d) for 3 generations. No effects on fertility, gestation, viability, or lactation were observed. Reproductive and developmental NOAEL at 0.1 mg/kg/d. Interpretation confounded presence of infection in controls and possibly all animals in study. (Also cited in the developmental and female repro sections.)
3. Good and Ware (1969), as cited in ATSDR.
   Mice (male and female) were treated orally (food) at 5 ppm (0.65 mg/kg/d) for 120 days beginning 30 days before mating. Mortality among 1/3 of treatment pairs during study was observed. Reduced litter size and increased fetal mortality was observed. No effect on fertility or fecundity was observed. (Also cited in developmental and female repro sections.)

Other relevant data

Endrin is atypical of organochlorine pesticides. It has a complex ring structure, with several unsubstituted carbons, and an epoxide group. Compared to other organochlorine pesticides, endrin has high toxicity (i.e. effects occur at low dosages) and is relatively rapidly metabolized. Potential for prolonged effects, and transfer during lactation, is less than other organochlorines (e.g. DDT, aldrin, chlordane).

Endrin was not detected in human breast milk in Brazilian women, although several other organochlorine pesticides were detected (as cited in Reprotext®).

Secondary Sources

ATSDR. (1994) Agency for Toxic Substances and Disease Registry. Toxicological Profile for Endrin.

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES JULY 31, 1995)

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