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. The primary use of chloroform is 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

There is a **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 of chloroform alone, although additional data are available from studies of trihalomethanes. 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 minimal reported maternal toxicity, or maternal toxicity was specifically considered and discounted as a mechanism for fetal effects, 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. Although chloroform is thought to exert its toxic effects in the dams through formation of active metabolites by action of cytochrome P450 CYP2E1, levels of which are low or absent in the fetus, the questions of whether some level of active metabolite is formed in the fetus (as would be possible even if only a low level of the responsible enzyme was present), whether active metabolites formed by the dam reach the fetus, or whether the parent compound is toxic to susceptible systems of the developing organism that are no longer susceptible in adulthood are unresolved.

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

There is a **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 released from water. A total of 216 million kilograms of chloroform was produced in the US in 1993. Under the Toxic Release Inventory (TRI), no releases of chloroform in California were reported in 2001. 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.

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. Aschengrau *et al*. (1993), as cited in TERIS.
   Case-control study of 1039 infants. No association observed with maternal consumption of chlorinated drinking water during pregnancy.
2. 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).
3. Bove *et al*. (1995), as cited in ATSDR, TERIS.
   Ecological study. A total of 80, 938 live births and 594 fetal deaths were studied. An association between maternal residence in an area where the water supply contained more than 80 μg/l of trihalomethanes and birth defects in 67 infants (relative risk = 1.59, 99% CI = 1.1 – 2.3) was observed. Exposure to trihalomethane levels >0.1 ppm resulted in a 70.4g reduction in mean birth weight among term babies, and increased odds ratios for low birth weight at term (1.42), reduced size at gestational age (1.50), and oral cleft defects (3.17). Exposure to trihalomethane levels >0.08 ppm resulted increased odds ratios for central nervous system defects (2.59) and neural tube defects (2.96). These results were correlated with trihalomethane concentrations rather than chloroform concentrations, however.
4. Gallagher *et al*. (1998), as cited in TERIS.
   Ecological study. An association of low birthweight and drinking water with a trihalomethane concentration of greater than 0.3 μg/l was observed in 29 term infants (OR 5.9, 95% CI 2.0-17.0)
5. Heinonen *et al*. (1977), as cited in Schardein.
   The Collaborative Perinatal Study found no significant association between usage of several specific food additives, including chloroform, during the first four months of gestation.
6. Kramer *et al*. (1992), as cited in Reprotox™, TERIS.
   Case-control study of 187 growth-retarded infants. Weak association (adj. OR 1.8, CI 1.1-2.9) with growth retardation in communities with drinking water chloroform concentrations above 10 μg/l. One secondary source notes serious methodological limitations to the study.
7. Savitz *et al*. (1995), as cited in Reprotox™, TERIS.
   No association between low birthweight and drinking water chloroform or other trihalomethane concentrations was seen in a study of similar size to that of Kramer *et al*. (1992).
8. Taskinen *et al*. (1994), as cited in TERIS.
   Case-control study. No association observed in 36 infants with malformations born to female laboratory workers with maternal use of halogenated solvents during the first trimester of pregnancy. No association with maternal chloroform exposure during the first trimester in a case-control study of 206 laboratory workers who had spontaneous abortions.
9. 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.

10. Waller *et al*. (1998), as cited in TERIS.
In a prospective study of 5144 pregnant women, an association was found between spontaneous abortion and consumption of five or more glasses of water per day containing 75 µg/l or more of trihalomethanes (OR 1.8, CI 1.1-3.0); no association was seen with chloroform content of the water.

Developmental toxicity in animals

1. Baeder and Hofmann (1988), as cited in ATSDR, USEPA Toxicological Review.
Wistar rats were exposed to 0, 30, 100 or 300 ppm (0, 146, 488, 1,464 mg/m^3) via inhalation for 7h/day on gd 7-16. A significant reduction in mean fetal weight was reported following exposure to 300 ppm. A dose-related increase in dead fetuses and decrease in crown-rump length was observed at all dose levels. Maternal food intake and body weight gain was also reduced in a dose-dependant fashion at all dose levels.
2. Baeder and Hofmann (1991), as cited in USEPA Toxicological Review.
Wistar rats were exposed to 0, 3.1, 10.7 or 30.2 ppm (0, 15, 52.2, 147 mg/m^3) via inhalation for 7h/day on gd 7-16. A significant increase in the number of fetuses with reduced ossification of skull bones was reported in the highest exposure group, and an exposure-related trend in fetuses with body weight <3 g as well a significant increase in this effects in the highest exposure group was reported. A ssignificant increase in the number of fetuses with fewer than two caudal vertebral centers was reported at all exposure levels. Maternal food consumption was significantly decreased at all exposure levels in an exposure-dependent fashion, as was maternal weight gain. Maternal body weight was significantly decreased at the two highest exposure levels.
3. Balster and Borzelleca (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.
4. Burkhalter and Balster (1979), as cited in ATSDR, HSDB, RTECS®, USEPA HAD, USEPA HEAD.
Mice were exposed to 31.1 mg/kg/day orally from 21 days prior to mating (males and females) through lactation (females), with pups gavaged with the same dose beginning on day 7 postpartum. Undefined effects on growth statistics and metabolic and biochemical parameters in newborns were reported. No effects on postnatal behavior of offspring were observed.
5. 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.
6. 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.
7. Halogenated Solvents Industry; Two Genotoxicity Studies on Chloroform and One Embryotoxicity Study on Chloroform (1988), as cited in HSDB.
Pregnant Wistar rats were exposed by inhalation to 0, 30, 100 or 300 ppm chloroform for 7 hours/day on gestation days 7-16. There was a dose-related depression of maternal food consumption and bodyweight gains, primarily during the first week of treatment; no further signs of maternal toxicity and no gross pathology were observed. Signs of embryotoxicity included dose-dependent early intrauterine loss of primordia with slightly reduced crown-rump length in the remaining live fetuses at all treatment levels. No toxicologically significant incidence of malformation was observed at day 21 terminal necropsy.
8. Heindel *et al*. (1995), as cited in ATSDR.
Swiss mice given water containing a mixture of contaminants including 7 ppm chloroform experienced no significant developmental effects. Sprague-Dawley rat pups of the F1 generation in the same study had lower body weights from birth through mating, but this was considered likely an artifact of decreased water intake. No other developmental effects were noted.
9. 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 decrease in embryonic development (unspecified as to endpoint).

10. Murray *et al*. (1979), as cited in ATSDR, RTECS®, Reprotox™, Reprotext®, TERIS, USEPA HAD, USEPA HEAD, USEPA Toxicological Review.
Mice (n=34-40/group) 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.
11. National Technical 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.
12. National Toxicology Program (1988), as cited in IRIS, USEPA Toxicological Review
In a two-generation reproduction study, CD-1 mice (n=20/treatment group and 40 control) were treated with 0, 6.6, 16 or 41 mg/kg/d chloroform in corn oil by gavage on 7d/w for 18 weeks. Systemic toxicity was not evaluated in the parental generation. F1 female offspring (but not male offspring) had increased liver weight and liver lesions.
13. Newell and Dilley (1978), as cited in ATSDR.
Female Sprague-Dawley rats were exposed to 0, 942, 2232 or 4117 ppm chloroform by inhalation for 1hour per day on days 7-14 of gestation. There were increased resorptions (45%, control incidence not give) and reduced fetal body weight in the high exposure group only. No gross teratologic effect or anomalies in ossification were observed.
14. 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).
15. Ruddick *et al*. (1983), as cited in ATSDR, RTECS®, Reprotext®, TERIS, USEPA HAD, USEPA HEAD.
a. Rats (n=8-14/group) were exposed via oral gavage to 50 (reported in USEPA Toxicological Review as 100), 200 or 400 mg/kg/day on gd 5-15. Decreased fetal weight was reported at 400 mg/kg/day. A higher incidence of sternebral anomalies was also reported at 200 and 400 mg/kg/day. Maternal toxicity was reported as significantly decreased weight gain, hemoglobin and hematocrit levels and enlargement of liver at all dose levels, and increase serum inorganic phosphorus, cholesterol levels and kidney weights as well as decreased RBC counts at the high dose tested.
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.
16. 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)
17. Schwetz *et al*. (1974), as cited in ATSDR, RTECS®, Reprotox™, Reprotext®, Barlow and Sullivan, TERIS, IARC, USEPA HAD, USEPA HEAD, USEPA Toxicological Review.
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. The USEPA Toxicological Review reported a concentration-related decrease in body weight gain and food consumption in dams of all exposure groups. Increase resorptions were not seen in a "starved" control group, however, indicating that resorptions in the high exposure group were not due to decreased maternal food intake .
18. Thompson *et al*. (1974), as cited in ATSDR, IRIS, RTECS®, Reprotox™, Reprotext®, Schardein, TERIS, IARC, USEPA HAD, USEPA HEAD, USEPA Toxicological Review.
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 (IRIS reports no effects at 50 mg/kg/day), 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. IRIS reports the results not to be considered treatment-related

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.

2. Waller *et al*. (1998), as cited in TERIS.
   In a prospective study of 5144 pregnant women, an association was found between spontaneous abortion and consumption of five or more glasses of water per day containing 75 µg/l or more of trihalomethanes (OR 1.8, CI 1.1-3.0); no association was seen with chloroform content of the water.

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®, 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. Chapin *et al*. (1997), as cited in TERIS.
   No adverse effects on reproductive performance was observed in a two-generation study in which mice were treated with 7 – 14 mg/kg/d of chloroform (route not specified).
4. 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.
5. 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.
6. Murray *et al*. (1979), as cited in ATSDR, RTECS®, Reprotox™, Reprotext®, TERIS, USEPA HAD, USEPA HEAD, USEPA Toxicological Review.
   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).
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 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.
8. National Toxicology Program (1988), as cited in IRIS, USEPA Toxicological Review
   In a two-generation reproduction study, CD-1 mice (n=20/treatment group and 40 control) were treated with 0, 6.6, 16 or 41 mg/kg/d chloroform in corn oil by gavage on 7d/w for 18 weeks. No adverse effects on fertility or reproduction were reported.
9. 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.

10. Schwetz *et al*. (1974), as cited in ATSDR, RTECS®, Reprotox™, Reprotext®, Barlow and Sullivan, TERIS, IARC, USEPA HAD, USEPA HEAD, USEPA Toxicological Review.
    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.
11. 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).
12. Whipple *et al*. (1912), as cited in Barlow and Sullivan.
    Dogs subjected to 2 hours of chloroform 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®, 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. Chapin *et al*. (1997), as cited in TERIS.
   No adverse effects on reproductive performance was observed in a two-generation study in which mice were treated with 7 – 14 mg/kg/d of chloroform (route not specified).
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. Hazdra *et al*. (1980), as cited in HSDB.
   Retarded reproduction rate observed in goldfish and guppies exposed to 160 and 300 ppm chloroform.
5. 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.
6. 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.
7. Land *et al*. (1979), as cited in ATSDR.
   Abstract - appears to be the same study as Land *et al*. (1981).
8. Land *et al*. (1981), as cited in ATSDR, HSDB, Reprotext®, Reprotox™.
   Mice were exposed via inhalation to 400 or 800 ppm (0.04% or 0.08%)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.
9. 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.
10. National Toxicology Program (1988), as cited in IRIS, USEPA Toxicological Review
    In a two-generation reproduction study, CD-1 mice (n=20/treatment group and 40 control) were treated with 0, 6.6, 16 or 41 mg/kg/d chloroform in corn oil by gavage on 7d/w for 18 weeks. No adverse effects on fertility or reproduction were reported.
11. 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.

12. Topham (1981), as cited in HSDB, Reprotox™.
    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.
13. Torkelson *et al*. (1976), as cited in ATSDR, 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. Brown-Woodman *et al.* (1986), as cited in Shepard's Catalog of Teratogenic Agents.
   Levels of 2.06 μmoles per ml of serum were toxic in whole embryo cultures (species not identified) while no effect was found at 1.05 μmoles per ml.
2. Danielson *et al*. (1986), as cited in HSDB.
   Pregnant mice were exposed to radiolabeled chloroform by inhalation on days 11, 14 and 17 of gestation, and 4-day-old mice were exposed to radiolabeled chloroform by ip injection. A high uptake of chloroform was noted in pregnant mice, especially in the respiratory epithelium, liver, fat, lung, brain and renal cortex. In the 4-day-old mice, notable accumulation of chloroform was noted in the respiratory epithelium, oral/osophageal mucosa, liver, salivary glands and the conjunctiva of the eye.
3. 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.
4. USEPA Toxicological Review.
   Metabolism of chloroform is essential to its toxicity. Metabolism by cytochrome P450 CYP2E1 is required for toxicity to liver and kidney of B6C3F1 and Sv/129 male mice. Studies in humans indicate CYP2E1 enzymatic activity in human fetuses is either absent or low compared with that in adult tissues. A few studies indicate CYP2E1 is expressed in fetal liver or cephalic tissue.

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