

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 C₆H₆O. 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, a disinfectant, in medical products, and as a reagent in research laboratories. In addition to the secondary sources usually reviewed, documents submitted by an interested party (the American Chemistry Council) were also reviewed.

Overview of Developmental/Reproductive Toxicity Concern

There is a **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 in newborns has caused death or grave illness. 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 urogenital tract.

A multi-generation reproductive toxicity study conducted by the drinking-water route in rats reported delayed puberty, as evidenced by increased age at vaginal opening, and decreases in absolute and relative uterine weights. 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 urogenital 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 reported delayed puberty, as evidenced by increased age at preputial separation, and decreased absolute and relative prostate weights.

Overview of Exposure Concern

There is a **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 1.188 billion pounds in 1988 (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 (Reprotex®).

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 Reprotex®.
“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. Kuntz (1976), as cited in Reprotex®.
“In one review, phenol was said to affect the human embryo or fetus.”
4. Malysheva (1976), as cited in Reprotex®.
“One study concluded that phenol altered the sex ratio in rats at 30 mg/m³ and also implied the same effect in humans.”
5. NIOSH (1976), as cited in HSDB.
Reports of abortion and other toxic symptoms after phenol exposure.

Developmental toxicity in animals

1. Bernardini *et al.* (1996), as cited in ATSDR.
A modified frog embryo teratogenesis assay using *Xenopus* (FETAX) showed malformations at concentrations of phenol that also resulted in lethality.
2. Chapman *et al.* (1994), as cited in Reprotex®, 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.”
3. Ciranni *et al.* (1988), as cited by ATSDR.
No evidence of cellular toxicity was observed in fetuses from pregnant mice given 265 mg phenol/kg on day 13 of gestation.
4. Hathaway *et al.* (1996), as cited in Reprotex®.
“Rats and mice given up to 120 and 280 milligram per kilogram of phenol, respectively, by gavage on days 6-15 of gestation showed dose-related signs of fetotoxicity.” “Rats exposed to up to 1.3 ppm of

phenol throughout pregnancy showed increased preimplantation loss and early postnatal death in the offspring.”

5. Heller and Pursell (1938), as cited in ATSDR.
No effect of phenol in drinking water (1,000 ppm) on growth, reproduction, and normal rearing of 5-generations of rats; similar lack of effect with 5,000 ppm for 4 generations. For dams given 30, 60, or 120 mg phenol/kg-day, offspring showed a dose-related decrease in the average live fetal body weight, and an increase in the proportion of gravid uteri with resorption sites at the low and medium doses, but not at the high dose.
6. Jones-Price *et al.* (1983A), as cited in TERIS, Reprotex[®], ATSDR, Schardein.
Same study cited as NTP (1983) by IRIS. 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. Schardein merely notes the reference in a table.
7. Jones-Price *et al.* (1983B), as cited in TERIS, Reprotex[®], ATSDR.
Same study cited as NTP (1983) by IRIS. 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.
8. 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.
9. 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.”
10. Kavlock (1990), as cited in ATSDR, TERIS.
This appears to be the full report of the in vivo data described in the abstract listed under number 6 above. Phenol was administered to rats by gavage on gestation day 11, at doses of 0, 100, 333, 667, and 1000 mg/kg. Limited endpoints were evaluated: maternal weight change (at 24 and 72 hours post dosing), litter size (postnatal days 1 and 6), perinatal loss, pup weight (postnatal days 1 and 6), and litter biomass (postnatal days 1 and 6). Maternal weight gain was significantly affected at the two highest doses. There was no effect on litter size. Offspring from the two highest dose groups showed a dose-related increase in the frequency a syndrome characterized by kinky tails and/or hindlimb paralysis (21.4% and 27.3% affected litters, respectively).
11. Korshunov (1974), as cited in Reprotex[®].
“. . . rats inhaling phenol at 0.5 or 5 mg/m³ for 3 months . . . caused preimplantation deaths and early postnatal....”
12. Malysheva (1976), as cited in Reprotex[®].
“One study concluded that phenol altered the sex ratio in rats at 30 mg/m³ and also implied the same effect in humans.”
13. Minor and Becker (1971), as cited in Reprotex[®], TERIS, Schardein, Shepard’s Catalog of Teratogenic Agents, Reprotex[®], RTECS, HSDB.
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.
14. Narotsky and Kavlock (1995), as cited in Reprotex[®], ATSDR, TERIS.
According to ATSDR, a significant decrease in the number of liveborn pups, associated with severe respiratory effects in their dams, was observed after gavage treatment with 53.3 mg phenol/kg-day on

- gestation days 6-19. Two of four surviving pups in one high-dose litter had kinked tails. According to TERIS, there was no significant effect of treatment on litter size.
15. NTIS (OTS-0537777), as cited in RTECS.
120 mg phenol/kg bw-day was given by the oral route to pregnant rats on gestation days 6-15.
Maternal effects.
 16. NTIS (PB83-247726), as cited in RTECS.
30 mg phenol/kg bw-day was given by the oral route to pregnant rats on gestation days 6-15. Post implantation mortality (dead or resorbed implants per total implants). At 120 mg/kg-day, fetotoxicity (stunted fetuses) was observed.
 17. NTIS (OTS-0573554), as cited in RTECS.
Pregnant rats were given phenol by the oral route at a dose of 360 mg/kg bw-day on each of gestation days 6-15. Maternal effects and fetotoxicity (stunted fetuses).
 18. NTIS (PB85-104461), as cited in RTECS.
Pregnant mice were given phenol by the oral route at a dose of 400 mg/kg-day on each of gestation days 6-15. Effects were noted on the fetal musculoskeletal system. Stunted fetuses were observed at a dose of 260 mg/kg-day. At 230 mg/kg-day, postimplantation mortality was observed.
 19. Price *et al.* (1986), as cited in IARC, TERIS, Reprotox®, 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.”
 20. Proctor & Gamble Co. (1993), as cited in HSDB.
Phenol was administered by gavage to mated Charles River Crl:CD VAF/Plus female rats (10/group) at dosage levels of 0 mg/kg/day (Control); 3 groups at 60 mg/kg/day; 3 groups at 120 mg/kg/day; or 180 mg/kg/day on gestation days 6 through 14. At 120 mg/kg/day, maternal toxicity included reduced body weight gain and feed consumption. There were treatment-related findings in regards to clinical signs, developmental toxicity, necropsy findings, organ weights, or pathology results.

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 and Pursell (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. For dams given 30, 60, or 120 mg phenol/kg-day, offspring showed a dose-related decrease in the average live fetal body weight, and an increase in the proportion of gravid uteri with resorption sites at the low and medium doses, but not at the high dose. Data were not considered to be reported in enough detail for 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/m³ for 3 months”
3. Korshunov (1974), as cited in Reprotext®.
“. . . rats inhaling phenol at 0.5 or 5 mg/m³ for 3 months . . . caused preimplantation deaths and early postnatal deaths . . .”

4. NCI (1980), as cited in ATSDR.
No histopathological effects on male or female reproductive organs in rats or mice exposed to phenol in drinking water for 13 weeks (100-10,000 ppm) or 103 weeks (2,500 or 5,000 ppm).
5. Proctor & Gamble Co. (1993), as cited in HSDB.
Phenol was administered by gavage to mated Charles River Crl:CD VAF/Plus female rats (10/group) at dosage levels of 0 mg/kg/day (Control); 3 groups at 60 mg/kg/day; 3 groups at 120 mg/kg/day; or 180 mg/kg/day on gestation days 6 through 14. At 120 mg/kg/day, maternal toxicity included reduced body weight gain and feed consumption. There were treatment-related findings in regards to clinical signs, developmental toxicity, necropsy findings, organ weights, or pathology results.

Male reproductive toxicity in humans

1. Ishchenko and Pushkina (1978), as cited in Reprotex®.
“Women and men working with phenol-formaldehyde resins were reported to suffer from uro-genital diseases.”
2. O’Donaghue (1985), as cited in Reprotex®.
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 and Pursell (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. NCI (1980), as cited in ATSDR.
No histopathological effects on male or female reproductive organs in rats or mice exposed to phenol in drinking water for 13 weeks (100-10,000 ppm) or 103 weeks (2,500 or 5,000 ppm).
3. Proctor & Gamble Co. (1993), as cited in HSDB.
Phenol was administered by gavage to mated Charles River Crl:CD VAF/Plus female rats (10/group) at dosage levels of 0 mg/kg/day (Control); 3 groups at 60 mg/kg/day; 3 groups at 120 mg/kg/day; or 180 mg/kg/day on gestation days 6 through 14. At 120 mg/kg/day, maternal toxicity included reduced body weight gain and feed consumption. There were treatment-related findings in regards to clinical signs, developmental toxicity, necropsy findings, organ weights, or pathology results.

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. American Medical Association (1994), as cited in HSDB.
Phenol is not recommended for use in pregnant women, in infants under 6 months, or for diaper rash. Phenolic disinfectants have produced epidemics of neonatal hyperbilirubinemia when used to clean bassinets and mattresses in poorly ventilated nurseries. Fatalities have been documented in infants.
2. Deichman (1969), as cited in RTECS.
Toxic effects in infants. LDLo, oral dose 10 mg/kg. Behavioral effects, muscle weakness, cyanosis.
3. 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.
4. Gray and Kavlock (1990), as cited in Shepard’s Catalog of Teratogenic Agents, Reprotex®.
“Gray and Kavlock (1990) fed C14ⁿ-labeled phenol to rats and determined that the levels in placenta and embryo were equivalent to maternal serum.” [Abstract].

5. 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. (1998) Agency for Toxic Substances and Disease Registry. Toxicological Profile for Phenol.

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (CHEMKNOWLEDGE JANUARY, 2002)

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. (CHEMKNOWLEDGE JANUARY, 2002)

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Reprotext®. Micromedex, Inc. (CHEMKNOWLEDGE JANUARY, 2002)

RTECS®. Registry of Toxic Effects of Chemical Substances. National Institute of Occupational Safety and Health. (CHEMKNOWLEDGE JANUARY, 2002)

Schardein J. L. (2000) *Chemically Induced Birth Defects*. Third Edition, Marcel Dekker.

Shepard's Catalog of Teratogenic Agents. Dr. Thomas H. Shepard. (CHEMKNOWLEDGE JANUARY, 2002)

TERIS. Teratogen Information System. University of Washington. (CHEMKNOWLEDGE JANUARY, 2002)

Other Sources (submitted by the American Chemistry Council)

Ryan, B.M. et al. (2001) *International Journal of Toxicology*. 20: 121-142

Bishop, J.B. et al. (1997) *Fundamental and Applied Toxicology*. 40: 191-204