

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

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. Numerous 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 from auto 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 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, Part A Exposure Assessment. Stationary Source Division. Sacramento, California.

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

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

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