TOXICITY SUMMARY FOR BENZO[*a*]PYRENE

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EXECUTIVE SUMMARY

Benzo[*a*]pyrene is a polycyclic aromatic hydrocarbon (PAH) that can be derived from coal tar. Occurring ubiquitously in products of incomplete combustion of fossil fuels, benzo[*a*]pyrene has been identified in ambient air, surface water, drinking water, and waste water, and in char-broiled foods (IARC, 1983). Benzo[*a*]pyrene is primarily released to the air and removed from the atmosphere by photochemical oxidation and dry deposition to land or water. Biodegradation is the most important tranformation process in soil or sediment (ATSDR, 1990).

Benzo[*a*]pyrene is readily absorbed following inhalation, oral, and dermal routes of administration (ATSDR, 1990). Following inhalation exposure, benzo[*a*]pyrene is rapidly distributed to several tissues in rats (Sun et al., 1982; Weyand and Bevan, 1986). The metabolism of benzo[*a*]pyrene is complex and includes the formation of a proposed ultimate carcinogen, benzo[*a*]pyrene 7,8 diol-9,10-epoxide (IARC, 1983). The major route of excretion is hepatobiliary followed by elimination in the feces (U.S. EPA, 1991).

No data are available on the systemic (non-carcinogenic) effects of benzo[*a*]pyrene in humans. In mice, genetic differences appear to influence the toxicity of benzo[*a*]pyrene. Subchronic dietary administration of 120 mg/kg benzo[*a*]pyrene for up to 180 days resulted in decreased survival due to hematopoietic effects (bone narrow depression) in a "nonresponsive" strain of mice (i.e., a strain whose cytochrome P-450 mediated enzyme activity is not induced as a consequence of PAH exposure). No adverse effects were noted in "responsive" mice (i.e., a strain capable of inducing increased cytochrome P-450 mediated enzyme activity as a consequence of PAH exposure) (Robinson et al., 1975). Immunosuppression has been reported in mice administered daily intraperitoneal injections of 40 or 160 mg/kg of benzo[*a*]pyrene for 2 weeks, with more pronounced effects apparent in "nonresponsive" mice (Blanton et al., 1986; White et al., 1985). In utero exposure to benzo[*a*]pyrene has produced adverse developmental/reproductive effects in mice. Dietary administration of doses as low as 10 mg/kg during gestation caused reduced fertility and reproductive capacity in offspring (Mackenzie and Angevine, 1981) and treatment by gavage with 120 mg/kg/day during gestation caused stillbirths, resorptions, and malformations (Legraverend et al., 1984). Similar effects have been reported in intraperitoneal injection studies (ATSDR, 1990)

Neither a reference dose (RfD) nor a reference concentration (RfC) has been derived for benzo[*a*]pyrene.

Numerous epidemiologic studies have shown a clear association between exposure to various mixtures of PAHs containing benzo[*a*]pyrene (e.g., coke oven emissions, roofing tar emissions, and cigarette smoke) and increased risk of lung cancer and other cancers. However, each of the mixtures also contained other potentially carcinogenic PAHs; thus, it is not possible to evaluate the contribution of benzo[*a*]pyrene to the carcinogenicity of these mixtures (IARC, 1983; U.S. EPA, 1991). There is an extensive data base for the carcinogenicity of benzo[*a*]pyrene in experimental animals. Dietary administration of benzo[*a*]pyrene has produced papillomas and carcinomas of the forestomach in mice (Neal and Rigdon, 1967) and treatment by gavage has produced mammary tumors in rats (McCormick et al., 1981) and pulmonary adenomas in mice (Wattenberg and Leong, 1970). Exposure by inhalation and intratracheal instillation has resulted in benign and malignant tumors of the respiratory and upper digestive tracts of hamsters (Ketkar et al., 1978; Thyssen et al., 1981). Numerous topical application studies have shown that benzo[*a*]pyrene induces skin tumors in several species, although mice appear to be the most sensitive species. Benzo[*a*]pyrene is a complete carcinogen and also an initiator of skin tumors (IARC, 1973; U.S. EPA, 1991). Benzo[*a*]pyrene has also been reported to induce tumors in animals when administered by other routes (intravenous, intraperitoneal, subcutaneous, intrapulmonary, transplacental).

Based on U.S. EPA guidelines, benzo[*a*]pyrene was assigned to weight-of-evidence group B2, probable human carcinogen. For oral exposure, the slope factor and unit risk are 7.3E+0 $(mg/kg/day)^{-1}$ and 2.1E-4 $(\mu g/L)^{-1}$, respectively (U.S. EPA, 1994).

1. INTRODUCTION

Benzo[*a*]pyrene (CAS Reg. No. 50-32-8), also known as 1,4-benzo[*a*]pyrene (BaP), is a polycyclic aromatic hydrocarbon (PAH) with a chemical formula of $C_{20}H_{12}$ and a molecular weight of 252.3. It exists as yellowish plates and needles, has a boiling point of 310-312°C at 10 mm Hg (Budavari et al., 1989), a melting point of 178°C, and a density of 1.35 (U.S. EPA, 1991). Benzo[*a*]pyrene is practically insoluble in water, but is soluble in benzene, toluene, xylene, and is sparingly soluble in alcohol and methanol (Budavari et al., 1989). It has a vapor pressure of 5.0×1^{-1} torr and a log octanol/water coefficient of 6.04 (U.S. EPA, 1991).

There is no commercial production or use of benzo[*a*]pyrene. It occurs ubiquitously in products of incomplete combustion and in fossil fuels. It has been identified in surface water, tap water, rain water, ground water, waste water, and sewage sludge (U.S. EPA, 1991). Benzo[*a*]pyrene is primarily released to the air and removed from the atmosphere by photochemical oxidation and dry deposition to land or water. Biodegradation is the primary tranformation process in soil or sediment (ATSDR, 1990). The estimated half-lives for benzo[*a*]pyrene are <1-6 days in the atmosphere, <1-8 hours in water, 5-10 years in sediment, and >14-16 months in soil (for complete degradation) (U.S. EPA, 1984). Benzo[*a*]pyrene is one of a number of PAHs on EPA's priority pollutant list (ATSDR, 1990).

2. METABOLISM AND DISPOSITION

2.1. ABSORPTION

Benzo[*a*]pyrene is readily absorbed by the oral, inhalation, and dermal routes of exposure (ATSDR, 1990). Rats given benzo[*a*]pyrene in starch solution by gavage (100 mg) or in the diet (250 mg) absorbed 40% or 60%, respectively, of the administered compound (Chang, 1943). The absorption of benzo[a]pyrene from the gastrointestinal tract of mice and cats is enhanced when it is solubilized in vehicles possessing both lipophilic and hydrophilic properties (Ekwall et al., 1951). Once benzo[a]pyrene has entered the small intestine, it is solubilized by bile salts and absorbed (Ermala et al., 1951).

In rats exposed by inhalation to 1 µg/L radiolabeled benzo[*a*]pyrene for 30 minutes, monitoring of excretion over a 2-week period showed nearly complete recovery of radioactivity (predominantly in feces), indicating nearly complete absorption (Sun et al., 1982).

Under *in vitro* conditions, 3% of an applied dose of benzo[*a*]pyrene permeated human skin after 24 hours. When tested in several animal species, the permeation was highest in the mouse (10%) and lowest in the guinea pig (0.1%) (Kao et al., 1985). Following topical application of radiolabeled benzo[*a*]pyrene to the skin of mice, Heidelberger and Weiss (1951) recovered most of the radioactivity in the feces within 16 days, indicating significant absorption of benzo[*a*]pyrene through the skin.

2.2. DISTRIBUTION

According to Rees et al. (1971), 10-20% of an intragastric dose of benzo[*a*]pyrene (10 mg) entered the thoracic lymph duct in rats (levels in other tissues were not determined). Other data concerning the tissue distribution of benzo[*a*]pyrene following oral exposure were not available.

In rats exposed by inhalation, distribution of absorbed benzo[*a*]pyrene is rapid, with highest levels found in the liver, esophagus, small intestine, and blood 30 minutes after exposure (Sun et al., 1982). Five minutes after intratracheal instillation of benzo[*a*]pyrene to rats, the percentages of the administered dose in tissues were: lungs (59.5%), carcass (14.4%), liver (12.5%); blood (3.9%); and intestines (1.9%). At 60 minutes, the percentages were: lungs (15.4%), carcass (27.1%), liver (15.8%), blood (1.6%), and intestines (9.9%) (Weyand and Bevan, 1986).

Topical administration of ^{14}C-benzo[*a*]pyrene in benzene to the shaved backs of mice was followed by a biphasic disappearance of radioactivity from the application site, with half-lives of 40 and 104 hours (Heidelberger and Weiss, 1951).

Benzo[*a*]pyrene can readily cross the placenta following oral, intravenous, or subcutaneous administration. This observation is consistent with the observed toxicity in the fetuses and offspring of maternally exposed rodents (IARC, 1983; ATSDR, 1990).

2.3. METABOLISM

The metabolism of benzo[*a*]pyrene has been extensively studied in the literature and only the most important pathways will be presented in this summary. As outlined in IARC (1983), benzo[*a*]pyrene is metabolized initially by the microsomal cytochrome P-450 monooxygenase system to several arene oxides, which may rearrange spontaneously to phenols, undergo hydration to the corresponding trans-dihydrodiols, or react covalently with glutathione, either spontaneously or in a reaction catalyzed by glutathione-S-transferases. One of the phenolic metabolites, 6-hydroxybenzo[*a*]pyrene, is further oxidized to the 1,6-, 3,6-, or 6,12-quinones. The phenols, quinones, and dihydrodiols can be detoxified by conjugation to glucuronides and sulfate esters and the quinones can also form glutathione conjugates. In addition to conjugation, the dihydrodiols undergo further oxidative metabolism. Benzo[*a*]pyrene 7,8-dihydrodiol is in part oxidized to the 7,8-diol-9,10-epoxide, a compound considered to be the ultimate carcinogenic metabolite of benzo[*a*]pyrene.

2.4. EXCRETION

Hepatobiliary excretion and elimination in the feces is the primary route in which metabolites of benzo[*a*]pyrene are excreted (U.S. EPA, 1991). Two weeks following inhalation exposure to radiolabeled benzo[*a*]pyrene for 30 minutes, most of the radioactivity was recovered in the feces of rats (Sun et al., 1982). Similarly, essentially all of the radioactivity was recovered in the feces of mice that had been treated topically with radiolabeled benzo[*a*]pyrene (Heidelberger and Weiss, 1951). Kotin et al. (1959) reported that approximately 75% of a subcutaneously injected dose of benzo[*a*]pyrene was recovered in the feces of mice within 6 days of injection, while only 12% was eliminated in the urine. In rats, 39% of an intravenous dose was found in the bile at 3 hours, and as much as 96% by 14 hours. Less than 1% of recovered benzo[*a*]pyrene in the bile was unmetabolized. In rats with bile duct cannulation, 3-4% of the dose was recovered in the urine, while intact rats had a urinary excretion of 7-14%, suggesting that enterohepatic circulation of metabolites. There was no evidence that benzo[*a*]pyrene is eliminated via expired air.

3. NONCARCINOGENIC HEALTH EFFECTS

3.1. ORAL EXPOSURES

3.1.1. Acute Toxicity

Information on the acute oral toxicity of benzo[*a*]pyrene in humans or animals was not available.

3.1.2. Subchronic Toxicity

3.1.2.1. Human

Information on the subchronic oral toxicity of benzo[*a*]pyrene in humans was not available.

3.1.2.2. Animal

Genetic differences appear to influence the oral toxicity of benzo[*a*]pyrene in mice. Robinson et al. (1975) investigated the effects of oral administration of benzo[*a*]pyrene in several strains of mice, classified as "responsive" (those capable of producing increased levels of cytochrome P-450 mediated enzymes as a consequence of PAH exposure) or "nonresponsive" (those not highly responsive to producing increased levels of cytochrome P-450 mediated enzymes as a consequence of PAH exposure). Following dietary administration of 120 mg/kg of benzo[*a*]pyrene for up to 180 days, survival of all "nonresponsive" mice was shortened. Death appeared to be due to bone marrow depression (aplastic anemia, pancytopenia). The "responsive" mice remained healthy for at least six months. The authors concluded that decreased survival in "nonresponsive" mice was associated with a single gene difference in PAH responsiveness.

3.1.3. Chronic Toxicity

Information on the chronic oral toxicity of benzo[*a*]pyrene in humans or animals was not available.

3.1.4. Developmental and Reproductive Toxicity
3.1.4.1. Human

Information on the developmental and reproductive toxicity of benzo[*a*]pyrene in humans following oral exposure was not available.

3.1.4.2. Animal

No reproductive or developmental toxicity was observed in male or female White Swiss mice fed diets containing 0, 250, 500, or 1000 mg/kg benzo[*a*]pyrene over various time periods during mating, gestation, and lactation (Rigdon and Neal, 1965). However, Mackenzie and Angevine (1981) reported that administration of 10 mg/kg to CD-1 mice by gavage during gestation produced decreased gonadal weights, and reduced fertility and reproductive capacity in the offspring. Higher doses (40 mg/kg) caused almost complete sterility in both sexes of offspring.

Legraverend et al. (1984) investigated the effect of genetic differences in benzo[*a*]pyrene metabolism on the reproductive or developmental toxicity in "responsive" and "nonresponsive" mice (benzo[*a*]pyrene metabolism occurs more readily in the "responsive" genotypes). Pregnant mice were fed 120 mg/kg/day on days 2 through 10 of gestation. Treatment with benzo[*a*]pyrene resulted in stillbirths, resorptions, and malformations in both genotypes of mice; however, the incidence of these effects was higher among "nonresponsive" embryos than among "responsive" embryos. The study suggests that it is benzo[a]pyrene and not a metabolite which is responsible for the noted adverse effects.

3.1.5. Reference Dose

An oral reference dose (RfD) for benzo[*a*]pyrene has not been derived.

3.2. INHALATION EXPOSURES
3.2.1. Acute Toxicity

Information on the acute toxicity of benzo[*a*]pyrene in humans or animals following inhalation exposure was not available.

3.2.2. Subchronic Toxicity

Information on the subchronic toxicity of benzo[*a*]pyrene in humans or animals following inhalation exposure was not available.

3.2.3. Chronic Toxicity

Information on the chronic toxicity of benzo[*a*]pyrene in humans or animals following inhalation exposure was not available.

3.2.4. Developmental and Reproductive Toxicity

Information on the developmental and reproductive toxicity of benzo[*a*]pyrene in humans or animals following inhalation exposure was not available.

3.2.5. Reference Concentration

An inhalation reference concentration (RfC) for benzo[*a*]pyrene has not been derived.

3.3. OTHER ROUTES OF EXPOSURE
3.3.1. Acute Toxicity
3.3.1.1. Humans

Information on the acute toxicity of benzo[*a*]pyrene in humans by other routes of exposure was not available.

3.3.1.2. Animals

The intraperitoneal (i.p.) LD_{50} for the mouse is 232 mg/kg (Salamone, 1981) and the subcutaneous (s.c.) LD_{50} for the rat is 50 mg/kg (RTECS, 1994). Reduced survival was reported in "responsive" mice administered a single i.p. injection of 500 mg/kg benzo[*a*]pyrene (Robinson et al., 1975). Subcutaneous injections of benzo[*a*]pyrene (5, 20, or 40 mg/kg) caused a dose-related suppression of both T-cell independent and T-cell dependent antigens in mice (White and Holsapple, 1984). Wojdani et al. (1984) injected two strains of mice with tumor target cells; this treatment was followed by i.p. injections of 0, 0.5, 5, or 50 mg/kg of benzo[*a*]pyrene. At the two higher doses, there were significant decreases in lymphocytes binding to target cells or killing target cells. The investigators indicated that lymphocyte-mediated immunity may be inhibited by benzo[*a*]pyrene and that this immunosuppresive effect may contribute to its carcinogenicity.

3.3.2. Subchronic Toxicity
3.3.2.1. Humans

Information on the subchronic toxicity of benzo[*a*]pyrene by other routes of exposure in humans was not available.

3.3.2.2. Animals

Immunotoxic effects as a consequence of benzo[*a*]pyrene have been studied by a number of investigators. For example, a 60% suppression of antibody response was reported in $B6C3F_1$ mice (a highly "responsive" strain) administered 14 daily s.c. injections of 160 µmol/kg benzo[*a*]pyrene. In DBA/2 mice (a strain not highly "responsive") subjected to the same dosing protocol, immunosuppression was more pronounced (White et al., 1985). Daily s.c. injections of 40 mg/kg benzo[*a*]pyrene for 14 days resulted in a 98% depression of the T-cell-dependent antibody response in $B6C3F_1$ mice. Polyclonal antibody responses were reduced 50 to 66% following benzo[*a*]pyrene (Blanton et al., 1986).

3.3.3. Chronic Toxicity

Information on the chronic toxicity of benzo[*a*]pyrene by other routes of exposure in humans or animals was not available.

3.3.4. Developmental and Reproductive Toxicity
3.3.4.1. Human

Information on the developmental or reproductive toxicity of benzo[*a*]pyrene by other routes of exposure in humans was not available.

3.3.4.2. Animal

Adverse developmental/reproductive effects were observed in several injection studies with benzo[*a*]pyrene. These studies are reviewed in ATSDR (1990), but experimental details were not provided. Intraperitoneal administration of benzo[*a*]pyrene to mice has resulted in stillbirths, resorptions, and malformations; decreases in follicular growth and corpora lutea; and in testicular changes. Subcutaneous injections of benzo[*a*]pyrene produced increased resorptions in rats and direct embryonal injection led to decreased fetal survival in mice.

3.4. TARGET ORGANS/CRITICAL EFFECTS
3.4.1. Oral Exposures
3.4.1.1. Primary Target Organs

1. Hematopoietic system: Subchronic oral exposure produced bone marrow depression (aplastic anemia and pancytopenia) and ultimately death in "nonresponsive" mice.

2. Reproduction/development: Exposure during gestation of mice produced decreased gonadal weights, reduced fertility, and sterility in offspring. Stillbirths, resorptions, and malformations were seen in "responsive" and "nonresponsive" mice; however, the incidence of these effects was higher in "nonresponsive" mice.

3.4.1.2. Other Target Organs

Other target organs for oral exposure were not identified.

3.4.2. Inhalation Exposures

Target organs for inhalation exposure to benzo[*a*]pyrene were not identified.

3.4.3. Other Routes of Exposure
3.4.3.1. Primary Target Organs

1. Immune system: Subcutaneous injections of benzo[*a*]pyrene administered over a 2-week period caused depressed antibody responses in mice.

2. Reproduction/development: Intraperitoneal injections of benzo[*a*]pyrene has resulted in stillbirths, resorptions, malformations, decreased follicular growth and corpora lutes, and in testicular changes in mice. Subcutaneous injections produced increased resorptions in rats.

3.4.3.2. Other Target Organs

Other target organs for other routes of exposure were not identified.

4. CARCINOGENICITY
4.1. ORAL EXPOSURES
4.1.1. Human

Information on the carcinogenicity of benzo[*a*]pyrene in humans following oral exposure was not available.

4.1.2. Animal

In a study by Brune et al. (1981), male and female Sprague-Dawley rats were fed 0.15 mg/kg every 9th day or 5 times/week for life. The incidence of tumors of the forestomach, esophagus, and larynx (combined) was 5% for controls and for rats fed benzo[*a*]pyrene every 9th day and 16% for rats fed benzo[*a*]pyrene 5 times/week. Administration of a single 50-mg dose of benzo[*a*]pyrene or of 8 weekly doses of 6.25 mg by gavage induced mammary tumors in LEW/Mai rats (McCormick et al., 1981). The incidence of mammary carcinomas after 90 weeks was 77% for the single exposure and 67% for the multiple exposures. Mammary tumors were observed in 30% of controls. Huggins and Yang (1962) reported that a single oral dose of 100 mg benzo[*a*]pyrene administered by gavage induced mammary tumors in 8/9 female Sprague-Dawley rats.

Neal and Rigdon (1967) fed male and female CFW-Swiss mice a diet containing 1 to 250 ppm benzo[*a*]pyrene for up to 197 days. No tumors were found in the control group and in groups treated with 1, 10, or 30 ppm. However, forestomach papillomas and carcinomas developed at dietary concentrations of $40 ppm. The authors indicated that the tumor incidence was related to both the concentration and the number of doses administered. Female mice administered 200 or 300 ppm benzo[*a*]pyrene in the diet for

a relatively short time (12 weeks) developed tumors of the forestomach (Triolo et al., 1977). Pulmonary adenomas developed in A/HeJ mice treated by gavage with two daily doses of 3 mg benzo[*a*]pyrene at 2-week intervals (Wattenberg and Leong, 1970). The pulmonary tumor count increased from 0.3 tumors/mouse in controls to 16.6 tumors/mouse in the treated group at 30 weeks of age.

4.2. INHALATION EXPOSURES

4.2.1. Human

Numerous epidemiologic studies have shown a clear association between inhalation exposure to various mixtures containing PAHs (e.g., coke oven emissions, roofing tar emissions, and cigarette smoke) in ambient air and increased risk of lung cancer and other cancers. Each of these mixtures contained benzo[*a*]pyrene as well as other carcinogenic PAHs and other potentially carcinogenic chemicals; thus, it is not possible to evaluate the contribution of benzo[*a*]pyrene to the carcinogenicity of these mixtures (IARC, 1983; U.S. EPA, 1991).

4.2.2. Animal

Thyssen et al. (1981) exposed Syrian hamsters to benzo[*a*]pyrene at concentrations of 0, 2.2, 9.5, or 46.5 mg/m^3, 4.5 hours/day for 10 days and then 3 hours/day for up to 675 days. No treatment-related tumors were observed in hamsters exposed to 2.2 mg/m^3 or in controls. Hamsters exposed to 9.5 mg/m^3 developed papillomas and squamous cell carcinomas located primarily in the nasal cavity, larynx, trachea, and pharynx. In addition to respiratory tract tumors, hamsters exposed to the highest concentration also developed tumors of the upper digestive tract.

Intratracheal administration of benzo[*a*]pyrene also induced neoplasms of the respiratory tract in male and female Syrian hamsters. Weekly intratracheal administration of benzo[*a*]pyrene (total doses 18.2 or 36.4 mg/animal) for 52 weeks produced a dose-related increase of tracheal papillomas/carcinomas and lung adenomas. Similar effects were reported following weekly intratracheal administration of doses ranging from 0.1 to 1 mg up to 40 weeks, but the response was not clearly dose-related (Ketkar et al., 1978).

4.3. OTHER ROUTES OF EXPOSURE

4.3.1. Human

Human tumorigenicity has been reported in a number of studies as a result of dermal exposure to complex mixtures of PAHs containing benzo[*a*]pyrene. An early report (Pott, 1775) described scrotal cancer in chimney sweeps. More recently, skin cancer has occurred in workers exposed to shale oil (Purde and Etlin, 1980) and creosote (Lenson, 1956). However, the contribution of benzo[*a*]pyrene to the carcinogenicity of these PAH mixtures is uncertain.

In an experimental study, epidermal changes (erythema, pigmentation, and desquamation) were reported following daily applications of a 1% solution of benzo[*a*]pyrene to the skin of humans over a 4-month period. Although reversible and benign, these changes were thought to represent early stages of neoplastic proliferation (Cottini and Mazzone, 1939). It should be noted that benzo[*a*]pyrene was applied as a solution in benzene and no benzene control was evaluated. Similar epithelial changes were reported in humans accidentally exposed to benzo[*a*]pyrene (U.S. EPA, 1984).

4.3.2. Animal

Benzo[*a*]pyrene is among the most potent and best documented skin carcinogens and is commonly used as a positive control in skin application assays of other chemicals. Benzo[*a*]pyrene has been shown to cause skin tumors in mice, rats, rabbits, and guinea pigs, although mice appear to be the most sensitive species. It is both an initiator and complete carcinogen in mouse skin (IARC, 1973; U.S. EPA, 1991).

Wynder and Hoffmann (1959) applied 0.001, 0.005, or 0.01% benzo[*a*]pyrene in acetone to the backs of female Swiss mice three times weekly for life. For the three dose groups, the incidence of skin papillomas was 95, 100, or 85%, respectively, and the incidence of skin carcinomas was 4, 86, or 95%, respectively. Data for a solvent control group were not provided. In initiation/promotion experiments,

Hoffmann and Wynder (1966) applied 10 doses of benzo[*a*]pyrene in dioxane (total dose 0.25 mg) every two days to the skin of mice. This treatment was followed by application of 2.5% croton oil in acetone. Skin papillomas developed in 80% of treated animals and in 7% of controls (receiving croton oil alone).

The modifying effects of solvents on the carcinogenicity of benzo[*a*]pyrene have been demonstrated in several studies. For example, Bingham and Falk (1969) treated C3H/He mice topically with different concentrations of benzo[*a*]pyrene in either *n*-dodecane or a *n*-dodecane/decalin mixture three times weekly for 50 weeks. When *n*-dodecane/decalin was used as solvent, malignant skin tumors appeared in 5/24 mice treated with 0.00002% benzo[*a*]pyrene and the tumor incidence increased at higher concentrations. With decalin alone as solvent, malignant skin tumors developed in 5/12 mice treated with 0.02%, but none were seen at lower concentrations. Other topical application studies with mice demonstrated synergistic effects of cigarette smoke condensates on skin tumor induction (IARC, 1973).

Benzo[*a*]pyrene has been shown to produce tumors at various sites by other modes of administration. A 94% incidence of lung adenomas was reported in newborn mice injected i.p. with 280 µg/mouse of benzo[*a*]pyrene (Busby et al., 1984). Newborn rats treated with a single i.p. injection of 0.59 µmol benzo[*a*]pyrene/kg and observed for life developed hepatic tumors. The tumor incidence was 37% for males and 57% for females (Peraino et al., 1984). Several studies reported injection site tumors in mice, rats, guinea pigs, hamsters, and some primates administered s.c. injections of benzo[*a*]pyrene (U.S. EPA, 1994). In addition to injection site sarcomas, newborn mice administered benzo[*a*]pyrene by s.c. injection developed hepatomas or lung adenomas (U.S. EPA, 1991; IARC, 1973). Benzo[*a*]pyrene has also been reported to induce tumors when administered by the intravenous and transplacental route; by implantation in the stomach wall, renal parenchyma, and brain; by injection in the renal pelvis; and by vaginal painting (U.S. EPA, 1994).

4. EPA WEIGHT-OF-EVIDENCE

Classification -- B2, probable human carcinogen (U.S. EPA, 1994).
Basis -- Human data specifically linking benzo[*a*]pyrene to a carcinogenic effect are lacking. There are, however, multiple animal studies in many species demonstrating benzo[*a*]pyrene to be carcinogenic by numerous routes (U.S. EPA, 1994).

Note: The carcinogenicity risk assessment for benzo[*a*]pyrene may change in the near future pending further review by EPA.

4.5. CARCINOGENICITY SLOPE FACTORS

4.5.1. Oral

SLOPE FACTOR: 7.3E+0 $(mg/kg/day)^{-1}$ (U.S. EPA, 1994)
UNIT RISK: 2.1E-4 $(\mu g/L)^{-1}$
PRINCIPAL STUDIES: Brune et al., 1981; Neal and Rigdon, 1967; Rabstein et al., 1973 (historical control data)

COMMENT: The slope factor, the geometric mean of four calculated slope factors [range 4.5E+0 to 11.7E+0 $(mg/kg/day)^{-1}$], was derived using multiple data sets from different studies employing more than one sex, strain, and species. EPA considered the data less than optimal, but acceptable.

4.5.2. Inhalation

An inhalation slope factor has not been calculated.

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