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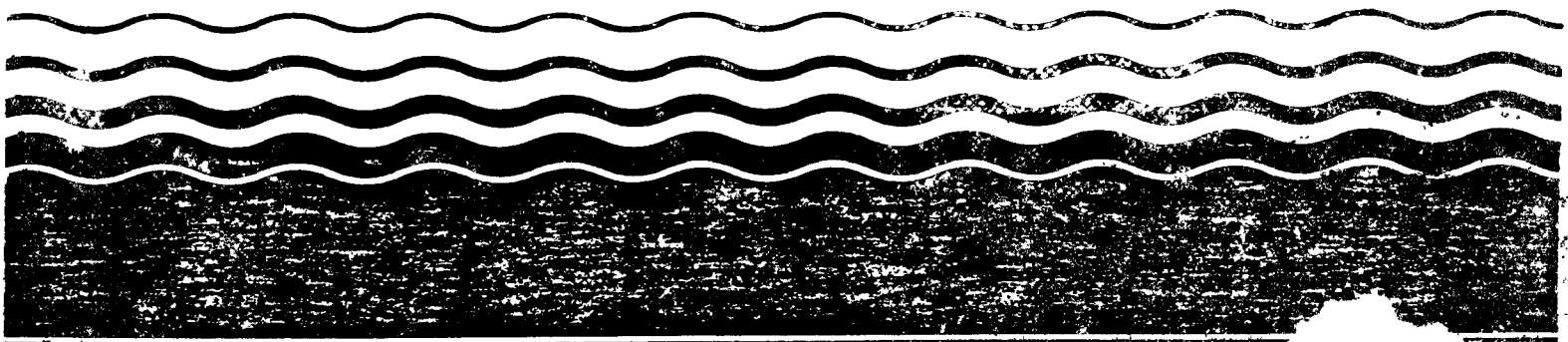
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HEALTH EFFECTS ASSESSMENT  
FOR BENZO(a)PYRENE



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September 1984

**HEALTH EFFECTS ASSESSMENT  
FOR BENZO(A)PYRENE**

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Office of Solid Waste and Emergency Response  
Washington, DC 20460**

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U.S. Environmental Protection Agency

## PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with benzo(a)-pyrene. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of the information have also been relied upon in the preparation of this report and represent large scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980b. Ambient Water Quality Criteria for Polynuclear Aromatic Hydrocarbons. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-069. NTIS PB 81-117806.

U.S. EPA. 1981. Hazard Profile for PAH. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983a. Review of Toxicologic Data in Support of Evaluation for Carcinogenic Potential of: Benzo[a]pyrene. Prepared by the Carcinogen Assessment Group, OHEA, Washington, DC for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983b. Reportable Quantity for Benzo[a]pyrene. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data was limited in scope tending to generate conservative (i.e. protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level which would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval which does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CS) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983c).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, any exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q1\*s have been computed based on oral and inhalation data if available.

## ABSTRACT

In order to place the risk assessment evaluation in proper context, the reader is referred to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Animal data indicate that benzo(a)pyrene is a potent carcinogen via inhalation, oral and dermal routes. Human data concerning exposure to benzo(a)pyrene and cancer are lacking; however, human data concerning increased cancer risk and exposure to PAH containing mixtures are convincing.

U.S. EPA (1980b) used the mouse data of Neal and Rigdon (1967) to compute a  $q_1^*$  of  $11.53 \text{ (mg/kg/day)}^{-1}$ . This risk assessment has been extensively peer reviewed.

The same methodology was used in the present document to compute a  $q_1^*$  of  $6.11 \text{ (mg/kg/day)}^{-1}$  from inhalation exposure data in Golden Syrian hamsters.

## ACKNOWLEDGEMENTS

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## LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
bw	Body weight
CAS	Chemical Abstract Service
CS	Composite score
DNA	Deoxyribonucleic acid
GI	Gastrointestinal
PAH	Polycyclic aromatic hydrocarbon
SCE	Sister chromatid exchange
TLV	Threshold limit value
TWA	Time-weighted average

## 1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of benzo[a]pyrene (CAS Registry No. 50-32-8) are given in Table 1-1.

The half-life for benzo[a]pyrene in the atmosphere has been estimated from the discussion in the NAS (1983) document regarding the chemical and its photochemical reaction and the estimation of its half-life due to physical removal processes as discussed by Cupitt (1980).

Pertinent data regarding the leachability of this compound in soils could not be located in the available literature. Considering the high octanol/water partition coefficient and low water solubility, the compound is expected to have very low mobility in soils, particularly in soils with high organic matter content.

TABLE 1-1

## Selected Physical and Chemical Properties and Half-lives for Benzo[a]pyrene

Properties	Values	Reference
Chemical class:	Polycyclic aromatic hydrocarbons (PAH)	NA
Molecular weight:	252	Mabey et al., 1981
Vapor pressure:	$5.6 \times 10^{-9}$ mm Hg at 25°C	Mabey et al., 1981
Water solubility:	1.2 µg/kg at 25°C	Wise et al., 1981
Log octanol/water partition coefficient:	6.06	U.S. EPA, 1980b
Bioconcentration factor:	28,200 (estimated)	U.S. EPA, 1980b
Half-lives in:		
Air:	<1-6 days (estimated)	NAS, 1983; Cupitt, 1980
Water:	<1-8 hours in aquatic phase 5-10 years in sediment	Smith et al., 1978 Smith et al., 1978
Soil:	>14-16 months for complete degradation	U.S. EPA, 1981

NA = Not applicable

## 2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

### 2.1. ORAL

Data regarding oral absorption of benzo[a]pyrene are limited; however, observed toxicity following oral administration indicates that benzo[a]pyrene is absorbed by this route (Smyth et al., 1962; U.S. EPA, 1980b, 1981; Santodonato et al., 1981).

Absorption of orally administered lipophilic PAH can be hampered by the mucous layer lining the GI tract (Grimmer, 1983). Rats given benzo[a]pyrene in starch solution (100 mg) by gavage or in the diet (250 mg) absorbed ~50% of the administered compound (Chang, 1943).

Regardless of the type of solvent used, benzo[a]pyrene readily penetrates the forestomach epithelium of mice. In the glandular stomach, however, the type of solvent used plays a decisive role in the absorption of benzo[a]pyrene (Ekwall et al., 1951; Setala, 1954). Hydrophilic solvents enhance the absorption of benzo[a]pyrene from the glandular stomach as compared to lipophilic solvents.

### 2.2. INHALATION

Data regarding the pulmonary absorption of benzo[a]pyrene are limited; however, observed toxicity after inhalation exposure indicates that benzo[a]pyrene is readily absorbed through the lungs (Kotin et al., 1969; Vainio et al., 1976). As a class, PAHs are highly lipid soluble and capable of passing across epithelial membranes (U.S. EPA, 1980b).

### 3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

#### 3.1. SUBCHRONIC

3.1.1. Oral. Differences in genetic constitutions appear to influence the subchronic oral toxicity of benzo[a]pyrene in mice. Specifically, the Ah locus, which determines the inducibility of aryl hydrocarbon hydroxylase, plays a major role in determining the oral toxicity of benzo[a]pyrene, presumably by influencing the pathways of biotransformation. Robinson et al. (1975) administered benzo[a]pyrene in the diet at a level of 120 mg/kg bw to nonresponsive (poorly inducible) AKR/N mice ( $Ah^d/Ah^d$  type) and to responsive (markedly inducible) mice ( $Ah^b/Ah^b$  type). Nonresponsive mice developed aplastic anemia and died within 4 weeks, whereas responsive mice remained healthy for at least 6 months.

3.1.2. Inhalation. Pertinent data regarding the non-tumor-related subchronic toxicity of benzo[a]pyrene administered by inhalation could not be located in the available literature.

#### 3.2. CHRONIC

3.2.1. Oral. The only available chronic bioassays for oral exposure of benzo[a]pyrene are investigations of carcinogenicity (U.S. EPA, 1980b). The lack of appropriate protocols (i.e., non-tumor pathology) and detailed reporting of symptoms render these carcinogenicity bioassays inadequate for use in evaluating non-carcinogenic endpoints.

3.2.2. Inhalation. There are no reports available concerning the non-tumor-related chronic toxicity of benzo[a]pyrene administered by inhalation.

#### 3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Rigdon and Rennels (1964) fed female rats a diet containing benzo[a]pyrene at a level of 1000 mg/kg (equivalent to 50 mg/kg/day) for up to 3.5 months. Of seven pregnant treated animals, only one dam carried viable fetuses to term, delivering four pups on the 23rd day of pregnancy.

Two of the four pups were stillborn, one of which was grossly malformed (not necessarily treatment-related). A third pup was killed for observational purposes, and evidently the fourth pup died of starvation 3 days after birth because the dam did not appear to be lactating. The authors were not certain whether this absence of lactation was treatment-related.

At autopsy, four dead fetuses were found in the right uterine horn of a second dam. Signs of toxicity (body weight changes or histopathological changes) were not observed in the treated dams.

In a teratogenicity and reproduction study, Rigdon and Neal (1965) fed male and female mice diets containing benzo[a]pyrene at a level of 0, 250, 500 or 1000 mg/kg over various time spans during mating, gestation and lactation. No apparent reproductive, teratogenic, embryotoxic or fetotoxic effects were observed in the experimental animals.

Mackenzie and Angevine (1981) administered benzo[a]pyrene orally at a level of 10 mg/kg bw to CD-1 mice during pregnancy. There was no effect on fetal body weights, but there was a marked and specific reduction of gonadal weight, and reduced fertility and reproductive capacity were observed among the offspring. At a level of 40 mg/kg/day, almost complete sterility was observed in both sexes of offspring.

3.3.2. Inhalation. Pertinent data regarding the teratogenic effects resulting from inhalation exposure to benzo[a]pyrene could not be located in the available literature.

#### 3.4. TOXICANT INTERACTIONS

U.S. EPA (1980b) has described extensively the synergistic and antagonistic interactions among different PAHs and between PAH and non-PAH chemicals. Briefly, metabolism of PAH by the microsomal mixed function oxidase



enzyme system yields several types of reactive and potentially carcinogenic intermediates. Chemicals that induce or inhibit this enzyme system alter the patterns of PAH metabolism and, hence, alter their toxic and carcinogenic properties.

## 4. CARCINOGENICITY

The carcinogenicity of benzo[a]pyrene has been tested extensively by applying it to the skin of mice, and only infrequently by other routes of administration. The studies discussed below have been summarized in U.S. EPA (1983a); however, more complete reviews of the carcinogenicity bioassays of benzo[a]pyrene are provided by IARC (1973, 1983), U.S. EPA (1980b, 1981, 1983b) and Santodonato et al. (1981).

### 4.1. HUMAN DATA

Few case reports are available regarding the direct carcinogenic effects of benzo[a]pyrene on humans. Cottini and Mazzone (1939) applied a 1% solution of benzo[a]pyrene in benzene to small areas of the exposed and unexposed skin of 26 patients. Up to 120 daily applications were applied over a 4-month period, within which time, regressive verrucae developed in each of the 26 patients. Although reversible and apparently benign, these changes were thought to represent early stages of neoplastic proliferation. Similar cases of epidermal changes were reported by Rhoads et al. (1954) and Klar (1938) to have occurred in men accidentally exposed to benzo[a]pyrene. Numerous epidemiologic studies of human populations (primarily worker groups) have shown a clear association between exposure to PAH-containing materials (e.g., soots, tars, oils) and increased cancer risk (Santodonato et al., 1981; IARC, 1973, 1983; U.S. EPA, 1981).

4.1.1. Oral. Pertinent data regarding the carcinogenicity of benzo[a]pyrene to humans following oral exposure could not be located in the available literature.

4.1.2. Inhalation. Pertinent data regarding the carcinogenicity of benzo[a]pyrene to humans following inhalation exposure could not be located in the available literature.

## 4.2. BIOASSAYS

4.2.1. Oral. Benzo[a]pyrene was administered in various concentrations in the diets of mice to test its carcinogenicity (Neal and Rigdon, 1967; Rigdon and Neal, 1966, 1969). These studies are summarized in Tables 4-1, 4-2 and 4-3. A dose-response relationship was noted for the incidence of stomach tumors (papillomas and carcinomas) in male and female CFW-Swiss mice treated with 1-250 ppm benzo[a]pyrene for up to 197 days (Neal and Rigdon, 1967). Stomach tumors were reported in animals treated with 20, 40, 45, 50, 100 and 250 ppm benzo[a]pyrene (5/23, 1/40, 4/40, 24/34, 19/23 and 66/73, respectively), while control animals (0/289) and those treated with 1, 10 and 30 ppm benzo[a]pyrene (0/25, 0/24 and 0/37, respectively) did not have stomach tumors. In addition to the increase in stomach tumors, increased incidences of lung adenoma and leukemia were noted in mice treated with 250 and 1000 ppm benzo[a]pyrene (Rigdon and Neal, 1966, 1969).

4.2.2. Inhalation. Thyssen et al. (1981) exposed groups of 24 hamsters by inhalation to benzo[a]pyrene at levels of 2.2, 9.5 or 45 mg/m<sup>3</sup> for 4.5 hours/day for 10 weeks and 3 hours/day 7 days/week thereafter, for up to 675 days (Table 4-4). No treatment-related tumors were observed in animals exposed to 2.2 mg/m<sup>3</sup>. Animals exposed to 9.5 mg/m<sup>3</sup>, however, developed tumors of the nasal cavity (12%), larynx (31%), trachea (4%) and pharynx (23%). Hamsters exposed to 44.8 mg/m<sup>3</sup> benzo[a]pyrene developed tumors of the respiratory tract (13/25) and upper digestive tract (14/25). No tumors of these types were seen in control animals (Thyssen et al., 1981).

Intratracheal administration of benzo[a]pyrene resulted in an increased incidence of respiratory tract neoplasms in both sexes of Syrian hamsters (Ketkar et al., 1978; Feron and Krusysse, 1978) (Tables 4-5 and 4-6). A dose-related response was reported for hamsters treated with 18.2 and 36.4 mg/animal (total dose) for 52 weeks followed by a 29-week latency period.

TABLE 4-1

Carcinogenicity of Benzo[a]pyrene Administered in the Diet to Male and Female CFM Mice at Levels of 1-250 ppm\*

Dose	Duration of Treatment (days)	Duration of Study (days)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
1 ppm (0.48 mg total dose)	110	140	NR	diet	stomach	papillomas/carcinomas	0/25
10 ppm (4.48 mg total dose)	110	140	NR	diet	stomach	papillomas/carcinomas	0/24
20 ppm (8.88 mg total dose)	110	226	NR	diet	stomach	papillomas/carcinomas	5/23
30 ppm (13.32 mg total dose)	110	143-177	NR	diet	stomach	papillomas/carcinomas	0/37
40 ppm (17.76 mg total dose)	110	143-211	NR	diet	stomach	papillomas/carcinomas	1/40
45 ppm (19.8 mg total dose)	110	141-183	NR	diet	stomach	papillomas/carcinomas	4/40
50 ppm (21.4-29.4 mg total dose)	107-197	124-219	NR	diet	stomach	papillomas/carcinomas	24/34
100 ppm (39.2-48.8 mg total dose)	98-122	118-146	NR	diet	stomach	papillomas/carcinomas	19/23
250 ppm (70-165 mg total dose)	70-165	88-185	NR	diet	stomach	papillomas/carcinomas	66/73
0.0 ppm	NA	70-300	NA	basal diet only	stomach	papillomas/carcinomas	0/289

\*Source: Neal and Rigdon, 1967

NA - Not applicable; NR - Not reported

TABLE 4-2

Carcinogenicity of Benzo[a]pyrene Administered in the Diet to Male and Female Swiss Mice at Levels of 250-1000 ppm\*

Dose	Duration of Treatment (days)	Duration of Study (days)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
1000 ppm (1 mg/g food)	73-83	73-83	NR	diet	stomach lung	papilloma/carcinoma adenoma	5/9 7/9
1000 ppm (1 mg/g food)	127-187	127-187	NR	diet	stomach lung	papilloma/carcinoma adenoma	13/13 3/13
250 ppm (0.25 mg/g food)	72-99	72-99	NR	diet	stomach lung	papilloma/carcinoma adenoma	12/52 26/52
250 ppm (0.25 mg/g food)	147-196	147-196	NR	diet	stomach lung	papilloma/carcinoma adenoma	9/13 10/13
0.0 ppm	NA	111-120	NA	diet only	stomach lung	papilloma/carcinoma adenoma	2/108 25/108

\*Source: Rigdon and Neal, 1966

NA = Not applicable; NR = Not reported

TABLE 4-3

Carcinogenicity of Benzo[a]pyrene Administered in the Diet to Male and Female Swiss CFW Mice at a Level of 250 ppm<sup>a</sup>

Dose	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
250 ppm (0.25 mg/g food)	80-140 days	80-140 days	NR	diet	stomach lung hematopoietic system	papilloma/carcinoma adenoma leukemia	69/108 52/108 40/108
0.0 ppm	NA	62-300 days	NA	diet only	stomach lung hematopoietic system	papilloma/carcinoma adenoma leukemia	2/175 <sup>b</sup> 33/151 0/175 <sup>b</sup>

<sup>a</sup>Source: Rigdon and Neal, 1969

<sup>b</sup>Incidence of tumors in a control group reported previously by Rigdon and Neal (1966).

NA - Not applicable; NR - Not reported

TABLE 4-4

Carcinogenicity of Benzo[a]pyrene to Male Syrian Golden Hamsters by Inhalation<sup>a,b</sup>

Dose	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type <sup>c</sup>	Tumor Incidence
2.2 mg/m <sup>3</sup> (29 mg total dose)	95.2	95.2	NR	NaCl vapor in air	respiratory tract upper digestive tract	tumors tumors	0/27 0/27
9.5 mg/m <sup>3</sup> (127 mg total dose)	96.4	96.4	NR	NaCl vapor in air	respiratory tract upper digestive tract	tumors tumors	9/26 <sup>d</sup> 7/26 <sup>d</sup>
46.5 mg/m <sup>3</sup> (383 mg total dose)	59.5	59.5	NR	NaCl vapor in air	respiratory tract upper digestive tract	tumors tumors	13/25 <sup>e</sup> 14/25 <sup>e</sup>
0.0 mg/m <sup>3</sup>	NA	96.4	NA	NaCl vapor only	respiratory tract upper digestive tract	tumors tumors	0/27 0/27

<sup>a</sup>Source: Thyssen et al., 1981<sup>b</sup>Exposure was for 4.5 hours/day for the first 10 weeks, 3 hours/day thereafter for 7 days/week.<sup>c</sup>Tumors were papillomas, papillary polyps, and squamous cell carcinomas.<sup>d</sup>3 nasal cavity, 8 laryngeal, 1 tracheal, 6 pharyngeal and 1 forestomach tumors<sup>e</sup>1 nasal cavity, 13 laryngeal, 3 tracheal, 14 pharyngeal, 2 esophageal and 1 forestomach tumor

NA = Not applicable; NR = Not reported

TABLE 4-5

Carcinogenicity of Benzo[a]pyrene in Syrian Hamsters Following Intratracheal Administration of 0.10-1.0 mg/week<sup>a</sup>

Sex	Dose (mg/week)	Duration of Treatment <sup>b</sup> (weeks)	Duration of Study <sup>b</sup> (weeks)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type <sup>c</sup>	Tumor Incidence
M	0.10	40	40	97%	bovine albumin	respiratory tract	various neoplasms	5/26
F	0.10	34	34	97%	bovine albumin	respiratory tract	various neoplasms	12/30
M	0.33	24	24	97%	bovine albumin	respiratory tract	various neoplasms	7/29
F	0.33	28	28	97%	bovine albumin	respiratory tract	various neoplasms	10/28
M	1.0	10	10	97%	bovine albumin	respiratory tract	various neoplasms	6/27
F	1.0	15	15	97%	bovine albumin	respiratory tract	various neoplasms	6/30
M	0.0	41	41	NA	bovine albumin only	respiratory tract	various neoplasms	0/29
F	0.0	35	35	NA	bovine albumin only	respiratory tract	various neoplasms	0/30

<sup>a</sup>Source: Ketkar et al., 1978<sup>b</sup>Mean survival time<sup>c</sup>Carcinomas, adenomas, adenocarcinomas and papillomas were reported.

NA = Not applicable



TABLE 4-6

Carcinogenicity of Benzo[a]pyrene in Golden Syrian Hamsters Following Intratracheal Administration of 18.2-36.4 mg/animal<sup>a</sup>

Sex	Dose	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type <sup>b</sup>	Tumor Incidence
M	18.2 mg/hamster total dose	52 (1 dose/week)	81	>99%	0.9% NaCl	respiratory tract	various	4/29
M	36.4 mg/hamster total dose	52 (1 dose/week)	81	>99%	0.9% NaCl	respiratory tract	various	19/30
M	0.0 mg/hamster total dose	52 (1 dose/week)	81	>99%	saline vehicle only	respiratory tract	various	0/30 <sup>c</sup>
F	18.2 mg/hamster total dose	52 (1 dose/week)	81	>99%	0.9% NaCl	respiratory tract	various	3/27
F	36.4 mg/hamster total dose	52 (1 dose/week)	81	>99%	0.9% NaCl	respiratory tract	various	7/24
F	0.0 mg/hamster total dose	52 (1 dose/week)	81	>99%	saline vehicle only	respiratory tract	various	0/28 <sup>c</sup>

<sup>a</sup>Source: Feron and Krusysse, 1978<sup>b</sup>Papillomas and carcinomas of the trachea and pulmonary adenomas were most prevalent.<sup>c</sup>Combined tumor incidence of untreated and vehicle controls

The incidence of tracheal papillomas and carcinomas, collectively, with lung adenomas was 4/29 and 3/27 for low dose males and females, respectively, and 19/30 and 7/24 for high dose males and females, respectively (Feron and Kruyse, 1978). Ketkar et al. (1978) reported a high dose-related mortality in hamsters treated at dose levels lower than those used by Feron and Kruyse (1978). Mean survival times ranged from 40 weeks for male hamsters treated with 0.1 mg benzo[a]pyrene/week to 10 weeks for males treated with 1.0 mg benzo[a]pyrene/week. An increase in the incidence of respiratory tract carcinoma, adenoma and papilloma in both sexes of hamsters in the treatment groups was reported, but a definite dose-related response was not evident (Ketkar et al., 1978).

#### 4.3. OTHER RELEVANT DATA

The mutagenicity of benzo[a]pyrene has been summarized by IARC (1982), U.S. EPA (1980b, 1981), Santodonato et al. (1981), deSerres and Ashby (1981) and Hollstein and McCann (1979). The reader is referred to these reviews for further information.

Benzo[a]pyrene is an indirect acting carcinogen, undergoing metabolism to a reactive electrophile capable of covalently binding to DNA (IARC, 1982; Lutz, 1979). Benzo[a]pyrene has been used extensively as a model carcinogen and as a positive control in a variety of short-term tests, yielding positive results in assays for bacterial DNA repair, bacteriophage induction and bacterial mutation, mutation in Drosophila melanogaster; DNA binding, DNA repair, SCE, chromosomal aberration, point mutation and transformation in mammalian cells in culture; and in tests in mammals in vivo, including DNA binding, SCE, chromosomal aberration, sperm abnormality and the specific locus (spot) test (IARC, 1982; deSerres and Ashby, 1981; Hollstein and McCann, 1979).

#### 4.4. WEIGHT OF EVIDENCE

Benzo[a]pyrene is both a local and a systemic carcinogen, producing tumors in rats, mice, hamsters, guinea pigs, rabbits and monkeys following oral, inhalation or dermal exposure. Benzo[a]pyrene is an initiator of skin carcinogenesis in mice and also produces tumors following single doses or prenatal exposure. Benzo[a]pyrene has been used extensively as a model carcinogen and as a positive control in a variety of short-term tests. IARC (1982) reported that there is sufficient evidence that benzo[a]pyrene is an animal carcinogen and limited evidence that it is a human carcinogen. Applying the classification criteria for weight of evidence proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984), benzo[a]pyrene is most appropriately designated a Group B2 chemical.

## 5. REGULATORY STANDARDS AND CRITERIA

Exposure criteria and TLVs have been developed for PAH as a class, as well as for several individual PAHs. The Occupational Safety and Health Administration has set an 8-hour TWA concentration limit of 0.2 mg/m<sup>3</sup> for the benzene-soluble fraction of coal tar pitch volatiles (anthracene, benzo[a]pyrene, phenanthrene, acridine, chrysene, pyrene) (Code of Federal Regulations, 1981). NIOSH (1977) recommends a concentration limit for coal tar, coal tar pitch, creosote and mixtures of these substances at 0.1 mg/m<sup>3</sup> of the cyclohexane-extractable fraction of the sample, determined as a 10-hour TWA. NIOSH (1977) concluded that these specific coal tar products, as well as coke oven emissions, are carcinogenic and can increase the risk of lung and skin cancer in workers. NIOSH (1977) also recommends a ceiling limit for exposure to asphalt fumes of 5 mg airborne particulates/m<sup>3</sup> of air.

Environmental quality criteria for PAH have been recommended for ambient water, which specify concentration limits intended to protect humans against adverse health effects. The U.S. EPA (1980b) has recommended a concentration limit of 28 ng/l for the sum of all carcinogenic PAHs in ambient water. This value is based on a mathematical extrapolation of the results from studies with mice treated orally with benzo[a]pyrene, and acknowledges the conservative assumption that all carcinogenic PAHs are equal in potency to benzo[a]pyrene. Daily consumption of water containing 28 ng/l of carcinogenic PAH over an entire lifetime is estimated on the basis of the animal bioassay data to keep the lifetime risk of cancer development below 1 chance in 100,000.

The U.S. EPA has not recommended an ambient water quality criterion for noncarcinogenic PAH as a class. The U.S. EPA (1980b) acknowledged that data suitable for quantitative risk assessment of noncarcinogenic PAH are essentially nonexistent.

## 6. RISK ASSESSMENT

### 6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

Benzo[a]pyrene is a known carcinogen for which data are sufficient for computing a  $q_1^*$ . It is, therefore, inappropriate to calculate an oral or inhalation AIS for benzo[a]pyrene.

### 6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

Benzo[a]pyrene is a known carcinogen for which data are sufficient for computing a  $q_1^*$ . It is, therefore, inappropriate to calculate an oral or inhalation AIC for benzo[a]pyrene.

### 6.3. CARCINOGENIC POTENCY ( $q_1^*$ )

6.3.1. Oral. A carcinogenic potency factor,  $q_1^*$ , for humans can be derived from the study of Neal and Rigdon (1967) in which benzo[a]pyrene at dose levels of 1-250 ppm in the diet was administered to strain CFW mice for ~110 days. The incidences of stomach tumors (mostly squamous-cell papillomas, but some carcinomas) were 0/289 for controls, 0/25 at the 1 ppm (0.13 mg/kg/day) level, 0/24 at 10 ppm (1.3 mg/kg/day), 1/23 at 20 ppm (2.6 mg/kg/day), 0/37 at 30 ppm (3.9 mg/kg/day), 1/40 at 40 ppm (5.2 mg/kg/day), 4/40 at 45 ppm (5.85 mg/kg/day), 24/34 at 50 ppm (6.5 mg/kg/day), 19/23 at 100 ppm (13.0 mg/kg/day) and 66/73 at 250 ppm (32.5 mg/kg/day). U.S. EPA (1980b) used these incidences of stomach tumors to derive a  $q_1^*$  of 11.53 (mg/kg/day)<sup>-1</sup>. The data used in derivation of this  $q_1^*$  are presented in Appendix C.

6.3.2. Inhalation. A carcinogenic potency factor,  $q_1^*$ , for humans can be derived from the study of Thyssen et al. (1981) in which Golden Syrian hamsters were exposed to benzo[a]pyrene by inhalation at levels of 0, 2.2, 9.5 or 46.5 mg/m<sup>3</sup> for 10-96.4 weeks. The incidences of respiratory tumors were 0/27 for controls, 0/27 for the low-dose group, 9/26 for the mid-dose

group and 13/25 for the high-dose group. The highest exposure level did have an adverse impact on survival time. Animals exposed to an average concentration of 46.5 mg benzo[a]pyrene/m<sup>3</sup> air had an average survival time of 59.5 weeks, as compared with controls which survived for an average of 96.4 weeks. Due to early mortality in the highest dose group, these data were excluded from the  $q_1^*$  derivation. Based on the respiratory tumor response of male hamsters and using the linearized multistage model adopted by the U.S. EPA (U.S. EPA, 1980a), a carcinogenic potency factor ( $q_1^*$ ) of  $\checkmark$  6.11 (mg/kg/day)<sup>-1</sup> can be derived for humans. The animal  $q_1^*$  was derived using transformed doses based on an inhalation rate of hamsters of 0.037 m<sup>3</sup>/day and assuming 100% absorption. The conversion factor used in the calculation of the human  $q_1^*$  from the animal data was the cube root of the body weight ratio, empirically accepted to adjust for species to species extrapolation. Complete data for derivation of the  $q_1^*$  are presented in Appendix B.

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APPENDIX A

Summary Table for Benzo[a]pyrene

Carcinogenic Potency	Species	Experimental Dose/Exposure	Effect	$q_1^*$ (mg/kg/day) <sup>-1</sup>	Reference
Inhalation	hamsters	2.2-9.5 mg/m <sup>3</sup>	respiratory tract tumors	6.11	Thyssen et al., 1981
Oral	mice	1-250 ppm	stomach tumors	11.53	Neal and Rigdon, 1967

APPENDIX B

Cancer Data Sheet for Derivation of  $q_1^*$

Compound: Benzo[a]pyrene

Reference: Thyssen et al., 1981

Species, strain, sex: hamsters/Syrian Golden/male

Body weight: 0.12 kg (assumed)

Length of exposure ( $t_e$ ) = 666.4 days for lower dose and 674.8 days for higher dose and controls

Length of experiment ( $L_e$ ) = 666.4 days for lower dose and 674.8 days for higher dose and controls

Lifespan of animal ( $L$ ) = 666.4 days for lower dose and 674.8 days for higher dose and controls

Tumor site and type: respiratory tract/papillomas, papillary polyps and squamous-cell carcinomas

Route, vehicle: inhalation/NaCl vapor in air

Experimental Doses or Exposures*	Input	
	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested (or Examined)
0 mg/m <sup>3</sup>	0	0/27
2.2 mg/m <sup>3</sup>	0.0892	0/27
9.5 mg/m <sup>3</sup>	0.385	9/26

\*See following page for conversions

$$q_1^*A = 0.731101 \text{ (mg/kg/day)}^{-1}$$

$$q_1^*H = 6.11 \text{ (mg/kg/day)}^{-1}$$



## CONVERSIONS

$$0 \text{ mg/m}^3 = 0 \text{ mg/kg/day}$$

$$2.2 \text{ mg/m}^3 \times \left[ \frac{10 \text{ weeks}}{95.2 \text{ weeks}} \times \frac{4.5 \text{ hours}}{24 \text{ hours}} + \left( \frac{85.2 \text{ weeks}}{95.2 \text{ weeks}} \times \frac{3 \text{ hours}}{24 \text{ hours}} \right) \right] \times \frac{7 \text{ days}}{7 \text{ days}} \times$$

$$0.037 \text{ m}^3/\text{day} \div 0.12 \text{ kg} \times \frac{666.4 \text{ days}}{666.4 \text{ days}} \times \left( \frac{666.4 \text{ days}}{666.4 \text{ days}} \right)^3 = 0.0892 \text{ mg/kg/day}$$

$$9.5 \text{ mg/m}^3 \times \left[ \frac{10 \text{ weeks}}{96.4 \text{ weeks}} \times \frac{4.5 \text{ hours}}{24 \text{ hours}} + \left( \frac{86.4 \text{ weeks}}{96.4 \text{ weeks}} \times \frac{3 \text{ hours}}{24 \text{ hours}} \right) \right] \times \frac{7 \text{ days}}{7 \text{ days}} \times$$

$$0.037 \text{ m}^3/\text{day} \div 0.12 \text{ kg} \times \frac{674.8 \text{ days}}{674.8 \text{ days}} \times \left( \frac{674.8 \text{ days}}{674.8 \text{ days}} \right)^3 = 0.385 \text{ mg/kg/day}$$

DATE

APPENDIX C

Cancer Data Sheet for Derivation of  $q_1^*$

Compound: Benzo[a]pyrene

Reference: Neal and Rigdon, 1967

Species, Strain, Sex: mouse, CFW, M,F

Body weight: 0.034 kg (assumed)

Length of exposure ( $t_e$ ) = 110 days

Length of experiment ( $L_e$ ) = 183 days

Lifespan of animal ( $L$ ) = 630 days

Tumor site and type: stomach, papilloma, carcinomas

Route, vehicle: oral, diet

Experimental Doses or Exposures (ppm)	Transformed Dose (mg/kg/day)*	Incidence
		No. Responding/No. Tested or Examined
0	0	0/289
1	0.078	0/25
10	0.781	0/24
20	1.563	1/23
30	2.344	0/37
40	3.126	1/40
45	3.516	4/40

\*Adjusted to reflect treatment on day 110 of a 183-day experimental period.

Unadjusted  $q_1^*$  from study =  $2.2213189 \times 10^{-2}$  (mg/kg/day) $^{-1}$

Human  $q_1^*$  = 11.53 (mg/kg/day) $^{-1}$

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