Benzo[a]pyrene (BaP); CASRN 50-32-8

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR BaP

File First On-Line 03/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	04/01/1992

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Benzo[a]pyrene (BaP)
CASRN — 50-32-8

Not available at this time.

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Benzo[a]pyrene (BaP)
CASRN — 50-32-8

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Benzo[a]pyrene (BaP)
CASRN — 50-32-8
Last Revised — 04/01/1992

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

NOTE: At the June 1992 CRAVE Work Group meeting, a revised risk estimate for benzo[a]pyrene was verified (see Additional Comments for Oral Exposure). This section provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000 or 1 in 1,000,000. The Carcinogenicity Background Document provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to the Oral Reference Dose (RfD) and Reference Concentration (RfC) sections for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — B2; probable human carcinogen

Basis — Human data specifically linking benzo[a]pyrene (BAP) to a carcinogenic effect are lacking. There are, however, multiple animal studies in many species demonstrating BAP to be carcinogenic following administration by numerous routes. BAP has produced positive results in numerous genotoxicity assays.

II.A.2. Human Carcinogenicity Data

Inadequate. Lung cancer has been shown to be induced in humans by various mixtures of polycyclic aromatic hydrocarbons known to contain BAP including cigarette smoke, roofing tar and coke oven emissions. It is not possible, however, to conclude from this information that BAP is the responsible agent.

II.A.3. Animal Carcinogenicity Data

Sufficient. The animal data consist of dietary, gavage, inhalation, intratracheal instillation, dermal and subcutaneous studies in numerous strains of at least four species of rodents and several primates. Repeated BAP administration has been associated with increased incidences of total tumors and of tumors at the site of exposure. Distant site tumors have also been observed after BAP administration by various routes. BAP is frequently used as a positive control in carcinogenicity bioassays.

BAP administered in the diet or by gavage to mice, rats and hamsters has produced increased incidences of stomach tumors. Neal and Rigdon (1967) fed BAP (purity not reported) at concentrations of 0, 1, 10, 20, 30, 40, 45, 50, 100 and 250 ppm in the diets of male and female CFW-Swiss mice. The age of the mice ranged from 17-180 days old and the treatment time from 1-197 days; the size of the treated groups ranged from 9 to 73. There were 289 mice (number of mice/sex not stated) in the control group. No forestomach tumors were reported in the 0-, 1- and 10-ppm dose groups. The incidence of forestomach tumors in the 20-, 30-, 40-, 45-, 50-, 100- and 250-ppm dose groups were 1/23, 0/37, 1/40, 4/40, 23/34, 19/23 and 66/73, respectively. The authors felt that the increasing tumor incidences were related to both the concentration and the number of doses administered. Historical control forestomach tumor data are not available for CFW-Swiss strain mice. In historical control data from a related mouse strain, SWR/J Swill, the forestomach tumor incidence rate was 2/268 and 1/402 for males and females, respectively (Rabstein et al., 1973).

Brune et al., (1981) fed 0.15 mg/kg BAP (reported to be "highly pure") in the diet of 32 Sprague-Dawley rats/sex/group either every 9th day or 5 times/week. These treatments resulted in annual average doses of 6 or 39 mg/kg, respectively. An untreated group of 32 rats/sex served as the control. Rats were treated until moribund or dead; survival was similar in all groups. Histologic examinations were performed on each rat. The combined incidence of tumors of the forestomach, esophagus and larynx was 3/64, 3/64 and 10/64 in the control group, the group fed BAP every 9th day and the group fed BAP 5 times/week, respectively. A trend analysis showed a statistically significant tendency for the proportion of animals with tumors of the forestomach, esophagus or larynx to increase steadily with dose (Knauf and Rice, 1992).

As part of the same study, Brune et al. (1981) administered BAP ("highly pure") orally to Sprague-Dawley rats by caffeine gavage. The rats were treated until moribund or dead; all rats were subjected to terminal histopathologic examination. Gavaged rats were divided into 3 dose groups of 32 rats/sex/group; the groups received 0.15 mg/kg per gavage either every 9th day (Group A), every 3rd day (Group B) or 5 times per week (Group C); these treatments resulted in annual average doses of 6, 18 or 39 mg/kg, respectively. Untreated and gavage (5 times/week) controls (32 rats/sex/group) were included. The median survival times for the untreated control group; the gavage control group; and groups A, B and C were 129, 102, 112, 113 and 87 weeks, respectively. The survival time of Group C was short compared with controls and may have precluded tumor formation (Knauf and Rice, 1992). The combined tumor incidence in the forestomach, esophagus and larynx was 3/64, 6/64, 13/64, 26/64 and 14/64 for the untreated control group, gavage control group, group A, group B and group C, respectively. There was a statistically significant association between the dose and the proportions of rats with tumors of the forestomach, esophagus or larynx. This association is not characterized by a linear trend. The linearity was affected by the apparently reduced tumor incidence that is seen in the high-dose group (Knauf and Rice, 1992).

Intratracheal instillation and inhalation studies in guinea pigs, hamsters and rats have resulted in elevated incidences of respiratory tract and upper digestive tract tumors (U.S. EPA, 1991a). Male Syrian golden hamsters (24/group) were exposed by inhalation to 0, 2.2, 9.5 or 46.5 mg BAP/cu.m in a sodium chloride aerosol (Thyssen et al., 1981). (Greater than 99% of the particles had diameters between 0.2 and 0.5 um.) For the first 10 weeks of the study, the hamsters were exposed to BAP daily for 4.5 hours/day; thereafter, daily for 3 hours/day. Animals dying within the first year of the study were replaced; the effective number of hamsters in the control, low-, mid- and high-dose groups was 27, 27, 26 and 25, respectively. (The total time of treatment, although over 60 weeks, was not stated.) During the first 10 weeks, animals in the 3 dose groups reportedly lost weight. After week 10, however, the body weights in all groups were similar until week 60 when the body weights of hamsters in the high-dose group decreased and the mortality increased significantly. The incidence of respiratory tract tumors (including tumors of the nasal cavity, larynx and trachea) in the control, low-, mid- and high-dose groups was 0/27, 0/27, 9/26

and 13/25, respectively; the incidences of upper digestive tract tumors (including tumors of the pharynx, esophagus and forestomach) were 0/27, 0/27, 7/26 and 14/25, respectively. Trend analysis for incidences of both respiratory tract tumors and upper gastrointestinal tract tumors showed a statistically significant tendency for the proportion of animals with either tumor type to increase steadily with increased dose (Knauf and Rice, 1992).

Intraperitoneal BAP injections have caused increases in the number of injection site tumors in mice and rats (reviewed in U.S. EPA, 1991a). Subcutaneous BAP injections have caused increases in the number of injection site tumors in mice, rats, guinea pigs, hamsters and some primates (IARC, 1983; U.S. EPA, 1991a). BAP is commonly used as a positive control in many dermal application bioassays and has been shown to cause skin tumors in mice, rats, rabbits and guinea pigs. BAP is both an initiator and a complete carcinogen in mouse skin (IARC, 1983). Increased incidences of distant site tumors have also been reported in animals as a consequence of dermal BAP exposure (reviewed in U.S. EPA, 1991a).

BAP has also been reported to be carcinogenic in animals when administered by the following routes: i.v.; transplacentally; implantation in the stomach wall, lung, renal parenchyma and brain; injection into the renal pelvis; and vaginal painting (U.S. EPA, 1991a).

II.A.4. Supporting Data for Carcinogenicity

Benzo[a]pyrene has been shown to cause genotoxic effects in a broad range of prokaryotic and mammalian cell assay systems (U.S. EPA, 1991a). In prokaryotes, BAP tested positive in DNA damage assays and in both reverse and forward mutation assays. In mammalian cell culture assays, BAP tested positive in DNA damage assays, forward mutation assays, chromosomal effects assays and cell transformation assays.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

NOTE: The range of oral slope factors calculated was: 4.5E+0 to 11.7E+0 per (mg/kg)/day.

II.B.1. Summary of Risk Estimates

Oral Slope Factor — 7.3E+0 per (mg/kg)/day

Drinking Water Unit Risk — 2.1E-4 per (ug/L)

Extrapolation Method — Risk estimate based on a geometric mean of four slope factors obtained by differing modeling procedures. Derived from the combination of multiple data sets from two different reports using more than one sex and species.

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	5E-1 ug/L
E-5 (1 in 100,000)	5E-2 ug/L
E-6 (1 in 1,000,000)	5E-3 ug/L

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type: forestomach, squamous cell papillomas and carcinomas
Test animals: CFW mice, sex unknown
Route: oral, diet
Reference: Neal and Rigdon, 1967

a) Conditional upper bound two-stage model with terms for promotion (modification of Moolgavkar-Venson-Knudson, generalized forms of two-stage model)

Administered Dose (ppm)	Tumor Incidence
0	0/289
1	0/25
10	0/24
20	1/23

Administered Dose (ppm)	Tumor Incidence
30	0/37
40	1/40
45	4/40
50	24/34
100	19/23
250	66/73

Tumor Type — squamous cell carcinoma of the forestomach
Test Animals — SWR/J Swill mice
Route — oral, diet
Reference — Rabstein et al., 1973

Administered Dose (ppm)	Tumor Incidence
0	2/268* male
0	1/402* female

*See additional comments concerning the use of control data from other studies that utilized similar mouse strains.

b) Same data as above. Upper bound estimate by extrapolation from 10% response point to background of empirically fitted dose-response curve. (Procedure using two-stage model described in (a)).

c) Same data as above except the additional 2 control groups (Rabstein et al., 1973) were excluded. Generalized Weibull-type dose-response model.

d) Tumor Type — forestomach, larynx and esophagus, papillomas and carcinomas (combined). Linearized Multistage Model, Extra Risk.

Test Animals — Sprague-Dawley rats, males and females
Route — oral, diet
Reference — Brune et al., 1981

Dose (mg/kg diet/year)	Tumor Incidence
0	3/64
6	3/64
39	10/64

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

At the June 1992 CRAVE Work Group meeting, it was noted that an error had been made in the 1991 document "Dose-Response Analysis of Ingested Benzo[a]pyrene" which is quoted in the Drinking Water Criteria Document for PAH. In the calculation of the doses in the Brune et al. (1981) study it was erroneously concluded that doses were given in units of mg/year, whereas it was in fact mg/kg/year. When the doses are corrected the slope factor is correctly calculated as 11.7 per (mg/kg)/day, as opposed to 4.7 per (mg/kg)/day as reported in the Drinking Water Criteria Document. The correct range of slope factors is 4.5 to 11.7 per (mg/kg)/day, with a geometric mean of 7.3 per (mg/kg)/day. A drinking water unit risk based on the revised slope factor is 2.1E-4 per (ug/L). Therefore, these values have been changed on IRIS and an Erratum to the Drinking Water Criteria Document is being prepared.

Risk estimates were calculated from two different studies in two species of outbred rodents (Neal and Rigdon, 1967; Brune et al., 1981). These studies have several commonalities including mode of administration, tumor sites, tumor types and the presumed mechanisms of action. The data

sets were not combined prior to modeling (the preferred approach) because they employed significantly dissimilar protocols.

The geometric mean from several slope factors, each considered to be of equal merit, was used to calculate a single unit risk. These four slope factor estimates span less than a factor of three and each is based on an acceptable, but less-than-optimal, data set. Each estimate is based on a low-dose extrapolation procedure which entails the use of multiple assumptions and default procedures.

Clement Associates (1990) fit the Neal and Rigdon (1967) data to a two- stage dose response model. In this model the transition rates and the growth rate of preneoplastic cells were both considered to be exposure-dependent. (The functional form for the dose-dependence of preneoplastic cell growth rate was simple saturation.) A term to permit the modeling of BAP as its own promoter was also included. Historical control stomach tumor data from a related, but not identical, mouse strain, SWR/J Swill (Rabstein et al., 1973) and the CFW Texas colony (Neal and Rigdon, 1967) were used in the modeling. In calculating the lifetime unit risk for humans several standard assumptions were made: mouse food consumption was 13% of its body weight/day; human body weight was assumed to be 70 kg and the assumed body weight of the mouse 0.034 kg. The standard assumption of surface area equivalence between mice and humans was the cube root of 70/0.034. A conditional upper bound estimate was calculated to be 5.9 per (mg/kg)/day (U.S. EPA, 1991a).

A U.S. EPA report (1991b) argued that the upper-bound estimate calculated in Clement Associates (1990) involved the use of unrealistic conditions placed on certain parameters of the equation. Other objections to this slope factor were also raised. The authors of this report used the Neal and Rigdon (1967) data to generate an upper-bound estimate extrapolated linearly from the 10% response point to the background of an empirically fitted dose-response curve (Clement Associates, 1990). Other results, from similar concepts and approaches used for other compounds, suggest that the potency slopes calculated in this manner are comparable to those obtained from a linearized multistage procedure for the majority of the other compounds. The upper bound estimate calculated in U.S. EPA (1991b) is 9.0 per (mg/kg)/day.

The authors of U.S. EPA (1991b) selected a model to reflect the partial lifetime exposure pattern over different parts of the animals' lifetimes. The authors thought that this approach more closely reflected the Neal and Rigdon (1967) regimen. A Weibull-type dose-response model was selected to accommodate the partial lifetime exposure; the upper-bound slope factor calculated from this method was 4.5 per (mg/kg)/day.

Using the dietary portion of the Brune et al. (1981) rat data, a linearized multistage procedure was used to calculate an upper bound slope factor for humans. In the interspecies conversion the

assumed human body weight was 70 kg and the rat 0.4 kg. The slope factor calculated by this method was 11.7 per (mg/kg)/day.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

The data are considered to be less than optimal, but acceptable. There are precedents for using multiple data sets from different studies using more than one sex, strain and species; the use of the geometric mean of four slope factors is preferred because it makes use of more of the available data. The use of the geometric means was based on arguments presented in a personal communication (Stiteler, 1991).

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Documentation -- U.S. EPA, 1991a, b

The 1991 Drinking Water Criteria Document for the polycyclic aromatic hydrocarbons has received Agency Review.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 01/07/1987, 12/04/1991, 06/03/1992, 08/05/1993, 02/02/1994, 06/09/1994

Verification Date — 12/04/1991

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Benzo [a] pyrene (BaP)
CASRN — 50-32-8

VI.A. Oral RfD References

None

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

Brune, H., R.P. Deutsch-Wenzel, M. Habs, S. Ivankovic and D. Schmahl. 1981. Investigation of the tumorigenic response to benzo[a]pyrene in aqueous caffeine solution applied orally to Sprague-Dawley rats. J. Cancer Res. Clin. Oncol. 102(2): 153-157.

Clement Associates. 1990. Ingestion dose-response model to benzo(a)pyrene. EPA Control No. 68-02-4601.

IARC (International Agency for Research on Cancer). 1983. Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds. Monographs on the Evaluation of Carcinogenic Risk of the Chemical to Man, Vol. 3. Lyon, France.

Knauf, L. and G. Rice. 1992. Statistical Evaluation of Several Benzo[a]pyrene Bioassays. Memorandum to R. Schoeny, U.S. EPA, Cincinnati, OH. January 2.

Neal, J. and R.H. Rigdon. 1967. Gastric tumors in mice fed benzo[a]pyrene -- A quantitative study. Tex. Rep. Biol. Med. 25(4): 553-557.

Rabstein, L.S., R.L. Peters and G.J. Spahn. 1973. Spontaneous tumors and pathologic lesions in SWR/J mice. J. Natl. Cancer Inst. 50: 751-758.

Stiteler, W. 1991. Syracuse Research Corporation, Syracuse, NY. Personal communication with R. Schoeny, U.S. EPA, Cincinnati, OH.

Thyssen, J., J. Althoff, G. Kimmerle and U. Mohr. 1981. Inhalation studies with benzo[a]pyrene in Syrian golden hamsters. J. Natl. Cancer Inst. 66: 575-577.

U.S. EPA. 1991a. Drinking Water Criteria Document for PAH. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC.

U.S. EPA. 1991b. Dose-Response Analysis of Ingested Benzo[a]pyrene (CAS No. 50-32-8). Human Health Assessment Group, Office of Health and Environmental Assessment, Washington, DC. EPA/600/R-92/045.

VII. Revision History

Substance Name — Benzo [a] pyrene (BaP)
CASRN — 50-32-8

Date	Section	Description
04/01/1992	II.	Summary revised; oral quantitative section added

VIII. Synonyms

Substance Name — Benzo [a] pyrene (BaP)
CASRN — 50-32-8
Last Revised — 03/31/1987

- 50-32-8
- BaP
- Benzo[a]pyrene
- BENZO(d,e,f)CHRYSENE
- 3,4-BENZOPIRENE
- 3,4-BENZOPYRENE
- 6,7-BENZOPYRENE
- BENZO(a)PYRENE
- 3,4-BENZPYREN
- 3,4-BENZPYRENE
- 3,4-BENZ(a)PYRENE
- BENZ(a)PYRENE
- 3,4-BENZYPYRENE
- BP
- 3,4-BP
- B(a)P
- RCRA WASTE NUMBER U022