Toxicological Profile for

BENZO[a]PYRENE

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

ATSDR/TP-88/05

TOXICOLOGICAL PROFILE FOR BENZO[a]PYRENE

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FOREWORD

The Superfund Amendments and Reauthorization Act of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law (also known as SARA) directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The list of the 100 most significant hazardous substances was published in the *Federal Register* on April 17, 1987.

Section 110 (3) of SARA directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following content:

> "(A) An examination, summary, and interpretation of available toxicological information and epidemiologic evaluations on a hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.
>
> (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.
>
> (C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans."

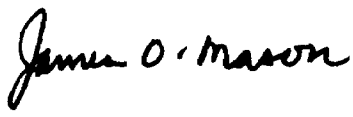
This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary, but no less often than every three years, as required by SARA.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature that describes a hazardous substance's toxicological properties. Other literature is presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the statement is material that presents levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Research gaps in toxicologic and health effects information are described in the profile. Research gaps that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the front of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public. We plan to revise these documents in response to public comments and as additional data become available; therefore, we encourage comment that will make the toxicological profile series of the greatest use.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, EPA, the Centers for Disease Control, and the National Toxicology Program. It has also been reviewed by a panel of nongovernment peer reviewers and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



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1.1 WHAT IS BENZO[a]PYRENE?

Benzo[a]pyrene (B[a]P) is one of the polycyclic aromatic hydrocarbon (PAH) compounds. Because it is formed when gasoline, garbage, or any animal or plant material burns, it is usually found in smoke and soot. This chemical combines with dust particles in the air and is carried into water and soil and onto crops. Benzo[a]pyrene is found in the coal tar pitch that industry uses to join electrical parts together. It is also found in creosote, a chemical used to preserve wood.

1.2 HOW MIGHT I BE EXPOSED TO BENZO[a]PYRENE?

People may be exposed to B[a]P from environmental sources such as air, water, and soil and from cigarette smoke and cooked food. Workers who handle or are involved in the manufacture of PAH-containing materials may also be exposed to B[a]P. Typically, exposure for workers and the general population is not to B[a]P alone but to a mixture of similar chemicals.

The general population may be exposed to dust, soil, and other particles that contain B[a]P. The largest sources of B[a]P in the air are open burning and home heating with wood and coal. Factories that produce coal tar also contribute small amounts of B[a]P to the air. People may come in contact with B[a]P from soil on or near hazardous waste sites, such as former gas-manufacturing sites or abandoned wood-treatment plants that used creosote. At this time, B[a]P has been found at 110 out of 1,117 sites on the National Priorities List (NPL) of hazardous waste sites in the United States. As more sites are evaluated by the Environmental Protection Agency (EPA), this number may change. The soil near areas where coal, wood, or other products have been burned is another source of exposure. Exposure to B[a]P and other PAHs may also occur through skin contact with products that contain PAHs such as creosote-treated wood, asphalt roads, or coal tar.

People may be exposed to B[a]P by drinking water from the drinking water supplies in the United States that have been found to contain low levels of the chemical. Foods grown in contaminated soil or air may contain B[a]P. Cooking food at high temperatures, as occurs during charcoal grilling or charring, can increase the amount of B[a]P in the food. Benzo[a]pyrene has been found in cereals, vegetables, fruits, meats, beverages, chewing tobacco, and in cigarette smoke.

The greatest exposure to B[a]P is likely to take place in the workplace. People who work in coal tar-production plants; coking plants; asphalt-production plants; coal-gasification sites; smoke houses; municipal trash incinerators; and facilities that burn wood, coal, or

oil may be exposed to B[a]P in the workplace air. Benzo[a]pyrene may also be found in areas where high-temperature food fryers and broilers are used.

1.3 HOW DOES BENZO[a]PYRENE GET INTO MY BODY?

The most common way B[a]P enters the body is through the lung when a person breathes in air or smoke containing it. It also enters the body through the digestive system when substances containing it are swallowed. Although B[a]P does not normally enter the body through the skin, small amounts could enter if contact occurs with soil that contains high levels of B[a]P (for example, near a hazardous waste site) or if contact is made with heavy oils containing B[a]P.

1.4 HOW CAN BENZO[a]PYRENE AFFECT MY HEALTH?

Benzo[a]pyrene causes cancer in laboratory animals when applied to their skin. This finding suggests that it is likely that people exposed in the same manner could also develop cancer.

Because studies of B[a]P are not complete, we don't know if B[a]P that is breathed in or swallowed could cause cancer.

Mice fed high levels of B[a]P during pregnancy had trouble reproducing, and so did their offspring. The newborn animals of pregnant mice fed B[a]P also had other harmful effects (for example, birth defects and lower-than-normal body weight). It is possible that similar effects could happen to people exposed to B[a]P.

1.5 IS THERE A MEDICAL TEST TO DETERMINE IF I HAVE BEEN EXPOSED TO BENZO[a]PYRENE?

Very few tests are available that can tell whether exposure to B[a]P has taken place. In the body, B[a]P is changed to related chemical substances called metabolites. The metabolites can bind with DNA, the genetic material of the body, and with hemoglobin, the oxygen-carrying protein in red blood cells. The body's response after exposure can be measured in the blood. However, this test is still being developed. Benzo[a]pyrene can also be found in the urine and blood of individuals exposed to PAHs. It is not possible to know from these tests how much B[a]P a person was exposed to or to predict what health effects may happen at certain levels. Also, none of these tests have been used in exposure situations outside the workplace.

1.6 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

No information has been found about specific levels of B[a]P that have caused harmful effects in people after breathing, swallowing, or touching the substance.

Figure 1.1 shows the amount of B[a]P found to cause harmful health effects in laboratory animals after eating B[a]P for short and long periods. Short- and long-term exposures to B[a]P caused death in experimental animals fed the chemical. The offspring of animals that ate 10 milligrams of B[a]P per kilogram of body weight (mg/kg) during pregnancy had trouble reproducing. Some of the offspring weighed less than normal at birth and had birth defects.

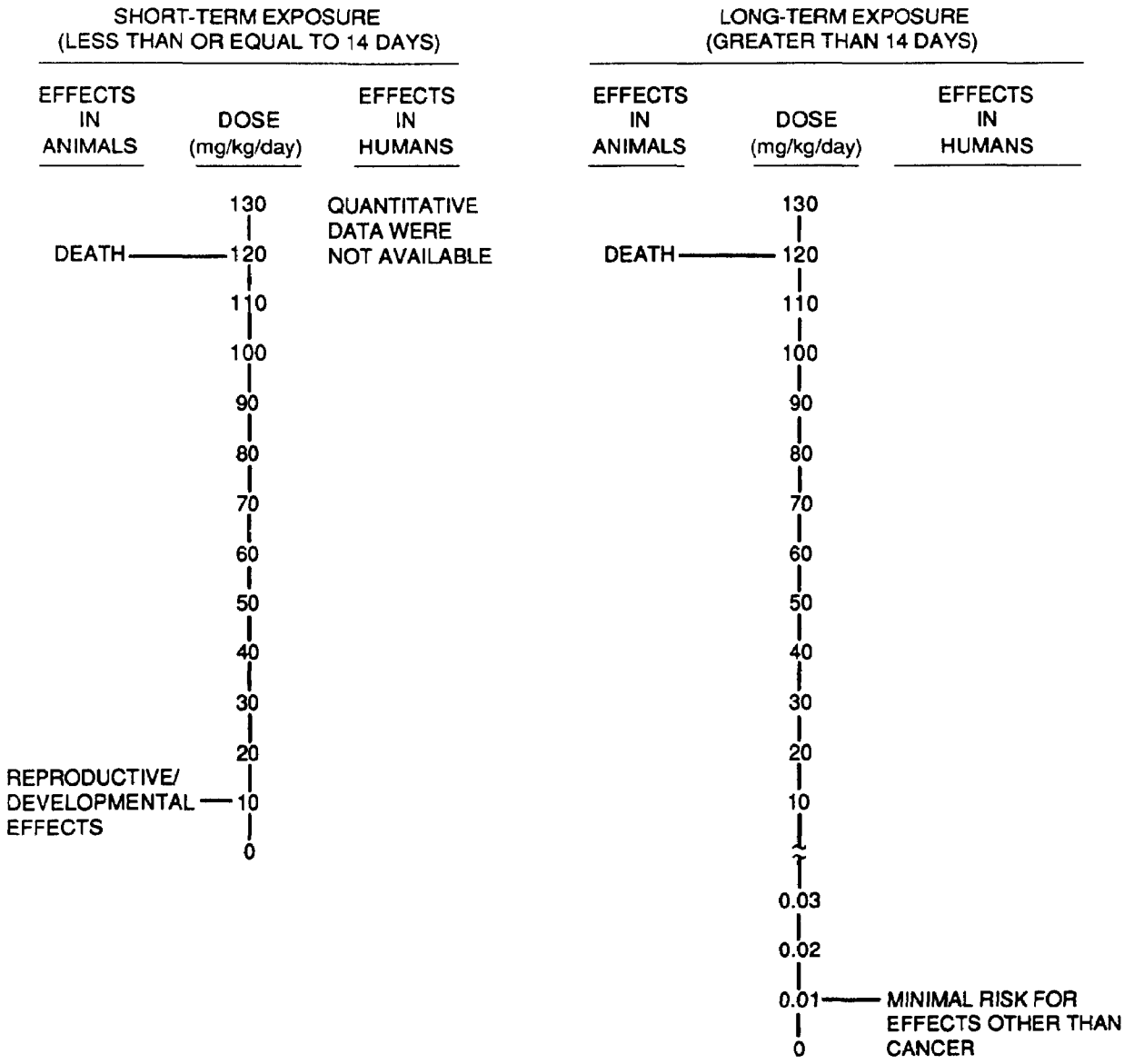


Fig. 1.1. Health effects from ingesting benzo[a]pyrene.

A Minimal Risk Level (MRL) is also included in Fig. 1.1. This MRL is based on experiments in animals, as described in Sect. 2. The MRL provides a basis for comparison with levels that people might be exposed to in food. If a person is exposed to PAHs at an amount less than the MRL, harmful (noncancer) health effects are not expected to occur.

Because this level is based only on information currently available, some uncertainty is always associated with it. Also, because the method for deriving MRLs does not use any information about cancer, an MRL does not imply anything about the presence, absence, or level of risk for cancer.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

Based on information from another PAH chemical, the federal government has developed standards and guidelines to protect individuals from the potential health effects of PAHs, including B[a]P, in drinking water. The U.S. Environmental Protection Agency (EPA) has provided estimates of levels of total cancer-causing PAHs in lakes and streams associated with various risks of developing cancer in people. EPA has also determined that any release of PAHs of more than 1 pound should be reported to the National Response Center.

Pure B[a]P is produced in the United States only as a laboratory chemical. However, B[a]P is a PAH, and PAHs are found in coal tar and in the creosote oils and pitches formed from the production of coal tar. The government's goal has been to protect workers involved with the production of coal tar products. These regulations are for exposure to B[a]P in workplace air. Although government standards are not B[a]P alone, they are useful in controlling exposure to total PAHs.

The National Institute for Occupational Safety and Health (NIOSH) has determined that workplace exposure to coal products can increase the risk of lung and skin cancer in workers and suggests a workplace exposure limit for coal tar products of 0.1 milligram of PAHs per cubic meter of air (0.1 mg/m^3) for a 10-hour workday, 40-hour workweek. NIOSH has not suggested a specific workplace limit for B[a]P. The Occupational Safety and Health Administration (OSHA) has set a legal limit of 0.2 milligram of all PAHs per cubic meter of air (0.2 mg/m^3).

2. HEALTH EFFECTS SUMMARY

2.1 INTRODUCTION

This section summarizes and graphs data on the health effects concerning exposure to B[a]P. The purpose of this section is to present levels of significant exposure for B[a]P based on key toxicological studies, epidemiological investigations, and environmental exposure data. The information presented in this section is critically evaluated and discussed in Sect. 4, Toxicologic Data, and Sect. 7, Potential for Human Exposure.

This Health Effects Summary section comprises two major parts. Levels of Significant Exposure (Sect. 2.2) presents brief narratives and graphics for key studies in a manner that provides public health officials, physicians, and other interested individuals and groups with (1) an overall perspective of the toxicology of B[a]P; and (2) a summarized depiction of significant exposure levels associated with various adverse health effects. This section also includes information on the levels of B[a]P that have been monitored in human fluids and tissues and information about levels of B[a]P found in environmental media and their association with human exposures.

The significance of the exposure levels shown on the graphs may differ depending on the user's perspective. For example, physicians concerned with the interpretation of overt clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with frank effects (Frank Effect Level, FEL). Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in humans or animals (Lowest-Observed-Adverse-Effect Level, LOAEL) or exposure levels below which no adverse effects (No-Observed-Adverse-Effect Level, NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels) are of interest to health professionals and citizens alike.

Adequacy of Database (Sect 2.3) highlights the availability of key studies on exposure to B[a]P in the scientific literature and displays these data in three-dimensional graphs consistent with the format in Sect. 2.2. The purpose of this section is to suggest where there might be insufficient information to establish levels of significant human exposure. These areas will be considered by the Agency for Toxic Substances and Disease Registry (ATSDR), EPA, and the National Toxicology Program (NTP) of the U.S. Public Health Service in order to develop a research agenda for benzo[a]pyrene.

2.2 LEVELS OF SIGNIFICANT EXPOSURE

2.2.1 Key Studies and Graphical Presentations

To help public health professionals address the needs of persons living or working near hazardous waste sites, the toxicology data summarized in this section are organized first by route of exposure--inhalation, ingestion, and dermal--and then by toxicological end points that are categorized into six general areas--lethality, systemic/target organ toxicity, developmental toxicity, reproductive toxicity, genetic toxicity, and carcinogenicity. The data are discussed in terms of three exposure periods--acute, intermediate, and chronic.

Two kinds of graphs are used to depict the data. The first type is a "thermometer" graph. It provides a graphical summary of the human and animal toxicological end points and levels of exposure for each exposure route for which data are available. The ordering of effects does not reflect the exposure duration or species of animal tested. The second kind of graph shows Levels of Significant Exposure (LSE) for each route and exposure duration. The points on the graph showing NOAELs and LOAELs reflect the actual dose (levels of exposure) used in the key studies. No adjustments for exposure duration or intermittent exposure protocol were made.

Adjustments reflecting the uncertainty of extrapolating animal data to man, intraspecies variations, and differences between experimental versus actual human exposure conditions were considered when estimates of levels posing minimal risk to human health were made for noncancer end points. Those minimal risk levels were derived for the most sensitive noncancer end point for each exposure duration by applying uncertainty factors. These levels are shown on the graphs as a broken line starting from the actual dose (level of exposure) and ending with a concave-curved line at its terminus. Although methods have been established to derive these minimal risk levels (Barnes et al. 1987), shortcomings exist in the techniques that reduce the confidence in the projected estimates. Also shown on the graphs under the cancer end point are low-level risks (10^{-4} to 10^{-7}) reported by EPA if available. In addition, the actual dose (level of exposure) associated with the tumor incidence is plotted.

2.2.1.1 Inhalation exposure

No information on the effects of short-term or intermediate inhalation exposure to B[a]P are available. The induction of cancer appears to be the key end point of toxicity following long-term exposure to B[a]P. This conclusion is based on observations of experimental animals since no data are available for human exposure. Available data are displayed in Figs. 2.1 and 2.2.

Lethality and decreased longevity. No information is available.

Systemic toxicity. No information is available.

Developmental toxicity. No information is available.

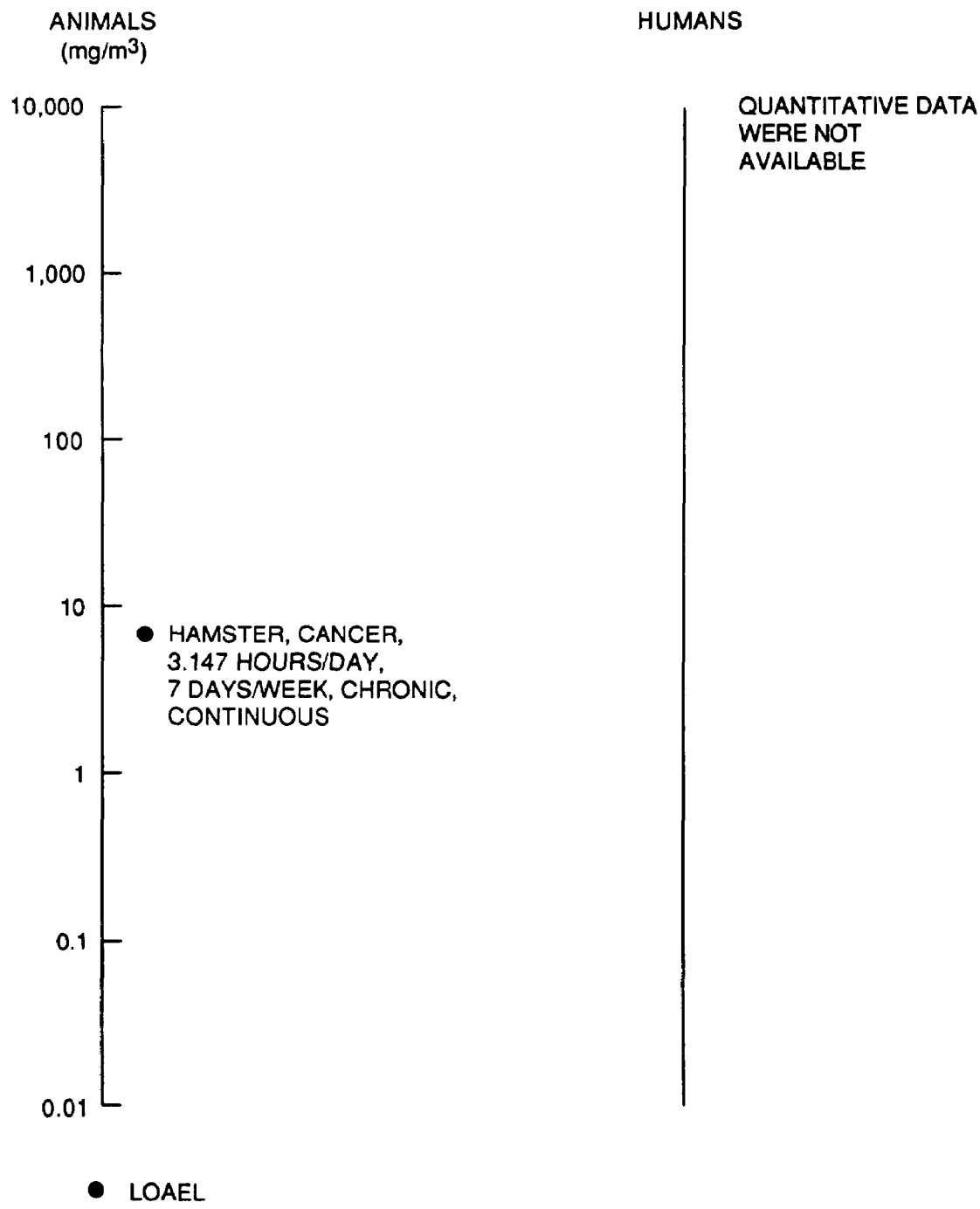


Fig. 2.1. Effects of benzo[a]pyrene—inhalation exposure.

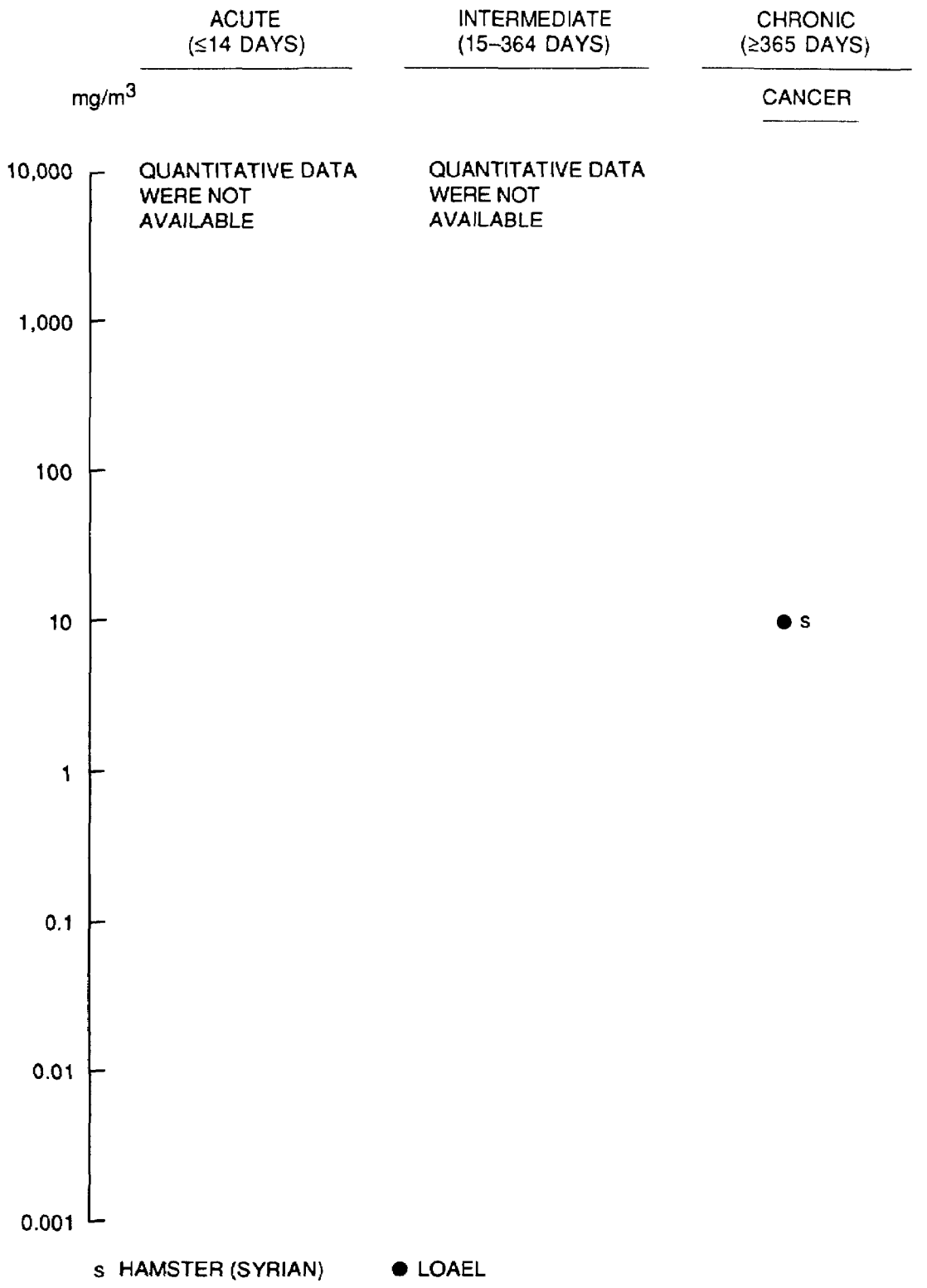


Fig. 2.2. Levels of significant exposure for benzo[a]pyrene—inhalation.

Reproductive toxicity. No information is available.

Genotoxicity. Only one study cited inhalation as a possible secondary route of exposure to B[a]P. Oral exposure of B[a]P to *Drosophila melanogaster* was the primary route and resulted in no mutagenic activity in the sex-linked recessive lethal test (Valencia and Houtchens 1981).

Carcinogenicity. No information directly correlating human inhalation exposure to B[a]P and cancer induction is available, although reports of lung tumors in individuals exposed to mixtures of polycyclic aromatic hydrocarbons containing B[a]P lend some qualitative support to its potential for human carcinogenicity (Lloyd 1971, Redmond et al. 1972, Mazumdar et al. 1975, Hammond et al. 1976, Wynder and Hoffmann 1967, Maclure and MacMahon 1980, Schottenfeld and Fraumeni 1982).

Studies in experimental animals have demonstrated the ability of B[a]P to induce respiratory tract tumors following long-term inhalation exposure. In Syrian golden hamsters exposed throughout their lives to B[a]P as an aerosol, concentrations above 9.5 mg/m^3 B[a]P produced an excess of respiratory tract tumors (Thyssen et al. 1981). Although EPA previously published an inhalation cancer risk estimate for B[a]P based on data from this study, this number is currently under review and was not included here pending recalculation.

2.2.1.2 Oral exposure

Short-term and intermediate oral exposure to very high levels of B[a]P resulted in death in experimental animals fed B[a]P in the diet. Deaths appeared to be caused by bone marrow depression. The results of oral studies conducted in mice and rats provide evidence that in utero exposure to B[a]P is associated with adverse reproductive and developmental effects. The induction of cancer appears to be the key end point of toxicity following intermediate and long-term oral exposure to B[a]P. Lower doses are required to induce tumors than other end points of toxicity. This conclusion is based on observations of experimental animals since no data are available for human exposure. Available data are summarized in Figs. 2.3 and 2.4.

Lethality and decreased longevity. No information is available on lethality and decreased longevity in humans following oral exposure to B[a]P. Subchronic oral exposure of mice to B[a]P (120 mg/kg/day B[a]P) for up to 6 months resulted in decreased survival time in "nonresponsive" strains [i.e., strains whose hepatic aryl hydrocarbon hydroxylase activity is not induced by PAH when compared to unexposed controls (Robinson et al. 1975)]. Half of the deaths occurred within 15 days of dosing. Death appeared to be caused by bone marrow depression that led to hemorrhage or infection.

Systemic toxicity. No information is available on the systemic toxicity of B[a]P in humans following oral exposure. Hematopoietic effects (e.g., aplastic anemia, pancytopenia) of B[a]P have been reported in a "nonresponsive" strain of mice following subchronic oral exposure to 120 mg/kg/day for up to 6 months (Robinson et al. 1975).

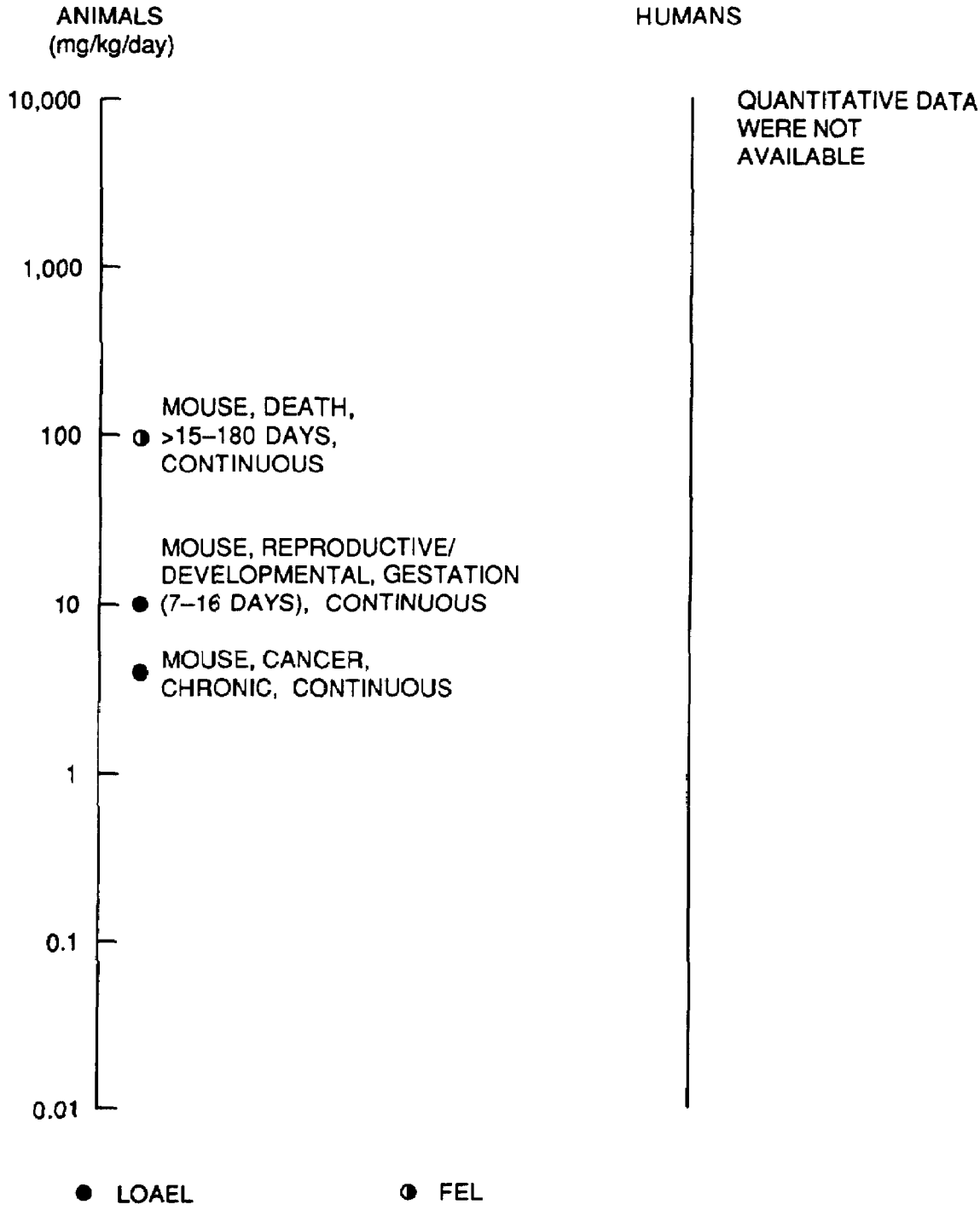


Fig. 2.3. Effects of benzo[a]pyrene—oral exposure.

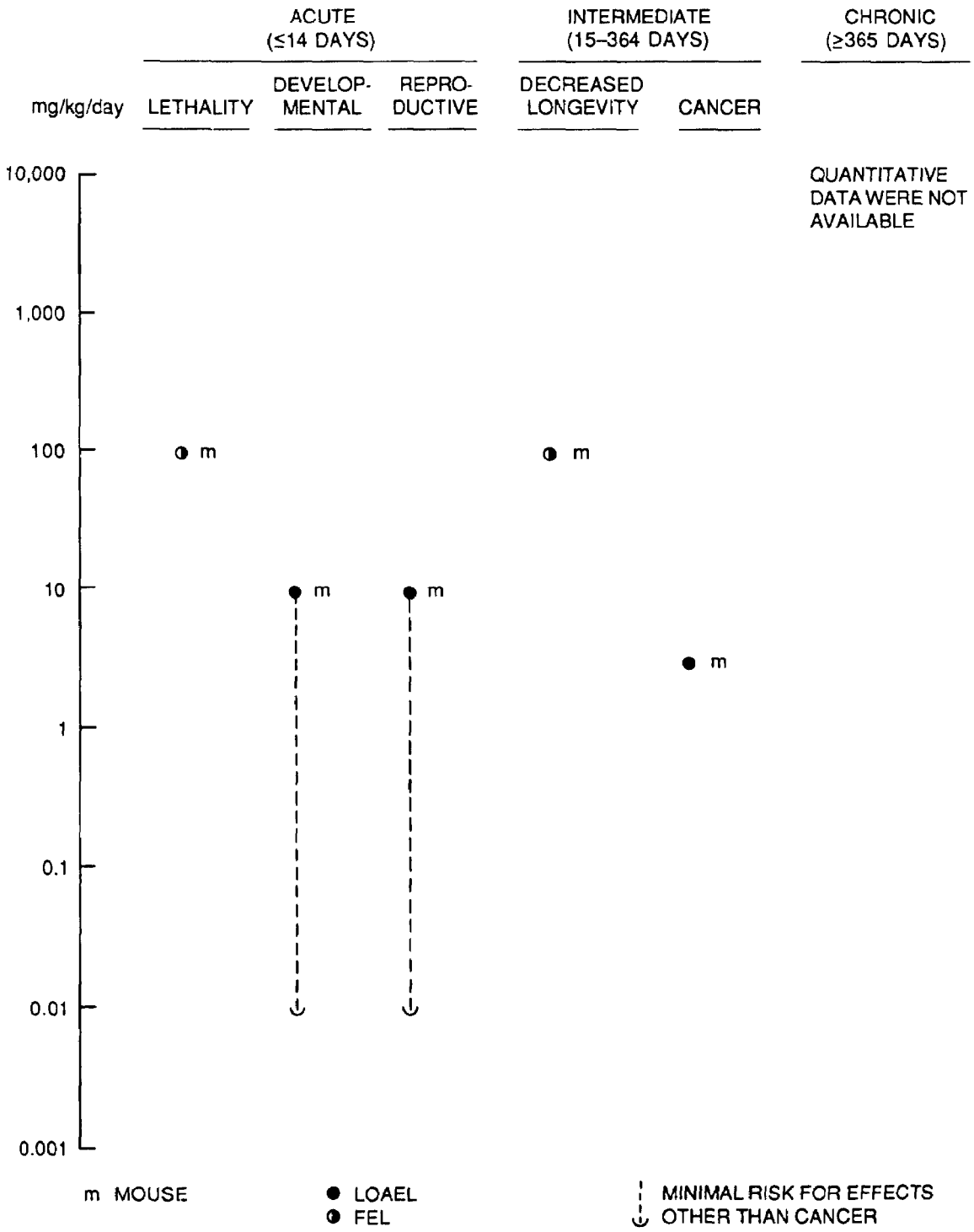


Fig. 2.4. Levels of significant exposure for benzo[a]pyrene—oral.

Only one dose was tested. At the single dose tested, the hematopoietic effects resulted in death; therefore, this study can not be used to identify a LOAEL.

Developmental toxicity. No information is available on the developmental toxicity of B[a]P in humans following oral exposure. Results of a modified two-generation oral study in mice indicated that in utero exposure to B[a]P throughout days 7 to 16 of gestation was associated with developmental toxicity (MacKenzie and Angevine 1981). The mean pup weight from rats that received 10, 40, or 160 mg/kg/day during pregnancy was significantly different from controls. Furthermore, prenatal exposure to B[a]P resulted in dramatic alterations in gonadal development by disrupting gonadal morphology and germ cell development in both males and females. Results from other rodent studies in which B[a]P was administered orally or by injection provide additional evidence that B[a]P may produce adverse reproductive/developmental effects (Rigdon and Rennels 1964, Legraverend et al. 1984, Shum et al. 1979, Hoshino et al. 1981, Swartz and Mattison 1985, Urso and Gengozian 1980, Bulay and Wattenberg 1971, Nikonova 1977).

Reproductive toxicity. No information is available on the reproductive toxicity of B[a]P in humans following oral exposure. The results of a modified two-generation oral study in mice indicated that B[a]P was associated with adverse reproductive effects (MacKenzie and Angevine 1981). The reproductive toxicity of B[a]P included a decreased fertility index and a high incidence of sterility in progeny. The impaired reproductive capacity resulted from in utero exposure to B[a]P administered throughout gestation (days 7-16) at doses of 10, 40, or 160 mg/kg/day. Results from other rodent studies in which B[a]P was administered orally or by injection provide additional evidence that B[a]P may produce adverse reproductive/developmental effects (Rigdon and Rennels 1964, Legraverend et al. 1984, Shum et al. 1979, Hoshino et al. 1981, Swartz and Mattison 1985, Wolfe and Bryan 1939, Barbieri et al. 1986).

Genotoxicity. Positive results in somatic mutations and heritable gene mutations have been reported in mice and *Drosophila melanogaster*, following oral exposure to B[a]P. Positive mutagenic activity has been reported in the mouse spot test (Davidson and Dawson 1977) and the somatic mutation and sex-linked recessive lethal mutation assays with *Drosophila melanogaster* (Fahmy and Fahmy 1980, Nguyen et al. 1979, Vogel et al. 1983). However, negative results have been reported in similar studies with *Drosophila* (Valencia and Houtchens 1981, Zijlstra and Vogel 1984). Mixed results have been reported for aneuploidy studies with *Drosophila melanogaster* via feeding (Vogel et al. 1983, Valencia et al. 1984, Fabian and Matoltsy 1946).

Carcinogenicity. No information is available on the potential for human carcinogenicity of B[a]P following oral exposure.

Studies in experimental animals have demonstrated the ability of ingested B[a]P to induce leukemia and tumors in the forestomach and lung following intermediate-term exposure. In mice receiving B[a]P in the diet for 110 days, dose levels of 5.2 mg/kg/day and above produced an excess of forestomach tumors (Neal and Rigdon 1967). Although EPA previously published an oral cancer risk estimate for B[a]P based on

data from this study, this number is currently under review and was not included here pending recalculation.

2.2.1.3 Dermal exposure

No information is available on the effects of short-term dermal exposure of humans to B[a]P. There are reports on the effects of B[a]P following short-term dermal exposures in animals and intermediate-term dermal exposure to B[a]P in humans and experimental animals. These studies suggest that B[a]P has adverse effects on the skin; however, these studies fail to employ control groups, and, therefore, definitive conclusions concerning the dermal toxicity of B[a]P cannot be made.

The induction of cancer appears to be the key end point of toxicity following long-term dermal exposure to B[a]P. This conclusion is based on observations of experimental animals because no data are available for human exposure to B[a]P alone; results are summarized in Figs. 2.5 and 2.6. The potential for dermal carcinogenicity in humans from B[a]P is supported by observations of skin cancer resulting from exposure to complex mixtures of PAHs that include B[a]P.

Lethality and decreased longevity. No information is available.

Systemic toxicity. There are no reports in the literature concerning the systemic toxicity of B[a]P following dermal exposures. There are reports in the literature, however, concerning the dermal toxicity of B[a]P following subchronic applications to human and animal skin (Cottini and Mazzone 1939, Elgjo 1968); however, these studies did not provide adequate quantitative information and failed to employ control groups, and, therefore, cannot be used to develop a significant human exposure level for the dermal toxicity of B[a]P.

Developmental toxicity. No information is available.

Reproductive toxicity. No information is available.

Genotoxicity. No information is available.

Carcinogenicity. No information directly correlating human dermal exposure to B[a]P and cancer induction is available, although reports of skin tumors among individuals exposed to mixtures of polycyclic aromatic hydrocarbons containing B[a]P lend some qualitative support to its potential for human carcinogenicity (Pott 1775, Purde and Etlin 1980).

Studies in experimental animals have demonstrated the ability of B[a]P to induce skin tumors following long-term dermal exposure. Mice receiving doses of 1.7 μg/day and above applied to their skin developed an excess of skin tumors following long-term exposure (Habs et al. 1980). No estimate of human risk has been calculated.

2.2.2 Biological Monitoring

The available biological monitoring techniques can be useful in predicting whether exposure to B[a]P or other PAHs has occurred, but they may not be useful in estimating body doses because there have been no population-based studies to determine normal body levels of PAHs (e.g., in smokers). Individual variability, confounding effects of drugs or cigarettes, and specificity of the techniques are likely to

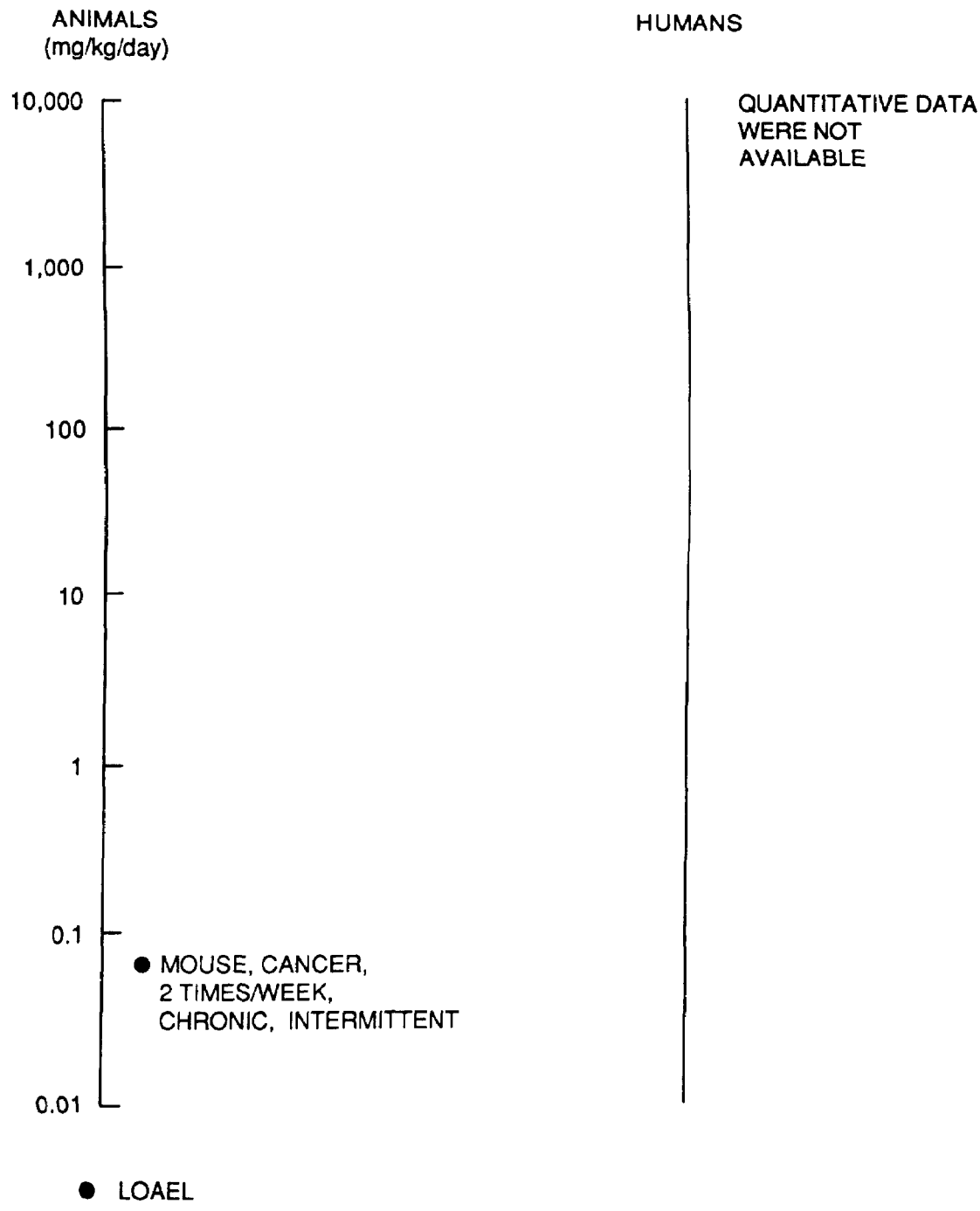


Fig. 2.5. Effects of benzo[a]pyrene—dermal exposure.

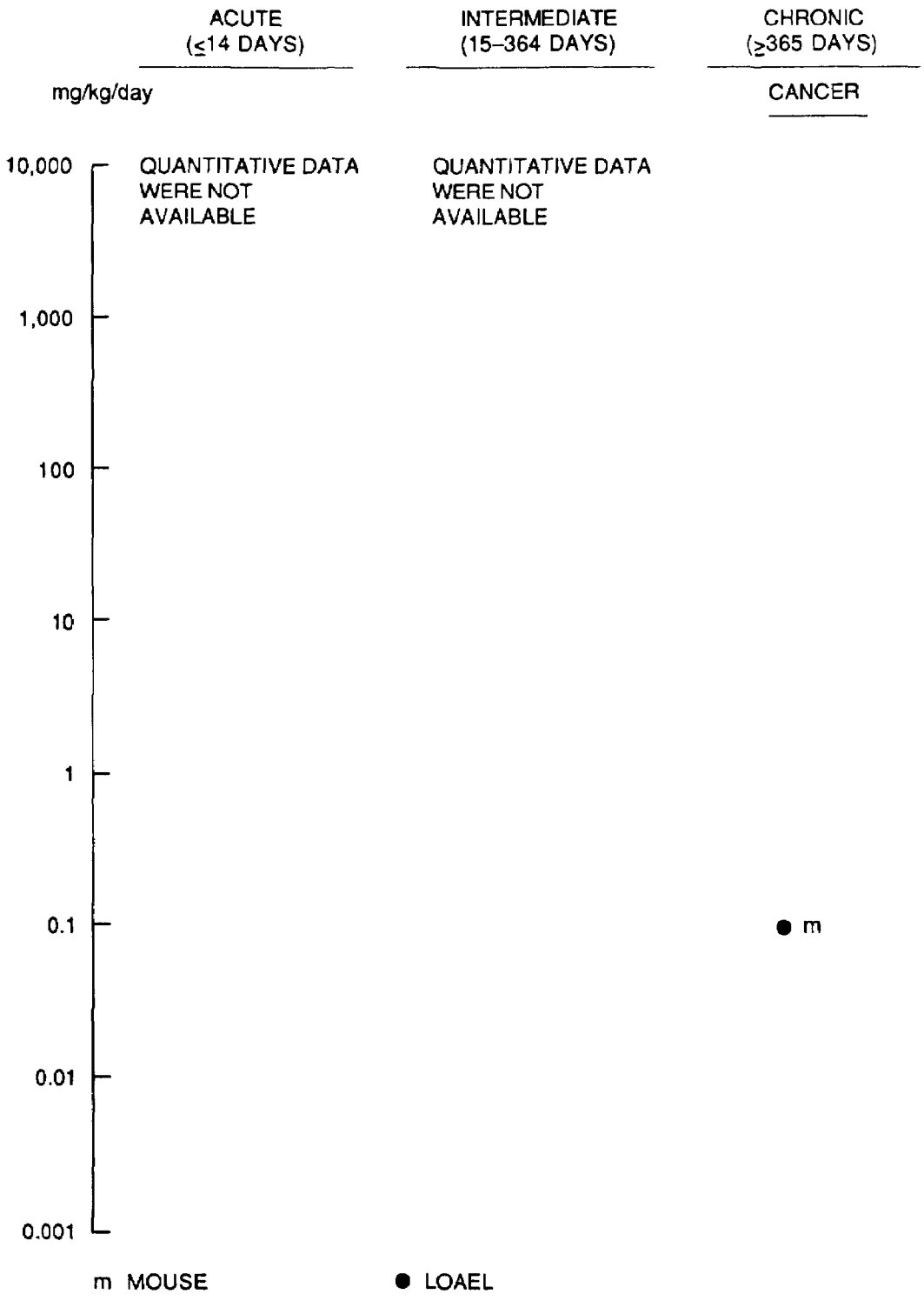


Fig. 2.6. Levels of significant exposure for benzo[a]pyrene—dermal.

complicate the association between B[a]P metabolites in the body and environmental exposure. The most common tests for determining exposure to B[a]P include examination of tissues, blood, and urine for the presence of B[a]P metabolites. Currently available biological monitoring techniques are discussed in detail in Sect. 8.

Modica et al. (1982) and Bartosek et al. (1984) used gas-liquid chromatography to determine the presence of PAHs in blood, mammary and adipose tissue, and liver and brain of rats. However, examples of examination of human tissue samples using this method were not located in the available literature.

In the tissues, B[a]P can be rapidly converted by specific cellular enzymes to a dihydrodiol and further metabolized to diol epoxides which can bind to DNA and form DNA adducts. A tissue sample can be taken from an exposed individual, and DNA from the exposed cells can be digested and labeled with radioactive phosphorus (^{32}P). Thin-layer chromatography is then used to determine the presence of altered DNA and scintillation counting used to quantify the adducts (Randerath et al. 1985). In another technique, the diol epoxides are removed from the DNA and quantified by fluorescence spectroscopy (Rahn et al. 1982, Vahakangas et al. 1985, Shugart 1985, 1986). It has recently been reported that these diol epoxides also form adducts with hemoglobin in the red blood cells, and the presence of these diol epoxide adducts can be determined in blood using fluorescence spectroscopy (see Fig. 2.7) (Shugart 1985, 1986). Although the presence of both DNA and hemoglobin adducts is directly associated with exposure to B[a]P, this technique of analyzing adducts is limited in its usefulness to predict body dose from environmental exposure because individual biochemistry may affect the conversion of B[a]P to diol epoxides and because of the limited specificity of fluorescence spectroscopy. A technique has been developed that tests for the presence of antibodies to the PAH-DNA adducts in blood using immunoassays (Perera et al. 1982, Harris 1985, Harris et al. 1985, Santella et al. 1985, Harris et al. 1986, Haugen et al. 1986). A patent has been submitted for a method and kit for detecting antibodies in human sera to B[a]P diol epoxide-DNA adducts using an immunoassay (Harris 1985). This method has been examined in occupationally exposed individuals and smokers.

The urine of exposed individuals has also been examined using chromatography for the presence of B[a]P and B[a]P metabolites (Becher and Bjorseth 1983, Becher et al. 1984, Jongeneelen et al. 1985, 1986, Clonfero et al. 1986).

A recent technique using an antibody-based fiber-optic biosensor is being tested to detect benzo[a]pyrene. This technique has been investigated in sample solutions containing B[a]P and may be useful for assessing the exposure of an individual to B[a]P or other PAHs, provided appropriate antibodies are used (Vo-Dinh et al. 1987).

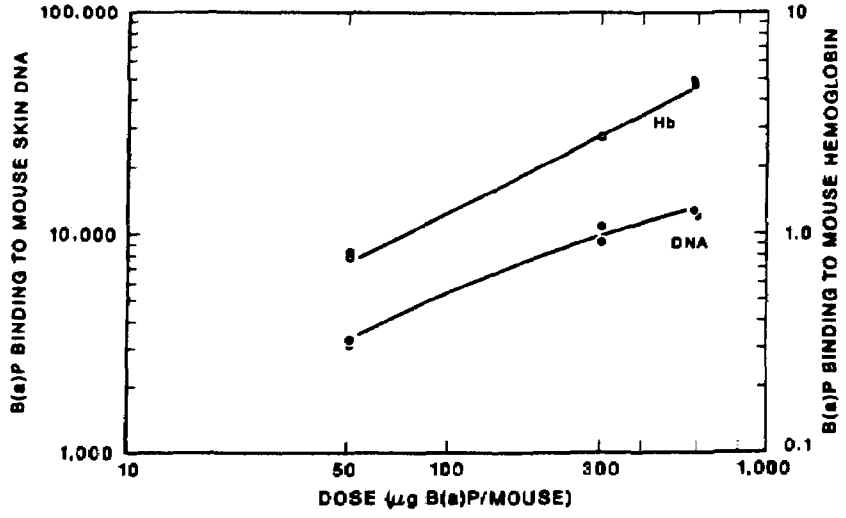


Fig. 2.7. Benzo[a]pyrene binding to mouse skin DNA and hemoglobin. Log-log plot relates the log dose of B[a]P binding and the log dose of B[a]P applied to mouse skin. (O): B[a]P binding hemoglobin expressed as pg Tetrol I-1/mg hemoglobin; and (●): B[a]P binding to DNA expressed as ng Tetrol I-1/g DNA. Each data point represents the average values from 2 mice. *Source:* Shugart 1985.

2.2.3 Environmental Levels as Indicators of Exposure and Effects

2.2.3.1 Levels found in the environment

B[a]P has been detected in air, water, and soils. B[a]P concentrations in urban air are up to 10 to 100 times greater than the concentrations in rural areas. Reported urban air concentrations range between 0.2 and 19.3 ng/m^3 (Pucknat 1981). Ambient B[a]P concentrations in nonurban areas ranged from 0.1 to 1.2 ng/m^3 (Pucknat 1981).

B[a]P has been detected in U.S. groundwater and surface water used as drinking water sources, but the data are limited. B[a]P concentrations in untreated water have been reported to range between 0.6 and 210 ng/L (EPA 1980). In treated waters, the concentrations have been reported to range between 0.3 and 2.0 ng/L.

In soils, limited data indicate B[a]P concentrations in the range of 40 to 1,300 µg/kg in relatively rural areas of the United States (Blumer 1961).

B[a]P may occur in the soil and on particulate matter in the air surrounding waste sites, such as former manufactured-gas plants and creosote wood treatment plants. However, exposure levels at these sites have not yet been published.

Data are not available that relate environmental levels to significant health effects in humans following exposures.

2.2.3.2 Human exposure potential

Humans may be exposed to B[a]P in air, water, soil, and food, each of which constitutes a normal route of background exposure. Much higher exposure concentrations are associated with tobacco smoke and with some occupational environments. At hazardous waste sites, humans will most likely be exposed to B[a]P via contact with soil or inhalation of particulate matter in air. Estimates of body doses or tissue levels associated with B[a]P intake require (1) information on the chemical concentrations in soil and air, (2) certain assumptions about factors controlling intake, and (3) information on absorption of B[a]P from soil or particulate matter.

Information on the first two of these data needs is relatively site-specific and cannot be generalized across all sites. Quantitative toxicological information on the absorption of B[a]P from soil or particulate matter is limited, although absorption is expected to be low (Becher et al. 1984). Consequently, estimates of dose following exposure to B[a]P in soil or air are based on limited toxicological data and on assumptions regarding dermal absorption of B[a]P from soil and absorption of incidentally ingested B[a]P on soil or inhaled B[a]P on particulate matter. Any risk assessment of potential health effects following environmental exposures has some degree of uncertainty in view of the necessary assumptions.

2.3 ADEQUACY OF DATABASE

2.3.1 Introduction

Section 110 (3) of SARA directs the Administrator of ATSDR to prepare a toxicological profile for each of the 100 most significant hazardous substances found at facilities on the CERCLA National Priorities List. Each profile must include the following content:

"(A) An examination, summary, and interpretation of available toxicological information and epidemiologic evaluations on a *hazardous substance in order to ascertain the levels of* significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.

(C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans."

This section identifies gaps in current knowledge relevant to developing levels of significant exposure for B[a]P. Such gaps are identified for certain health effect end points (lethality, systemic/target organ toxicity, developmental toxicity, reproductive toxicity, and carcinogenicity) reviewed in Sect. 2.2 of this profile in developing levels of significant exposure for B[a]P and for other areas such as human biological monitoring and mechanisms of toxicity. The present section briefly summarizes the availability of existing human and animal data, identifies data gaps, and summarizes research in progress that may fill such gaps.

Specific research programs for obtaining data needed to develop levels of significant exposure for B[a]P will be developed by ATSDR, NTP, and EPA in the future.

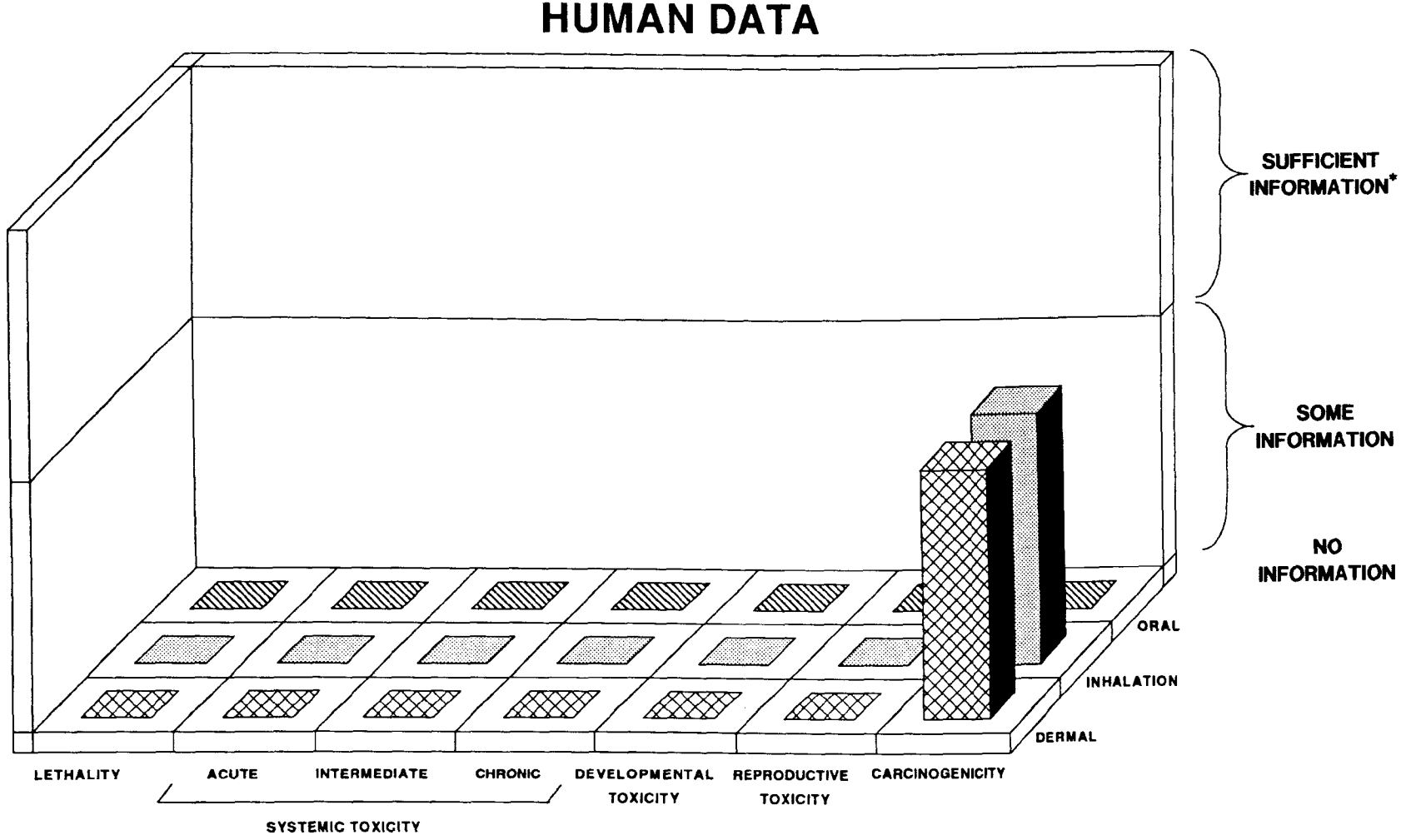
2.3.2 Health Effect End Points

2.3.2.1 Introduction and graphic summary

The availability of data for health effects in humans and animals is depicted on bar graphs in Figs. 2.8 and 2.9, respectively.

The bars of full height indicate that there are data to meet at least one of the following criteria:

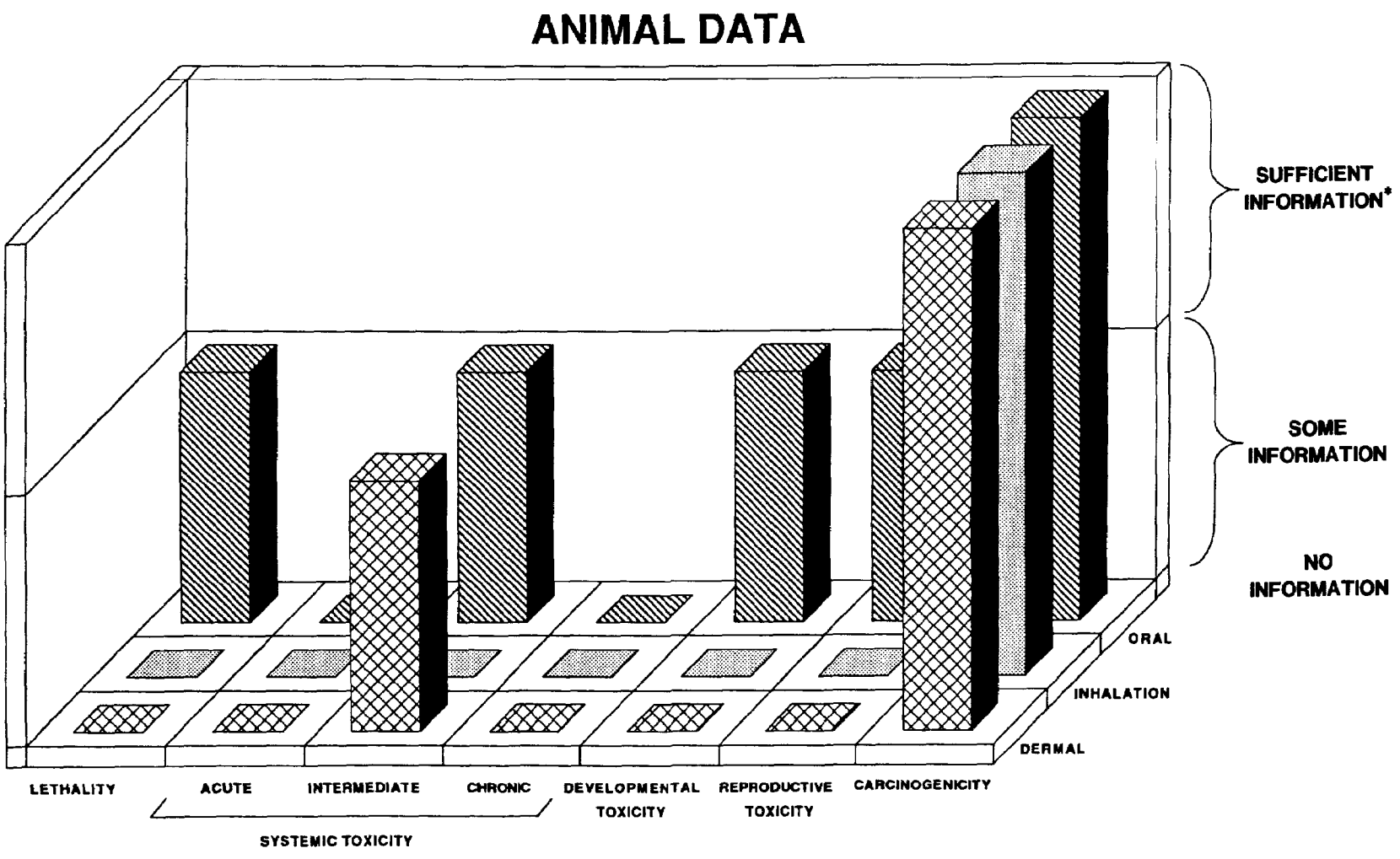
1. For noncancer health end points, one or more studies are available that meet current scientific standards and are sufficient to define a range of toxicity from no effect levels (NOAELs) to levels that cause effects (LOAELs or FELs).
2. For human carcinogenicity, a substance is classified as either a "known human carcinogen" or "probable human carcinogen" by both EPA



*Sufficient information exists to meet at least one of the criteria for cancer or noncancer end points.

NOTE: The adequacy of the database for the carcinogenicity of benzo[a]pyrene by the inhalation and dermal routes of exposure has been assessed on the basis of human exposure to complex mixtures of chemicals containing this compound, not on the basis of the compound alone.

Fig. 2.8. Availability of information on health effects of benzo[a]pyrene (human data).



*Sufficient information exists to meet at least one of the criteria for cancer or noncancer end points.

Fig. 2.9. Availability of information on health effects of benzo[a]pyrene (animal data).

and the International Agency for Research on Cancer (IARC) (qualitative), and the data are sufficient to derive a cancer potency factor (quantitative).

3. For animal carcinogenicity, a substance causes a statistically significant number of tumors in at least one species and the data are sufficient to derive a cancer potency factor.
4. There are studies which show that the chemical does not cause this health effect via this exposure route.

Bars of half height indicate that "some" information for the end point exists, but does not meet any of these criteria.

The absence of a column indicates that no information exists for that end point and route.

2.3.2.2 Description of highlights of graphs

Figure 2.8 indicates that no data are available to establish significant exposure levels for humans. Regressive verrucae were reported following subchronic dermal application to human skin (Cottini and Mazzone 1939); however, this study was seriously flawed, and the dermal effects reported cannot be definitively linked to B[a]P. No other data concerning the toxicity of B[a]P alone in humans following inhalation, oral, or dermal exposures were located in the available literature. Although reports of adverse health effects such as carcinogenicity do exist for inhalation and dermal exposure to mixtures of chemicals that include B[a]P, they provide inadequate information to assess quantitatively the role of B[a]P alone and have, therefore, been indicated as providing "some" data.

Figure 2.9 indicates the data available to establish significant exposure levels for animals. A subchronic mouse study provided some but inadequate data to establish a significant exposure level for the lethal effects of B[a]P following oral exposure. In this study, 120 mg/kg/day of B[a]P administered in the diet decreased survival time in a "nonresponsive" strain of mice (Robinson et al. 1975). Half of the deaths occurred within 15 days of dosing. However, only a single dose was tested, and information is not available on the effects of lower doses on survival times. No data are available concerning the effect of B[a]P on lethality following dermal or inhalation exposures.

No data are available on the systemic toxicity of B[a]P following inhalation or dermal exposures. Data are available in animals that suggest that B[a]P may adversely affect the skin following acute and subchronic dermal application (Bock and Mund 1958, Suntzeff et al. 1955, Elgjo 1968). Because these studies failed to evaluate control groups, conclusions concerning the dermal toxicity of B[a]P cannot be made. Some data are available to suggest that intermediate oral exposures to B[a]P adversely affected the hematopoietic system in a "nonresponsive" strain of mice leading to death due to hemorrhage or infection (Robinson et al. 1975). Only one dose was tested, which resulted in death; therefore, this study cannot be used to identify a LOAEL. No other data are available concerning the systemic toxicity of B[a]P following dermal or oral exposures. There are reports in the literature concerning B[a]P-induced immune suppression following intraperitoneal and subcutaneous

injection of mice. However, reports concerning the immunotoxicity of B[a]P following inhalation, oral, or dermal exposure could not be located in the available literature.

Some (albeit inadequate) data are available to establish a significant exposure level for the reproductive/developmental effects of B[a]P following oral exposures. Based on a modified two-generation study in mice, a LOAEL of 10 mg/kg/day was identified (MacKenzie and Angevine 1981). However, it must be emphasized that this study did not identify a NOAEL. Therefore, the LOAEL may actually be lower than 10 mg/kg/day. The fact that B[a]P causes developmental/reproductive effects is supported by results from other studies conducted in rodents in which B[a]P was administered orally or by injection. No information is available concerning these effects following inhalation or dermal exposure.

Adequate data are available to assess the carcinogenicity of B[a]P in animals. B[a]P is a well-studied, moderately potent carcinogen in animals, for which dose-response data are adequate for all three routes of exposure.

2.3.2.3 Summary of relevant ongoing research

Research is ongoing in the areas of B[a]P's molecular dosimetry as well as its biological mechanisms of action for carcinogenesis including DNA adduct formation and repair and potential for oncogene activation. B[a]P has been listed in NTP's Fiscal Year 1986 Annual Plan and Review of Current Department of Health and Human Services (DHHS), Department of Energy (DOE), and EPA Research Related to Toxicology. B[a]P will be tested by the following agencies: National Institute of Environmental Health Sciences; the Food and Drug Administration (FDA) National Center for Toxicological Research; National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases; and EPA's Office of Research and Development. A comparative potency method to assess quantitatively the carcinogenic effects for PAHs is under development by the Carcinogen Assessment Group, the Office of Solid Waste, the Office of Drinking Water, and the Office of Air Quality Planning and Standards of the EPA (EPA Contract Number 68-02-4403) and is being applied to the data available for B[a]P.

2.3.3 Other Information Needed for Human Health Assessment

2.3.3.1 Toxicokinetics and mechanisms of action

The metabolism of B[a]P has been studied extensively in human cells, tissue homogenates, and microsomal preparations. The toxicokinetics profiles for inhalation exposure to B[a]P in animals have been established. The role of metabolism in the absorption process has been delineated. There is no information on the tissue distribution of B[a]P after oral administration, although the information available on the toxicokinetics of B[a]P suggests that significant quantitative differences in tissue distribution are not expected as a result of different routes of administration.

B[a]P requires metabolic activation to exert its mutagenic and carcinogenic effects. The initial steps in the proposed mechanism of action of B[a]P-induced carcinogenesis involve metabolic formation of

bay-region diol epoxides followed by covalent interaction of these reactive metabolites with DNA (Conney 1982).

2.3.3.2 Adequacy of data on biological monitoring

The biological monitoring techniques for quantifying DNA adducts or hemoglobin adducts are limited, because inborn factors, environmental chemistry, and drugs can alter the activity of the enzymes responsible for converting B[a]P to the diol epoxides that bind to DNA or hemoglobin. In addition, fluorescence spectrometry may measure other compounds that can adduct to DNA or hemoglobin. There is a lack of information concerning the use of these techniques in occupationally or environmentally exposed individuals. Additional research should include further investigation of the quantitative relationship between hemoglobin adducts and DNA adducts and an examination of the formation of adducts following occupational exposure.

The techniques that use immunoassays to determine the presence of antibodies to adducts in blood have been tested in experimental animals and humans (Perera et al. 1982, Harris 1985, Harris et al. 1985, Harris et al. 1986, Haugen et al. 1986). This technique has shown an association between sera positive for antibodies and occupational exposure or smoking. The reliability of this method should be further examined in other, nonoccupational, exposure situations.

The presence of B[a]P or B[a]P metabolites in urine is an indication that exposure has occurred. However, in occupational studies, the amount of B[a]P concentrated in the urine did not adequately reflect environmental B[a]P concentrations (Becher and Bjorseth 1983). This discrepancy was reported to result from the nonbioavailability of particle-bound PAHs; therefore, this method should be further examined for its applicability in other exposure situations (Becher et al. 1984).

In addition, the smoking of cigarettes results in human exposure to PAHs, and the determination of biological levels of PAHs in smokers and in the general population must be further examined to properly assess environmental or occupational exposure.

2.3.3.3 Environmental considerations

The accuracy and precision of the analytical methods used to measure ambient B[a]P are somewhat limited. But the current methods, if properly conducted, are sufficient to record ambient levels of B[a]P. However, some analytical methods are of limited sensitivity.

Information on the fate of B[a]P sorbed onto particulate matter in air is, at present, unclear. The role of photochemical oxidation in the removal of B[a]P from air needs to be elucidated. Also, additional information on biodegradation processes and rates in terrestrial systems is needed.

Only limited information is available on the interactions of B[a]P with other chemicals typically found in the environment and at hazardous waste sites. Consequently, risks associated with exposure to B[a]P in the environment are not completely understood.

Recent studies on the fate of B[a]P in the environment have been published (e.g., Coover and Sims 1987, Bossert and Bartha 1986). It is likely that additional research in this area is continuing.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

The chemical formula, structure, synonyms, and identification numbers for B[a]P are listed in Table 3.1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Important physical and chemical properties of B[a]P are given in Table 3.2.

Table 3.1. Chemical identity of benzo[a]pyrene

Chemical name: Benzo[a]pyrene (IARC 1983)

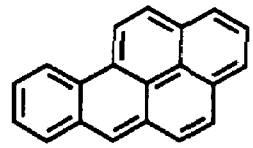
Synonyms: Benzo[def]chrysene; 3,4-benzopyrene, 3,4-benzpyrene; benz[a]pyrene; BP; B[a]P (IARC 1983)[a]

Trade name: Not applicable

Chemical formula: $C_{20}H_{12}$ (IARC 1983)

Wiswesser line notation: L D6 B6666 2AB TJ (HSDB 1987)

Chemical structure:



Identification numbers:

CAS Registry No.: 50-32-8
NIOSH RTECS No.: DJ3675000
EPA Hazardous Waste No.: U022
OHM-TADS No.: 8200129
DOT/UN/NA/IMCO Shipping No.: Not available
STCC No.: Not available
Hazardous Substances Data Bank No.: 2554
National Cancer Institute No.: Not available

[a]Confusion exists in the literature concerning the naming of this compound, mainly because two different systems (Richter and IUPAC) of numbering the pyrene ring structure have been used; the IARC reference, unfortunately, does not acknowledge that this confusion exists and that the nomenclature of some of *the synonyms listed is incorrect.*

Table 3.2. Physical and chemical properties of benzo[a]pyrene

Property	Value	References
Molecular weight	252.3 g/mol	IARC 1983
Color	Pale yellow; fluoresces yellow-green in ultraviolet light	IARC 1983, CRC 1987
Physical state	Plates or needles (recrystallized from benzene/ligroin)	CRC 1987
Odor	Unknown	
Melting point	179-179.3°C	CRC 1987
Boiling point	310-312°C (at 10 mm Hg) 495°C (at 760 mm Hg)	CRC 1987, Aldrich 1986
Autoignition temperature	Unknown	
Solubility		
Water	3.8×10^{-6} g/L	EPA 1982,
Organic solvents	Sparingly soluble in ethanol and methanol; soluble in benzene, toluene, xylene, acetone, DMSO, and ether	IARC 1983
Biological fluids	Unknown	
Density	1.351	
Partition coefficients		
Octanol-water (K_{ow})	1.15×10^{6}	EPA 1982
Log K_{ow}	6.06	
Soil-organic carbon-water (K_{oc})	5.5×10^{6}	EPA 1982
Vapor pressure (25°C)	5.6×10^{-9} mm Hg	EPA 1982
Henry's law constant	4.9×10^{-7} atm-m^3/mol	EPA 1982
Flash point	Unknown	
Flammability limits	Unknown	
Conversion factors[a]	1 ppm = 10.32 mg/m^3	Verschueren 1983

[a]Calculated based on the ideal gas law, $PV = nRT$ at 25°C.

4. TOXICOLOGICAL DATA

4.1 OVERVIEW

B[a]P is readily absorbed by all routes of exposure. Absorbed B[a]P is distributed rapidly throughout the body, metabolized to conjugated derivatives, and eliminated.

B[a]P is a well-studied, well-established experimental carcinogen. Its carcinogenicity has been demonstrated in laboratory animals by all routes for which humans would normally expect to be exposed. In addition, it has elicited tumors by several experimental routes of exposure. B[a]P's carcinogenic mechanism of action is thought to result from its metabolism to a reactive diol epoxide derivative prior to conjugation and elimination. This derivative can interact with DNA. As a result, B[a]P has been demonstrated to cause mutations in many experimental systems. Mutation is considered a necessary (albeit insufficient) step for the carcinogenic activity of B[a]P.

Few reports are available on the noncarcinogenic systemic effects of B[a]P in humans or experimental animals following inhalation, oral, or dermal exposures. Occupational exposures to complex mixtures and industrial processes that incude PAHs have been evaluated by IARC (1973). Toxic effects include a variety of skin lesions and noncancer lung diseases such as bronchitis. However, it is not possible to determine from those studies the effect of individual PAHs.

Lethality and decreased longevity have been reported in a "nonresponsive" strain of mice (i.e., strains whose hepatic aryl hydrocarbon hydroxylase activity is not induced by PAH) that were exposed orally to high levels of B[a]P (120 mg/kg/day). Death appeared to be caused by bone marrow depression leading to hemorrhage or infection.

There are reports in the literature concerning the dermal toxicity of B[a]P following acute applications to animal skin and subchronic applications to human and animal skin. Because these studies failed to employ control groups, definitive conclusions concerning the dermal toxicity of B[a]P cannot be made.

Although there are no studies available on the reproductive/developmental effects of B[a]P in humans, results from studies in rodents indicate that in utero exposure to B[a]P either by the oral route or by injection is associated with developmental toxicity and adverse reproductive effects. Adverse reproductive/developmental effects resulted from oral exposures to doses of B[a]P as low as 10 mg/kg/day.

B[a]P-induced immune suppression has been reported in mice and in the offspring of mice treated intraperitoneally with B[a]P. However,

similar reports could not be located in the available literature following inhalation, oral, or dermal exposures.

4.2 TOXICOKINETICS

4.2.1 Overview

B[a]P is readily absorbed by inhalation, oral, and dermal routes of administration. Metabolism plays an important role in the absorption of B[a]P via the lungs and the skin; intestinal absorption appears to be less dependent on metabolic factors.

Absorbed B[a]P is rapidly distributed to several tissues. Benzo[a]pyrene metabolites are subject to enterohepatic circulation as evidenced by time-dependent increases in the intestinal tissue concentrations of these intermediates.

The metabolism of B[a]P is complex and includes the formation of proposed ultimate carcinogens, that is, B[a]P 7,8-diol-9,10-epoxide (Fig. 4.1). A unified concept to explain and predict the carcinogenic potential of polycyclic aromatic hydrocarbons has been proposed, based on this mechanism of activation of B[a]P. This concept, the "bay-region" theory, postulates that specific structural features may be used as an indicator to predict the formation of diol epoxide metabolites and, thus, the potential carcinogenicity of an aromatic hydrocarbon. The "bay-region" theory does not preclude other activation mechanisms that may result in the initiation of cancer but simply identifies a likely pathway for activation. The formation of other reactive metabolites of B[a]P generated under specific situations (i.e., free radical intermediates) has also been demonstrated, although these pathways have not been shown to be relevant to the in vivo toxicity of B[a]P.

4.2.2 Absorption

4.2.2.1 Inhalation

Human. No quantitative information on the absorption of B[a]P via the respiratory tract was found for human subjects. Absorption of B[a]P via this route is inferred from the isolation of urinary metabolites of B[a]P in subjects exposed to polycyclic aromatic hydrocarbons in an industrial environment (Becher and Bjorseth 1983).

Animal. The biological fate and mechanisms of absorption of inhaled B[a]P adsorbed on particles were studied in the rat (Sun et al. 1982). A [^{3}H]-benzo[a]pyrene concentration of 0.6 μg/L adsorbed on ultrafine Ga_2O_3 particles (diam ~0.1 μm) was administered to rats as an aerosol. A parallel study was conducted with a pure [^{3}H]-B[a]P aerosol (no carrier) at a concentration of 1 μg/L. Total exposure time for both groups was 30 min. The amount of aerosol particles deposited in the lung after termination of exposure was ~20% for Ga_2O_3 (corresponding to 3% [^{3}H]-B[a]P) and ~10% for the pure hydrocarbon aerosol. These values represent the percentage of the total inhaled mass that was actually deposited in the lungs. The excretion of hydrocarbon was monitored for over 2 weeks at which time a nearly quantitative recovery of radioactivity was obtained, indicating complete absorption of the initially deposited hydrocarbon. Consistent with administration of B[a]P

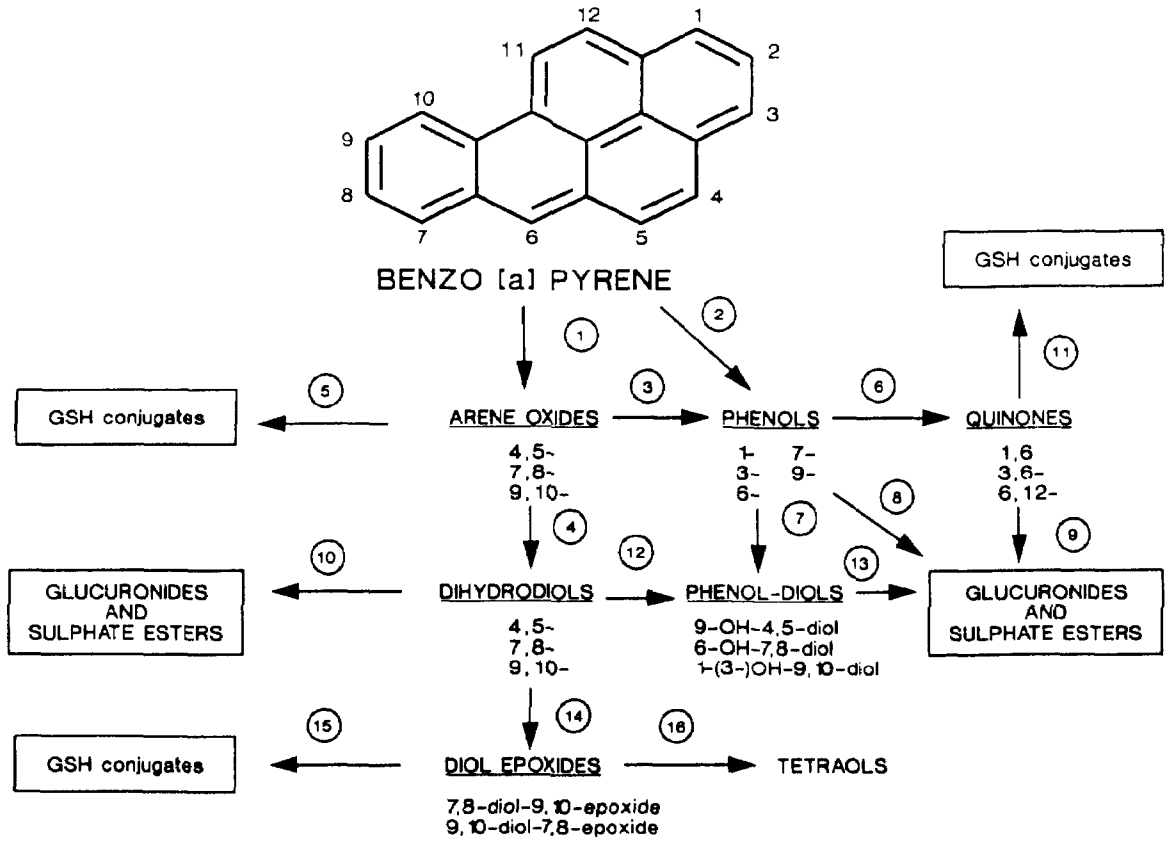


Fig. 4.1. Metabolic fate of benzo[a]pyrene. *Source:* IARC 1983.

by other routes, inhaled hydrocarbon was excreted predominantly in the feces (94% for B[a]P on Ga_2O_3 particles and 86% for the pure aerosol). Significant differences in the clearance times of Ga_2O_3-adsorbed and pure B[a]P strongly suggested that a substantial amount of B[a]P coated on Ga_2O_3 particles was cleared from the lungs by mucociliary clearance and subsequent ingestion. The pure B[a]P aerosol particles retained by the lungs were cleared by absorption into the blood stream. In contrast, particle association of B[a]P increased its retention in the lung and increased the relative amount of B[a]P that was cleared by mucociliary action and subsequently ingested. This resulted in an increased absorption of B[a]P in the alimentary tract and thereby increased the dose of this compound and its metabolites to the stomach, liver, and kidneys relative to pure B[a]P. Similar observations have been reported by other workers (Creasia et al. 1976, Tornquist et al. 1985).

The effect of dose on the pulmonary clearance of B[a]P in the rat was studied by intratracheal instillation of [^{14}C]-B[a]P (16, 90, and 6,400 μg of hydrocarbon). Clearance was determined to be biphasic with a fast component (half-life ≤ 1 day) and a slow component (half-life ≥ 1 day). As dose increased (16 to 6,400 μg B[a]P), an increased percentage (from 89 to 99.76%) was cleared with a half-life ≤ 1 day and a decreased percentage (from 11 to 0.24%) with a half-life ≥ 1 day (Medinsky and Kampcik 1985). The slower component is clearly subject to saturation at the high dose levels.

4.2.2.2 Oral

Human. No data on the absorption of B[a]P via the gastrointestinal tract in human subjects were identified.

Animal. The gastrointestinal tract absorption of B[a]P was studied in the rat. Carbon-14-labeled B[a]P (0.04 μmol, 0.4 μmol and 4.0 μmol), dissolved in peanut oil, was administered to rats by gavage (Hecht et al. 1979). Absorption of hydrocarbon was determined by measuring radioactivity in feces and urine. Total excretion of label in feces averaged 74 to 79% from 0 to 48 h and 85% from 0 to 168 h; excretion in urine was significantly less (1 to 3% of administered dose). The role of metabolism in the excretion of B[a]P was briefly explored. The amount of unchanged B[a]P excreted decreased as dose increased (13, 7.8, and 5.6%, respectively) for the three doses studied.

The absorption of B[a]P from the gastrointestinal tract has been reported to be enhanced in mice and cats when solubilized in vehicles possessing both lipophilic and hydrophilic properties (Setala and Ekwall 1950, Ermalla et al. 1951). These vehicles can solubilize and stabilize fat-soluble B[a]P in aqueous solution. Once B[a]P has entered the small intestine it is solubilized by the bile salts and absorbed by the epithelial cells of the small intestine (Laher and Barrowman 1983).

4.2.2.3 Dermal

Human. Dermal absorption of B[a]P through human skin (leg skin) was determined under in vitro conditions (Kao et al. 1985). The extent of permeation after 24 h was established as 3% of an applied dose of [^{14}C] benzo[a]pyrene (10 μg/cm^2).

Animal. The percutaneous absorption of ^{14}C-B[a]P was studied in adult Swiss Webster mice (Sanders et al. 1986). Absorption was measured by analyzing radioactivity in excreta (feces and urine) and by analysis of residual label at the site of application. Disappearance of radiolabel from the application site was rapid: 6% (of an applied dose) in 1 h and 40% in 24 h. After 7 days, 93% of the radioactivity was recovered in excreta, mostly in the feces.

The skin penetration of an applied dose of [^{14}C] B[a]P (10 $\mu g/cm^2$) was determined in several mammalian species under in vitro conditions (Kao et al. 1985). Dorsal skin from marmoset, guinea pig, rabbit, rat, and mouse were used for the permeation experiments. The mouse showed the highest permeation at 10% (24 h), followed by the rat, rabbit, and marmoset (1 to 3%); the guinea pig exhibited the lowest permeation at 0.1%. The authors (Kao et al. 1985) suggested that first-pass cutaneous metabolism was an important factor in determining the extent of B[a]P penetration through the skin. They consider that, in addition to diffusion, metabolic pathways play a decisive role in the percutaneous absorption of B[a]P.

4.2.3 Distribution

Absorbed B[a]P is rapidly and widely distributed among several tissues. Hydrocarbon levels in the various tissues reflect the influence of the route of administration, vehicle formulation (if any), and metabolism.

There is no quantitative information available concerning the distribution of B[a]P after oral administration. Indirect evidence is available from inhalation experiments on rats for which a significant contribution from ingestion of B[a]P (coated or particles) was established (Sun et al. 1982).

Absorption and distribution of inhaled B[a]P is rapid; maximum levels of radioactivity found in the liver, esophagus, small intestine, and blood were detected 30 min after exposure. After 12 h, maximum levels of radioactivity were detected in the cecum, stomach, and large intestine.

The distribution pattern for inhaled Ga_2O_3 particles coated with B[a]P was similar. However, there were significant differences in the levels of B[a]P delivered to the different tissues. In most cases, absorption of B[a]P from Ga_2O_3 particles led to higher levels of hydrocarbon. An explanation advanced to explain these differences was that inhalation of B[a]P adsorbed on insoluble particles is cleared predominantly by mucociliary transport and ingestion. This latter mechanism of absorption leads to the increased levels in the liver and kidneys. An additional conclusion is that B[a]P absorbed via the intestinal tract is distributed in an analogous pattern to inhaled B[a]P.

The disposition of [^3H]-B[a]P in rats following intratracheal instillation was reported by Weyand and Bevan (1986). The percentages of dose detected in various tissues were: at 5 min, lungs (59%), carcass (14%), liver (12.5%), blood (3.9%), and intestines (1.9%); at 60 min, lungs (15%), carcass (27%), liver (17%), blood (1.6%), and intestines

(9.9%); and at 360 min, lungs (5%), carcass (21.5%), liver (4.6%), blood (1.7%), and intestines (14.9%). The percentages include both parent hydrocarbons and metabolites. The systemic availability of unchanged B[a]P administered intratracheally was lower relative to B[a]P delivered intravenously. The reduction was attributed to a significant contribution of lung enzymes to metabolism of B[a]P.

The data in this study (Weyand and Bevan 1986) and others (Sun et al. 1982, Mitchell 1982) provide evidence for the enterohepatic circulation of B[a]P metabolites. The concentration of B[a]P metabolites in the intestines increases with time, suggesting active intestinal reabsorption.

4.2.4 Metabolism

Mammalian metabolism of B[a]P follows the general scheme established for smaller aromatic hydrocarbons (Williams 1959). This general scheme involves initial oxidative and hydrolytic steps, collectively known as Phase I metabolism, and subsequent conjugation of Phase I metabolites with glutathione, sulfate, or glucuronic acids to form Phase II metabolites. Typically, for PAH, Phase I biotransformations are considered activating steps because of the reactive nature of the metabolites that can be formed; Phase II transformations are considered detoxifying steps, since these conjugated metabolites are suitable for excretion and are removed from the system (Cooper et al. 1983, Levin et al. 1982, Thakker et al. 1985).

The metabolism of B[a]P has been studied both in vitro and in vivo (Sims and Grover 1974). The use of in vitro systems was justified by comparing the profiles of Phase I metabolites excreted in vivo with those generated under in vitro conditions and noting the similarities. The observed differences are due to the absence of conjugating systems under in vitro conditions. The most commonly used in vitro system is the rat liver microsomal fraction, although numerous other species have been used (Sims and Grover 1974). More recently, the use of cells and cultured tissues has allowed the study of both Phase I and Phase II metabolism under in vitro conditions.

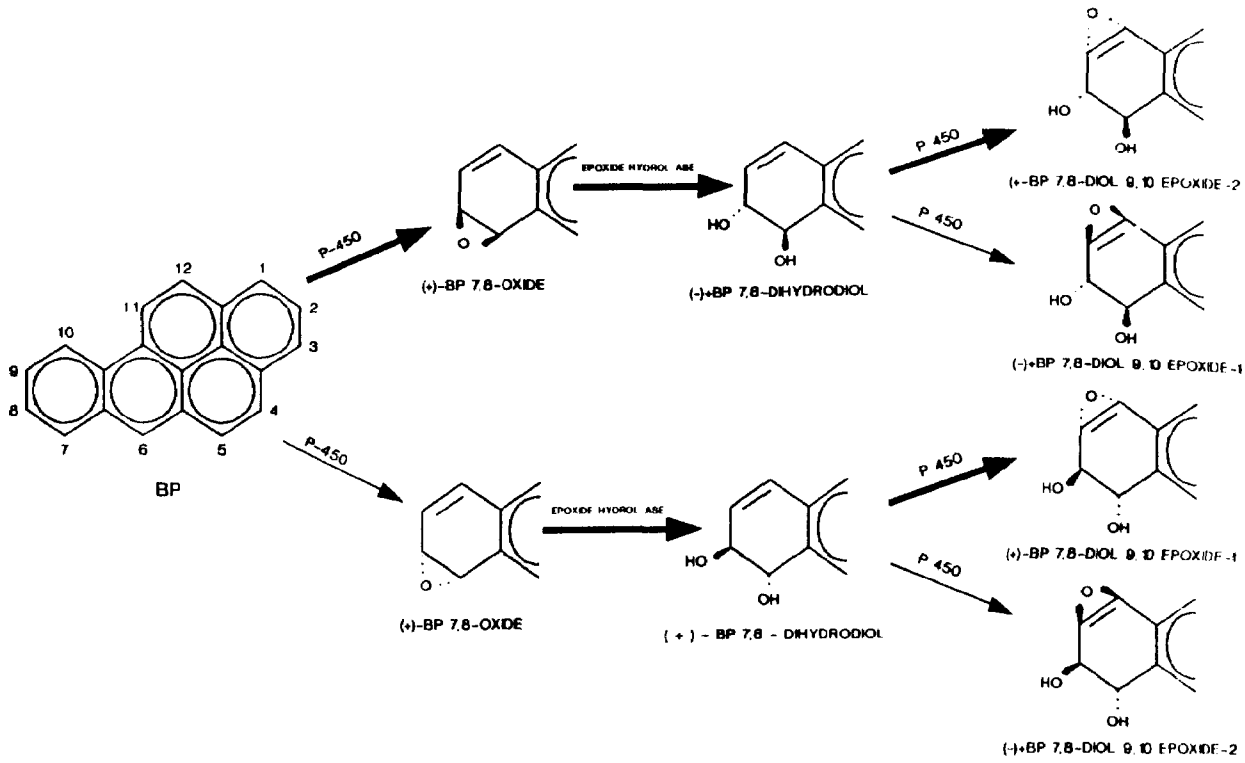
The metabolism of B[a]P in human tissues has received considerable attention. Studies have been conducted using bronchus (Cohen et al. 1976), colon (Autrup et al. 1978), kidney (Prough et al. 1979), liver (Selkirk et al. 1975a), lung (Prough et al. 1979, Mehta et al. 1979), lymphocytes (Selkirk et al. 1975b), macrophages (Marshall et al. 1979), skin epithelium (Fox et al. 1975), tracheobronchial tissue (Autrup et al. 1980), mammary epithelial cells (Bartley and Stampfer 1985), bladder (Selkirk et al. 1983), and esophagus (Harris et al. 1979).

In general, similar metabolites are formed from B[a]P in the many microsomal, cell, and cultured tissue preparations that have been examined. There are differences in the relative levels and rates of formation of specific metabolites among tissues and cell preparations used and among animal species and strains. These differences are susceptible to change as a result of pretreatment of the animals with either inducers or inhibitors of particular enzymes. The metabolism of B[a]P is summarized in Fig. 4.1. B[a]P is metabolized initially by the microsomal cytochrome P-450 monoxygenase system to several arene oxides

(reaction 1, Fig. 4.1). Once formed, these arene oxides may rearrange spontaneously to phenols (reaction 3), undergo hydration to the corresponding *trans*-dihydrodiols in a reaction catalyzed by microsomal epoxide hydrolase (reaction 4), or react covalently with glutathione, either spontaneously or in a reaction catalyzed by cytosolic glutathione *S*-transferases (reaction 5). Phenols may also be formed by the cytochrome P-450 monooxygenase system by direct oxygen insertion (reaction 2), although unequivocal proof for this mechanism is lacking. 6-Hydroxybenzo[a]pyrene is further oxidized either spontaneously or metabolically to the 1,6-, 3,6-, or 6,12-quinones (reaction 6), and this phenol is also a presumed intermediate in the oxidation of B[a]P to the three quinones catalyzed by prostaglandin endoperoxide synthetase. Evidence exists for the further oxidation metabolism of two additional phenols: 3-hydroxybenzo[a]pyrene is metabolized to the 3,6-quinone (reaction 6), and 9-hydroxybenzo[a]pyrene is oxidized to the K-region 4,5-oxide, which is hydrated to the corresponding 4,5-dihydrodiol (reaction 7). The phenols, quinones, and dihydrodiols can all be conjugated to glucuronides and sulphate esters (reactions 8-10); the quinones also form glutathione conjugates (reaction 11).

In addition to being conjugated, the dihydrodiols undergo further oxidative metabolism. The cytochrome P-450 monooxygenase system metabolizes B[a]P 4,5-dihydrodiol to a number of uncharacterized metabolites, while the 9,10-dihydrodiol is metabolized predominantly to its 1- and/or 3-phenol derivative (reaction 12) with only minor quantities of a 9,10-diol, 7,8-epoxide being formed (reaction 14). In contrast to 9,10-dihydrodiol, metabolism of B[a]P 7,8-dihydrodiol is to a 7,8-diol, 9,10-epoxide (reaction 14), and phenol-diol formation is a relatively minor pathway. The diol epoxides can be conjugated with glutathione either spontaneously or by glutathione *S*-transferase-catalyzed reaction (reaction 15). They may also hydrolyze spontaneously to tetraols (reaction 16, although epoxide hydrolase does not catalyze the hydration).

The primary oxidative metabolites of B[a]P are substrates for further oxidative metabolism by the cytochrome P-450 dependent monooxygenase system (Levin et al. 1982, Cooper et al. 1983, Ribeiro et al. 1985). B[a]P 7,8-diol-9,10-epoxide has been established as an ultimate carcinogen. The conversion of B[a]P oxides to *trans*-dihydrodiols is catalyzed by epoxide hydrolase (Jerina and Daly 1974, Sims and Grover 1974); the stereochemistry of the steps leading to the formation of dihydrodiols has been elucidated and plays an important role in their toxicity. The sequence of reactions leading to B[a]P 7,8-diol-9,10-epoxide from B[a]P proceeds with varying degrees of stereoselectivity (Thakker et al. 1977). The pathways leading to stereoisomeric diol epoxides of B[a]P are shown in Fig. 4.2. There are significant differences in the mutagenic and carcinogenic activities of diastereomeric and enantiomeric intermediates. (+)-Diol epoxide-2 is the major stereoisomer formed by rat liver microsomes (Jerina et al. 1980, 1976). The significance of this finding is that this isomer has high tumorigenic activity (Levin et al. 1982) and gives rise to the major adduct formed upon reaction with DNA. The structure of this adduct has been established as a diol epoxide-deoxyguanosine adduct where alkylation takes place at the exocyclic nitrogen (N-2) of



ADAPTED FROM LEVIN ET AL. (1980) IN IARC (1983). Absolute stereochemistry of all metabolites is as shown. Heavy arrows indicate the predominant pathways. Diol epoxides exist as diastereoisomeric pairs in which the benzylic hydroxyl group and the epoxide oxygen are either *cis* (variously called diol epoxide 1, diol epoxide 2, or syn-diol epoxide) or *trans* (variously called diol epoxide 2, diol epoxide 1, or anti-diol epoxide).

Fig. 4.2. Stereoselective metabolism of benzo[a]pyrene to an ultimate carcinogenic metabolite by rat liver microsomes.

deoxyguanosine. This diol epoxide-deoxyguanosine has been isolated from several animal species (Horton et al. 1985, Autrup and Seremet 1986) and human tissue preparations (Harris et al. 1979).

The formation of Phase II metabolites from epoxides, dihydrodiols, phenols, and diol epoxides is generally believed to constitute a detoxication step leading to the elimination of the hydrocarbon metabolites. Enzyme systems active in the conjugative metabolism of B[a]P include the UDP-glucuronyl transferase (Cooper et al. 1983), sulfate transferase (Moore and Cohen 1979), and glutathione transferase (Grover 1977, Hernandez et al. 1980).

The formation of B[a]P 7,8-diol-9,10-expoxide from B[a]P 7,8-diol can also be catalyzed by the prostaglandin synthetase system. In the presence of arachidonic acid, this microsomal enzyme catalyzes the formation of diol epoxide-2 from racemic 7,8-dihydrodiol (Panthanickal and Marnett 1981). The activity of the prostaglandin is low in the liver, but significant levels are found in the lung; the highest activity is found in seminal vesicles. The importance of this pathway in the in vivo metabolic formation of tumorigenic diol epoxides from 7,8-diol remains an open question.

Elucidation of the mechanistic aspects of the metabolic steps leading to the formation of B[a]P 7-8-diol-9,10-epoxide and the identification of this intermediate as an ultimate carcinogen suggested a unified concept to explain and predict the carcinogenic potential of other polycyclic aromatic hydrocarbons. This concept, known as the "bay region" theory (Jerina et al. 1980), stipulates that epoxides on saturated angular benzo-rings (bay region or phenanthrene-like structure) should exhibit high chemical reactivity if the epoxide is located in the bay region. This premise is supported by molecular orbital calculations that predict the ease of formation of carbonium ions by ring opening of bay-region epoxides (Jerina and Lehr 1977, Mohammad 1985). This chemical reactivity is reflected in biological activity, and thus bay-region diol epoxides are likely candidates as ultimate carcinogens of a series of polycyclic aromatic hydrocarbons.

4.2.5 Excretion

Metabolism of B[a]P is a prerequisite for hepatobiliary excretion and elimination through the feces, regardless of the route of administration. The rate-determining step in the biliary excretion of B[a]P administered intravenously has been shown to be metabolism and not biliary transport (Schlede et al. 1970). Because of "first-pass" metabolism in the liver, orally administered B[a]P would be expected to show an enhanced rate of excretion relative to other administration routes. B[a]P and its metabolites are reabsorbed by enterohepatic circulation (Chipman et al. 1982). The time required to recover administered B[a]P in the feces roughly follows the sequence according to route of administration: dermal $\geq$ lung $\geq$ oral.

4.3 TOXICITY

4.3.1 Lethality and Decreased Longevity

4.3.1.1 Overview

Pertinent data about lethality and decreased longevity in humans following exposure to B[a]P could not be found in the available literature.

Lethality data for experimental animals acutely exposed to B[a]P by the inhalation, oral, and dermal routes could not be found in the available literature. The effects of subchronic oral exposure to B[a]P were a decreased survival time in "nonresponsive" strains of mice (i.e., strains whose hepatic aryl hydrocarbon hydroxylase activity is not induced by PAH when compared with corresponding controls) (Robinson et al. 1975). Half of the deaths occurred within 15 days of dosing. Death appeared to be caused by bone marrow depression, leading to hemorrhage or infection.

4.3.1.2 Inhalation

Pertinent data about lethality and decreased longevity resulting from inhalation exposure of humans or experimental animals to B[a]P could not be found in the available literature.

4.3.1.3 Oral

Human. Pertinent data about lethality and decreased longevity resulting from oral exposure of humans to B[a]P could not be found in the available literature.

Animal. Pertinent data about the acute oral toxicity of B[a]P in experimental animals could not be found in the available literature.

Robinson et al. (1975) investigated the effects of oral administration of B[a]P on the life spans of several inbred strains of mice. Strains of mice were classified as either "responsive" or "nonresponsive," based on the strain's susceptibility to the induction of cytochrome P-450 and associated enzymes by PAHs. The strains tested differed at a gene site generally described as the Ah locus. The responsive strains tested were C57Bl/6, C3H/HeN, and BALB/CAnN. The nonresponsive strains were DBA/2 and AKR/N. Treatment groups, consisting of 30 animals/strain, were fed a laboratory diet ad libitum, which had been soaked in corn oil containing B[a]P; the estimated oral dose was ~120 mg/kg/day. Responsive and nonresponsive control groups, each consisting of 30 animals, were fed the same diet which had been soaked in unadulterated corn oil. The number of deaths were observed for a 180-day period. Following oral administration of 120 mg/kg/day B[a]P for up to 6 months, survival time of all nonresponsive mice was shortened significantly when compared to corresponding controls, while survival time of treated responsive mice was not significantly different from their corresponding paired control. Among the "nonresponsive" strains, all of the mice in the treatment groups died, with at least half the deaths occurring within 15 days. Only two mice died in the "nonresponsive" control group (DBA/2) over the same period of time.

Death appeared to be caused by bone marrow depression (aplastic anemia; pancytopenia) leading to hemorrhage or infection. The authors concluded that decreased survival was associated with a single gene difference in aromatic hydrocarbon responsiveness.

4.3.1.4 Dermal

Pertinent data about lethality and decreased longevity resulting from dermal exposure of humans or experimental animals to B[a]P could not be found in the available literature.

4.3.1.5 General discussion

Pertinent data about lethality and decreased longevity in humans exposed to B[a]P could not be found in the available literature. Lethality and decreased longevity have been reported in "nonresponsive" strains of mice following subchronic oral exposure to 120 mg/kg body weight B[a]P and in "responsive" mice following a single intraperitoneal dose of 500 mg/kg body weight B[a]P (Robinson et al. 1975). No LD_{50} values have been reported for experimental animals exposed by the oral or dermal routes of exposure, nor have LC_{50} values been reported for experimental animals exposed to B[a]P by inhalation. The acute lethality of B[a]P has been investigated following intraperitoneal injection. The LD_{50} for B[a]P administered intraperitoneally to male $B6C3F_1$ mice is ~250 mg/kg body weight (Salamone 1981).

4.3.2 Systemic/Target Organ Toxicity

4.3.2.1 Overview

Few reports are available on the systemic effects of B[a]P in humans or experimental animals. Occupational exposures to complex mixtures and industrial processes that include PAHs have been evaluated by IARC (1973); however, it is not possible to determine from these studies the effects of individual PAHs. In addition, systemic toxicity associated with B[a]P exposure is generally not evident, except at doses sufficient to produce a high tumor incidence in experimental animals.

Regressive verrucae were reported following subchronic dermal application of B[a]P to human skin (Cottini and Mazzone 1939). However, this study was seriously flawed in that B[a]P was dissolved in benzene and a benzene control was not evaluated. Therefore, the dermal effects reported in this study may have been due to the benzene vehicle.

In a subchronic oral animal study, B[a]P adversely affected the hematopoietic system of a "nonresponsive" strain of mice leading to death due to hemorrhage or infection (Robinson et al. 1975). Alterations in epidermal cell growth following subchronic dermal application of B[a]P to the skin of hairless mice have also been reported (Elgjo 1968). However, the latter experiment was flawed in that no acetone-vehicle control was evaluated. Therefore, the dermal effects reported in this study may in fact be due to the acetone vehicle, rather than the B[a]P. There are a number of older reports in the literature that show that topical application of B[a]P for an acute exposure period (e.g., 4 days) suppresses sebaceous glands in mouse skin (Bock and Mund 1958, Suntzeff et al. 1955). These studies also did not employ control groups;

therefore, it is not possible to determine if the effects seen were due to the solvent and/or the preparation procedures.

There are reports in the literature concerning the immunotoxicity of B[a]P following intraperitoneal and subcutaneous injection. B[a]P-induced immune suppression was reported in male B6CF1 mice (Lyte and Bick 1985) and in the offspring of C3H/Anf mice treated intraperitoneally with B[a]P (Urso and Gengozian 1980). Subcutaneous injections of B[a]P in female B6C3F1 mice produced a dose-related suppression of antibody production to both T-cell-independent and T-cell-dependent antigens (White and Holsapple 1984). Reports concerning the immunotoxicity of B[a]P following inhalation, oral, or dermal exposure could not be found in the available literature.

No other reports were found in the available literature concerning the systemic toxicity of B[a]P.

4.3.2.2 Hematopoietic toxicity

Overview. Hematopoietic effects (e.g., aplastic anemia, pancytopenia) of B[a]P have been reported in a "nonresponsive" strain of mice following subchronic oral exposure to 120 mg/kg body weight B[a]P (Robinson et al. 1975). Hematopoietic effects of B[a]P have not been reported in humans.

Inhalation. Pertinent data about the hematopoietic toxicity of B[a]P in humans or experimental animals following inhalation exposure could not be found in the available literature.

Oral. Pertinent human data about the hematopoietic toxicity of B[a]P resulting from oral exposure could not be found in the available literature.

As stated (see Sect. 4.3.1.3 on oral toxicity), aplastic anemia and ultimately death in experimental animals have been linked to subchronic oral exposures to 120 mg/kg body weight B[a]P (Robinson et al. 1975).

Dermal. Pertinent data about the hematopoietic toxicity of B[a]P following dermal exposure of humans or experimental animals could not be found in the available literature.

General discussion. Results from one experiment suggest that decreased survival in a "nonresponsive" strain of mice following subchronic oral exposure to B[a]P appeared to be caused by bone marrow depression (i.e., aplastic anemia, pancytopenia). The investigators concluded that decreased survival in "nonresponsive" versus "responsive" mice was associated with a single gene difference in aromatic hydrocarbon responsiveness reflected as ability to induce aryl hydrocarbon hydroxylase and consequently activate B[a]P to its reactive metabolite. No other data regarding the hematopoietic toxicity of B[a]P in humans or in experimental animals were found in the available literature, regardless of the route of exposure.

4.3.2.3 Dermal toxicity

Overview. There are reports in the literature concerning the dermal toxicity of B[a]P following acute applications to animal skin and subchronic applications to human and animal skin. However, these studies

failed to employ control groups, and, therefore, definitive conclusions concerning the dermal toxicity of B[a]P cannot be made. No data on oral and inhalation exposures of humans or experimental animals to B[a]P were found in the literature.

Inhalation. Pertinent data about the dermal toxicity of B[a]P following inhalation exposure of humans or experimental animals could not be found in the available literature.

Oral. Pertinent data about the dermal toxicity of B[a]P following oral exposure could not be found in the available literature.

Dermal. Cottini and Mazzone (1939) applied a 1% solution of B[a]P in benzene to small areas of exposed and unexposed skin in 26 human patients. Up to 120 daily applications were applied in 4 months. Regressive verrucae developed in all 26 patients within this time. Although reversible and apparently benign, the 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) in men accidentially exposed to B[a]P. However, it should be emphasized that the experiment conducted by Cottini and Mazzone (1939) is seriously flawed in that B[a]P was applied as a 1% solution in benzene and no benzene control was evaluated. In addition, due to the lack of adequate information regarding dose quantification, significant human exposure levels cannot be developed from these studies.

Effects of B[a]P on the skin of patients with preexisting dermal conditions of periphigus vulgaris and xeroderma pigmentosum were also tested by Cottini and Mazzone (1939). Following 20 applications of B[a]P, patients with periphigus developed local bullous eruptions characteristic of the disease. The patients having xeroderma pigmentosum were exposed to 85 applications. Only pigmentary and slight verrucous effects were exhibited. Additional tests were conducted on patients with preexisting active skin lesions due to squamous cell cancer. Initial results indicated a general improvement and/or retardation of the lesion; in one case, an actual analgesic effect was observed. The severity of the manifestation on abnormal skin appeared to be related to age. That is, those in the lowest age range exhibited fewer and less severe effects than those in the mid-range groups, and so on. No such age relationship on effects involving those patients with normal or preexisting skin lesions was noted.

In a number of older investigations, topical application of B[a]P has been reported to suppress or even destroy sebaceous glands in mouse skin (Bock and Mund 1958). Bock and Mund (1958) applied 0.2 mL of B[a]P, twice daily, to two-thirds of the shaved backs of Swiss mice. Four days after the last application, the mice were sacrificed. The treated skin was then subjected to an elaborate preparation and staining procedure and was qualitatively examined. B[a]P was reported to suppress sebaceous glands. However, controls were not employed; therefore, it is not possible to determine if the effects seen were due to the solvent and/or the preparation procedures. In vitro preparations of mouse skin have also been reported to undergo degeneration of sebaceous glands following exposure to B[a]P (Suntzeff et al. 1955). These studies also failed to employ control groups.

Alterations in epidermal cell growth after dermal application in mice of B[a]P were reported by Elgjo (1968). In this study 0.05 mL of a 1% B[a]P solution was dermally applied to the interscapular area of hairless mice. Groups of eight mice were sacrificed 1, 2, 4, 7, and 14 days following application. Increases in cellular mitotic rates, mitotic counts, and mitotic duration that, according to the authors, were indicative of a regenerative reaction were observed. All values for these parameters were higher than normal values supplied by the author; however, concurrent controls were not utilized. The authors concluded that the alterations in the kinetics of epidermal cell growth produced by B[a]P were more sustained than after application of croton oil. The study by Elgjo (1968) is limited for drawing conclusions concerning the dermal toxicity of B[a]P in that (1) experimental data were compared with historical controls only, (2) no acetone-vehicle control was evaluated, and (3) the statistical significance of the increased values was not determined. Therefore, a LOAEL for dermal effects cannot be identified from this study.

General discussion. No data on oral and inhalation exposures to B[a]P producing toxic effects in humans or experimental animals were found in the literature. Conclusions concerning the dermal toxicity of B[a]P following dermal exposures cannot be made. Regressive verrucae were noted to have occurred in 26 patients within a 4-month period when they were given daily applications of a 1% solution of B[a]P (Cottini and Mazzone 1939). This study did not employ a control group; therefore, definitive conclusions concerning the dermal toxicity of B[a]P cannot be made. However, occupational exposures to complex mixtures and industrial processes that include PAHs have been evaluated by IARC (1973). Toxic effects included a variety of skin lesions and noncancer lung diseases such as bronchitis. However, it is not possible to determine from these studies the effect of individual PAHs.

A single subchronic dermal study conducted in hairless mice suggests that dermal application of 0.05 mg of a 1% B[a]P solution had adverse effects on the skin (Elgjo 1968). This study did not employ a control group; therefore, definitive conclusions concerning the dermal toxicity of B[a]P cannot be made. In a number of older investigations, acute topical application (e.g., 4 days) of B[a]P has been reported to suppress or even destroy sebaceous glands in mouse skin (Bock and Mund 1958, Suntzeff et al. 1955). These studies also did not employ control groups; therefore, it is not possible to determine if the effects seen were due to solvent and/or the preparation procedures.

No other studies were identified in the literature concerning the dermal toxicity of B[a]P by any other routes of administration.

4.3.3 Reproductive and Developmental Toxicity

4.3.3.1 Overview

There are no studies available on the reproductive/developmental effects of B[a]P in humans. The reproductive/developmental toxicity of B[a]P following inhalation or dermal exposure has not been investigated in experimental animals. The results of two oral studies in mice (MacKenzie and Angevine 1981, Legraverend et al. 1984) and one in rats

(Rigdon and Rennels 1964) indicate that in utero exposure to B[a]P is associated with developmental toxicity and adverse reproductive effects. A modified two-generation oral study in mice demonstrated the reproductive toxicity of B[a]P, which included a decreased fertility index and a high incidence of sterility in progeny (Mackenzie and Angevine 1981). Developmental toxicity was also observed; the mean pup weight of mice was significantly different from the controls. Other investigators have reported an increased incidence of stillbirths, resorptions, and malformations in selected mouse strains occurring following oral exposure (Legraverend et al. 1984). These investigators indicated that B[a]P-induced in utero toxicity and teratogenicity are directly related to the maternal and/or embryonal genotype controlled by the Ah locus (Legraverend et al. 1984).

4.3.3.2 Inhalation

Pertinent data about the reproductive and developmental toxicity of B[a]P in humans or experimental animals following inhalation exposure could not be found in the available literature.

4.3.3.3 Oral

Pertinent data about the reproductive and developmental toxicity of B[a]P in humans following oral exposure could not be found in the available literature.

Rigdon and Rennels (1964) conducted two series of experiments in rats to examine the effect of dietary B[a]P on reproductive consequences. The studies are suggestive of a reproductive effect of B[a]P; however, the small numbers of animals used in this experiment do not permit any firm conclusions. In the first experiment, 8 male and 8 female rats were administered 1 mg of B[a]P per gram of food. Control groups consisting of 6 males and 6 females were fed a standard diet. Treated females were mated with control males, and control females were mated with B[a]P-treated males. Vaginal smears were taken during a 28-day period beginning with the first day of B[a]P feeding. No treatment-related effects on estrus were observed. Of the treated females, 5 became pregnant compared to 3 pregnant controls. However, only 1 of the treated females delivered; it delivered a total of 4 pups. Two of the 4 pups were stillborn; one was grossly malformed. The pups born alive died 3 days postpartum, presumably of starvation. In the second experiment, 7 control male and female rats were mated as were 7 B[a]P-fed males and females. Control rats had normal pregnancies. Only 2 B[a]P-fed females of 7 mated became pregnant. An autopsy revealed that 1 dam carried 4 dead fetuses and that fetal resorption occurred in the other. Rigdon and Neal (1965) did not find deleterious reproductive/developmental effects in Swiss mice fed diets containing 0.25, 0.50, or 1.0 mg B[a]P per gram of food over various time spans during mating, gestation, and postpartum.

Sheveleva (1978) administered B[a]P by gavage to rats at doses of 0, 0.05, 0.5, or 5 mg/kg/day on days 1-15, 3-4, or 9-10 of pregnancy. The dams receiving 0.5 and 5 mg/kg on days 1-15 showed signs of maternal toxicity including decreased weight gain and hematological changes. At these doses there were dose-related increases in preimplantation and

postimplantation losses, decreased live fetuses/dam, and decreased fetal weights on day 20. At all dose groups, fetuses showed hydronephrosis and bladder dilation. When B[a]P was administered on days 3-4 and 9-10, postimplantation losses and decreased fetal weights were reported. It is not clear if those results applied to all three dose levels. These experiments provide suggestive evidence that B[a]P produces adverse reproductive/developmental effects in rats at doses that are not associated with maternal toxicity. However, no quantitative data were reported; therefore, the results cannot be validated.

Mackenzie and Angevine (1981) investigated the effects of B[a]P on pregnancy maintenance and on fetal development and survival. Groups of CD-1 mice were administered daily oral (intubation) B[a]P doses of 0, 10, 40, or 160 mg/kg maternal body weight from the 7th to 16th days of gestation. There were 30 to 60 females per dose group. No maternal toxicity was observed at any dose tested. The mean litter size was comparable among groups, and all litters appeared normal by gross observation. The percentage of pregnant females and viable litters at parturition was significantly reduced in the 160 mg/kg/day dosage group. The mean pup weight by 42 days of age was significantly different from controls in all three groups administered B[a]P. The F_1 progeny were bred to untreated animals and further studied for postnatal development and reproductive function. The fertility index was significantly decreased for F_1 males and females in all treatment groups. Total sterility was observed in F_1 males from the 160 mg/kg/day treatment group and in F_1 females from both the 40 and 160 mg/kg/day treatment groups. Fertility was severely reduced in animals in the 10 mg/kg/day dose group; the mean number of litters and litter size of F_1 females in this group were significantly lower than in the controls. This infertility was associated with significant alterations in gonadal morphology and germ-cell development. There was a significant decrease in testicular weight, atrophic seminiferous tubules, and germ-cell aplasia. Most of the females had no ovaries or only remnants of ovarian tissue. Ovarian tissue in females exposed to 10 mg/kg/day was hypoplastic with reduced follicles and corpora lutea. There were no gross abnormalities in the F_2 offspring from the F_1 breeding studies and no significant differences among treatment groups in the F_2 offspring body weights at 4 and 20 days of age. The authors concluded that in utero exposure to B[a]P at doses of 10 mg/kg/day throughout the period of major organogenesis resulted in impaired reproductive capacity and developmental effects in male and female mice. Based on this study, a LOAEL for reproductive toxicity and developmental effects of 10 mg/kg/day was determined. The study by Mackenzie and Angevine (1981) was generally well conducted, and the data were appropriately analyzed; however, treated fetuses were not examined for skeletal effects and effects on other internal organs. A NOAEL could not be identified.

The effect of genetic differences in B[a]P metabolism on in utero toxicity and teratogenicity has been evaluated by the oral route (Legraverend et al. 1984). B[a]P metabolism occurs more readily in mice that are genetically Ah-responsive than in those that are Ah-nonresponsive. Legraverend et al. (1984) fed pregnant mice, either B6AKF1 Ah-responsive or AKR/J Ah-nonresponsive, ~120 mg/kg/day B[a]P on days 2 through 10 of gestation. Control mice received food soaked in the

corn oil vehicle alone. β-Naphthoflavone was given intraperitoneally on day 16 of gestation in order to help distinguish between fetuses of different Ah-genotypes. Oral B[a]P treatment in the AKR/J mouse resulted in more stillbirths, resorptions, and malformations among Ah-nonresponsive compared with the Ah-responsive embryos. No differences in in utero toxicity or teratogenicity were observed in Ah-genetically different litter mates from an Ah-responsive mother. Legraverend et al. (1984) concluded that the differences are specific to the route of administration and can be attributed to "first-pass" liver metabolism occurring with oral dosing. Although this was a well-designed and well-conducted experiment, only one dose group was evaluated in this study, and no quantitative comparisons between treated groups and corresponding control animals were presented for any of the reported in utero toxic or teratogenic effects.

4.3.3.4 Dermal

Pertinent data about the reproductive and developmental toxicity of B[a]P in humans or experimental animals following dermal exposure could not be found in the available literature.

4.3.3.5 General discussion

There are no studies available on the reproductive/developmental effects of B[a]P in humans. Placental transfer of B[a]P has been shown in the mouse (Shendrikova et al. 1974, Shendrikova and Aleksandrov 1974) following intravenous injection and oral administration, respectively. The results of two oral studies in mice (Mackenzie and Angevine 1981, Legraverend et al. 1984) and one in rats (Rigdon and Rennels 1964) indicate that in utero exposure to B[a]P is associated with developmental toxicity and adverse reproductive effects. Adverse developmental/reproductive effects resulted from oral exposure to doses of B[a]P of 10 mg/kg/day (Mackenzie and Angevine 1981). Investigations by Legraverend et al. (1984) suggest that it is B[a]P and not a metabolite of B[a]P which is responsible for these adverse effects. No data were available in experimental animals regarding the reproductive and developmental effects of B[a]P following inhalation or dermal exposures. However, adverse reproductive/developmental effects were observed in several injection studies. Adverse effects observed following intraperitoneal injection of B[a]P in mice included: stillbirths, resorptions, and malformations (Shum et al. 1979, Hoshino et al. 1981); decreases in follicular growth and corpora lutea (Swartz and Mattison 1985, Payne 1958); testicular changes (i.e., atrophy of seminiferous tubules with absent spermatids and spermatozoa, interstitial cell tumors) (Payne 1958); immunosuppression (Urso and Gengozian 1980); and tumor induction (Bulay and Wattenberg 1971). Adverse effects observed following subcutaneous injection of B[a]P include increased fetal resorptions in rats (Wolfe and Bryan 1939) and tumor induction in mice (Nikonova 1977). Decreased fetal survival was reported in Swiss mice following direct embryonal injection of B[a]P (Barbieri et al. 1986).

4.3.4 Genotoxicity

4.3.4.1 Overview

The genetic toxicity of B[a]P has been evaluated experimentally in a variety of short-term genetic toxicology assays. B[a]P has been tested extensively in vivo in rodents and insects, measuring genotoxic effects at various genetic end points in both germ cells and somatic cells. In addition, B[a]P has been tested extensively in several bacterial and mammalian cell systems and has been chosen as a positive control or model test compound for the validation of some of these test systems. The test systems used to evaluate B[a]P's genotoxicity and the results of each are summarized in Tables 4.1 and 4.2.

B[a]P undergoes metabolism to form reactive electrophilic intermediates capable of interacting with nucleophilic macromolecules within the target cell, most notably, binding covalently to DNA (Williams and Weisburger 1986, Miller 1970, Lutz 1979). These reactive metabolites form bulky DNA adducts, which are generally regarded as an important determinant in mutagenesis and in clastogenesis (Brendel and Ruhland 1984, Fahl et al. 1981). The genotoxicity of B[a]P is dependent on metabolic activation, either exogenously supplied or endogenously present.

4.3.4.2 General discussion

B[a]P has been tested for in vivo heritable genetic effects. The most extensively used test for the induction of heritable mutations is the mouse-specific locus test. B[a]P exposure via injection produced negative results in this assay (Russell and Russell 1978, Russell 1978, Russell et al. 1981). Mixed results have been reported in mutation studies with *Drosophila melanogaster*. Positive results were reported for sex-linked recessive lethal mutations (Nguyen et al. 1979, Vogel et al. 1983) and dominant lethal mutations (Nguyen et al. 1979), as well as somatic mutations (Fahmy and Fahmy 1973, 1980) in this insect species. However, negative results were reported for sex-linked recessive lethal mutations in *Drosophila* by other researchers (Valencia and Houtchens 1981, Zijlstra and Vogel 1984).

B[a]P has also been tested in vivo for other genetic end points in both germ cells and somatic cells. B[a]P exposure via injection produced negative results in the mouse germ cell heritable translocation assay (Generoso et al. 1982), but positive results were observed in the mouse germ cell dominant-lethal mutation test (Generoso et al. 1982, Epstein et al. 1972, Epstein and Shafner 1968). In vivo B[a]P exposure has resulted in aneuploidy (male sex chromosome loss) in *Drosophila melanogaster* (Vogel et al. 1983), chromosomal aberrations in hamster spermatogonia (Basler and Rohrborn 1978), morphological abnormality in mouse spermhead (Bruce and Heddle 1979, Topham 1980, Wyrobek et al. 1981), and unscheduled DNA synthesis (UDS) in male mouse germ cells (Sega 1979). There is no evidence to indicate that the occurrence of UDS in germ cells of male mice affect mutation frequencies in these cells. Generally, positive genotoxic responses have been reported in somatic cells. Positive results were observed in the mouse somatic mutation or spot test following oral exposure (Davidson and Dawson 1976, 1977;

Table 4.1. Genetic toxicity of benzo[a]pyrene (in vitro)

End points	Species (test systems)	Results w or w/o activation[a]	References
DNA damage	*Escherichia coli K12* (prophage induction)	Positive w activation	Ho and Ho 1981, Moreau et al. 1976
	Escherichia coli (pol A−/pol A+)	Positive w activation	Rosenkranz and Poirier 1979
	Escherichia coli (rec+/rec−)	Positive w activation	Mamber et al. 1983, Ichinotsubo et al. 1977, Tweats 1981
	Bacillus subtilis (rec+/rec−)	Positive w activation	McCarroll et al. 1981
	Rat hepatocytes (DNA single strand breaks)	Positive w/o activation	Sina et al. 1983
Mitotic recombination	*Saccharomyces cerevisiae*	Negative w activation	Simmon 1979b, Kassinova et al. 1981
DNA damage/repair (UDS)	Syrian hamster embryo cells	Positive w/o activation	Casto et al. 1977
	Rat tracheal epithelial cells	Positive w/o activation	Ide et al. 1981
	Primary rat hepatocytes	Positive w/o activation	Probst et al. 1981; Tong et al. 1981a,b; Williams et al. 1982
	Human fibroblasts	Positive w activation	Agrelo and Amos 1981, Agrelo and Severn 1981, Robinson and Mitchell 1981
	Human amnion cells	Positive w activation	Yu et al. 1983
	Human foreskin epithelial cells	Positive w activation	Lake et al. 1978
	HeLa cells	Positive w activation	Martin et al. 1978, Martin and McDermid 1981
Gene mutations	*Salmonella typhimurium, strain* TM677 (8AGs/8AGr)	Positive w activation	Kaden et al. 1979
	Salmonella typhimurium (his+/his−): strains TA98, TA100, TA1538	Positive w activation	Glatt et al. 1981, Hollstein et al. 1979, Probst et al. 1981, Rosenkranz and Poirier 1979, Simmon 1979a, Wislocki et al. 1976, Bruce and Heddle 1979
	Salmonella typhimurium (rodent body fluids) TA98, TA100, TA1538	Positive w/o activation	Connor et al. 1979, Battzinger et al. 1978

Table 4.1 (continued)

End points	Species (test systems)	Results w or w/o activation[a]	References
Gene mutations (continued)	*Salmonella typhimurium* host-mediated assay	Negative w/o activation	Glatt et al. 1985, Simmon et al. 1979
	Chinese hamster lung cells (V79)/APRT (8-AG)	Positive w activation	Huberman 1975, Wislocki et al. 1976, Kuroki et al. 1979
	V79/HGPRT (6-TG)	Positive w activation	Jones et al. 1983, Krahn and Heidelberger 1977
	V79/Na+,K+ ATPase (Ouabain)	Positive w activation	Bradley et al. 1981, Hsu et al. 1979, Langenbach et al. 1978, Kuroki et al. 1979
	Chinese hamster ovary (CHO)/HGPRT	Positive w activation	Bermudez et al. 1982, Li 1982, Gupta and Singh 1982, Machanoff et al. 1981
	CHO/Na+,K+ ATPase (Ouabain)	Positive w activation	Li 1982, Gupta and Singh 1982
	C3H 10T1/2/Na+,K+ ATPase (Ouabain)	Positive w activation	Gehly et al. 1982
	Mouse lymphoma L5178Y/TK+/−	Positive w activation	Amacher and Paillet 1982, 1983; Clive et al. 1979; Jotz and Mitchell 1981; Thornton et al. 1982
	Adult rat liver (ARL)/HGPRT	Positive w/o activation	Tong et al. 1980, 1981b
	Human fibroblasts/HGPRT	Positive w activation	Tong et al. 1981c
	Human fibroblasts (diphtheria toxin)	Positive w activation	Gupta and Goldstein 1981
	Human EUE epithelial-like cells (diphtheria toxin)	Positive w/o activation	Rocchi et al. 1980
Sister chromatid exchange	V79	Positive w activation	Popescu et al. 1977, Wojciechowski et al. 1981
	Don cells	Positive w/o activation	Baker et al. 1983
	CHO	Positive w activation	Hopkins and Perry 1980, Pal et al. 1978
	Syrian hamster cells	Positive w/o activation	Popescu et al. 1981
	ARL	Positive w/o activation	Tong et al. 1981a
	H4-II-E (rat hepatoma cells)	Positive w/o activation	Dean et al. 1983

Table 4.1 (continued)

End points	Species (test systems)	Results w or w/o activation[a]	References
Sister chromatid exchange (continued)	HTC (rat hepatic tumor cells)	Positive w/o activation	Dean et al. 1980
	Human hepatoma cells (C-HC-4 and C-HC-20)	Positive w/o activation	Abe et al. 1983a,b
	Human lymphocytes	Positive w activation	Hopkins and Perry 1980, Rudiger et al. 1976
	Human lymphocytes	Positive w/o activation	Craig-Holmes and Shaw 1977
Chromosomal aberrations	V79	Positive w activation	Matsuoka et al. 1979, Popescu et al. 1977
	V79	Positive w/o activation	Kocchar 1982
	Mouse C3H 10T1/2 fibroblasts	Positive w activation	Gehly et al. 1982
	Rat cells	Positive w/o activation	Dean 1981
	CHO	Positive w activation	Whitehead et al. 1983
Cellular transformation	Syrian hamster embryo cells (clonal assay)	Positive w/o activation	DiPaolo et al. 1969, 1971; Popescu et al. 1981; Huberman 1975; Pienta et al. 1977; Amacher and Zelljadt 1983
	Syrian hamster embryo cells (focal assay)	Positive w/o activation	Casto et al. 1977
	RLV/Fischer rat embryo cells	Positive w activation	Mishra et al. 1978, Dunkel et al. 1981, Rhim et al. 1972
	Mouse embryo AKR	Positive w/o activation	Rhim et al. 1972, 1973, 1974
	Mouse BALB/C3T3 cells	Positive w/o activation	Sivak et al. 1980, Dunkel et al. 1981
	Mouse C3H10T1/2 cells	Positive w/o activation	Lubet et al. 1983
	Mouse C3H10T1/2 fibroblasts	Positive w activation	Gehly et al. 1982
	SA7/Syrian hamster embryo cells	Positive w/o activation	Casto et al. 1977
	SA7/rat embryo cells	Positive w/o activation	DiPaolo and Casto 1976
	Mouse C3H/M2 prostate cells	Positive w/o activation	Marquardt et al. 1976

[a]The results presented in Tables 4.1 and 4.2 are based on the activity profiles prepared by Waters et al. (1987), Gene-Tox listings from John S. Wassom, and/or personal review of the original citation.

Table 4.2. Genetic toxicity of benzo(a)pyrene (in vivo)

End points	Species (test systems)	Results[a]	References
DNA damage (UDS)	Rat hepatocytes	Negative	Mirsalis et al. 1982
	Mouse germ cells (male)	Positive	Sega 1979
Gene mutations	*Drosophila melanogaster* (somatic mutation)	Positive	Fahmy and Fahmy 1973, 1980
	Drosophila melanogaster (sex-linked recessive lethal)	Positive	Vogel et al. 1983, Nguyen et al. 1979
	Drosophila melanogaster (sex-linked dominant lethal)	Positive	Nguyen et al. 1979
	Drosphila melanogaster (sex-linked recessive lethal)	Negative	Valencia and Houtchens 1981, Zijlstra and Vogel 1984
	Mouse somatic cell (spot test)	Positive	Brusick 1980; Russell 1977, 1978; Davidson and Dawson 1976, 1977
	Mouse-specific locus test	Negative	Russell and Russell 1978, Russell 1978, Russell et al. 1981
Sister chromatid exchange	Mouse bone marrow cells	Positive	Schreck and Latt 1980, Paika et al. 1981
	C3H mouse diffusion chamber (V79 - target cell)	Positive	Sirianni and Huang 1978
	Chinese hamster bone marrow cells	Positive	Bayer and Bauknecht 1977, Basler et al. 1979, Roszinsky-Kocher et al. 1979
Chromosomal aberrations	*Drosophila melanogaster* (aneuploidy: male sex chromosome loss)	Positive	Vogel et al. 1983
	Drosophila melanogaster (aneuploidy: female germ cell chromosome gain)	Negative	Valencia et al. 1984, Fabian and Matoltsy 1946
	Chinese hamster bone marrow cells	Positive	Roszinsky-Kocher et al. 1979
	Chinese hamster bone marrow cells	Negative	Basler et al. 1979
	Hamster spermatogonia	Positive	Basler and Rohrborn 1978
	Long Evans rat bone marrow cells	Positive	Rees et al. 1970
	Mouse micronuclei	Positive	Kirkhart 1981, Salamone et al. 1981
	Mouse micronuclei	Negative	Bruce and Heddle 1979
	Mouse germ cell dominant lethal	Positive	Epstein and Shafner 1968, Epstein et al. 1972, Generoso et al. 1982
	Mouse germ cell heritable translocation	Negative	Generoso et al. 1982
Morphological abnormality	Mouse sperm head	Positive	Bruce and Heddle 1979, Topham 1980, Wyrobek et al. 1981

[a]The results presented in Tables 4.1 and 4.2 are based on the activity profiles prepared by Waters et al. (1987), GeneTox listings from John S. Wassom, and/or personal review of the original citation.

Russell 1977, 1978). B[a]P has been chosen as a positive control in the mouse spot test (Brusick 1980, Russell 1977). The induction of sister chromatid exchange (SCE) by B[a]P in bone marrow cells of mice (Schreck and Latt 1980, Paika et al. 1981) and Chinese hamsters (Basler et al. 1979, Bayer and Bauknecht 1977, Roszinsky-Kocher et al. 1979) has been demonstrated. Mixed results have been reported for chromosomal aberrations in Chinese hamster bone marrow cells (Basler et al. 1979, Roszinsky-Kocher et al. 1979) and mouse micronuclei (Bruce and Heddle 1979, Kirkhart 1981, Salamone et al. 1981).

B[a]P shows positive mutagenic activity in vitro in several strains of *Salmonella typhimurium* in the presence of either rodent microsomes or hepatocytes for exogenous metabolic activation. Negative results were reported for host-mediated activation (Glatt et al. 1985, Simmon et al. 1979). Body fluids from rodents exposed in vivo to B[a]P showed positive mutagenic activity in three strains of *Salmonella typhimurium* (Batzinger et al. 1978, Connor et al. 1979). Generally, B[a]P shows positive genotoxic activity in in vitro mammalian cell systems with either exogenous or endogenous metabolic activation.

Several established cell lines, both rodent and human, have recently been shown to possess endogenous bioactivating capabilities for *many agents, along with providing targets for measures of genotoxicity.* For example, the induction of point mutations at the HGPRT locus and/or SCEs in intact cell systems of adult rat-liver (ARL) epithelial cells (Tong et al. 1981a,b) and rat hepatoma (HTC and H4-II-E) cells (Dean et al. 1980, 1983) has been demonstrated following in vitro B[a]P exposure. Metabolic activation of B[a]P has been demonstrated by several cultured human hepatoma cell lines. Two of these human hepatoma cell lines, CHC-4 and CHC-20, acted as targets for genotoxic action (e.g., SCE induction) (Abe et al. 1983a,b), while the other human cell lines served as mediators of activation, resulting in SCE induction in human fibroblasts (Huh et al. 1982) and point mutations in V79 cells (Diamond et al. 1980). Other human cells and tissues have also been shown to metabolize B[a]P (Huh et al. 1982).

There is sufficient evidence from short-term in vivo and in vitro genetic toxicology tests to prove that B[a]P is a potent genotoxic agent when metabolically activated. There is sufficient evidence that B[a]P interacts with mammalian gonads or germ cell DNA and it induces such end points as unscheduled DNA synthesis (Sega 1979), chromosomal aberrations (Basler and Rohrborn 1978), and morphological abnormalities (Wyrobek et al. 1981). However, B[a]P is present as a component of the total content of PAHs in the environment. How interactions among various PAHs affect their potential for human genotoxicity is uncertain. Other components of PAH mixtures also demonstrate genotoxicity. Therefore, it is reasonable to assume that exposure to genotoxic components of PAH mixtures will present a risk to humans by inducing heritable genetic damage and potential human carcinogenesis.

4.3.5 Carcinogenicity

4.3.5.1 Overview

B[a]P is a moderately potent experimental carcinogen in many species by many routes of exposure (IARC 1983). There are no reports directly correlating human B[a]P exposure and tumor development, although humans are likely to be exposed by all routes. There are a number of reports associating human cancer and exposure to mixtures of PAHs that include B[a]P. In view of these observations and its well-established carcinogenic activity in laboratory animals, it is reasonable to conclude that B[a]P would be expected to be carcinogenic in humans by all routes of exposure.

4.3.5.2 Inhalation

Human. No studies on the carcinogenicity of B[a]P in humans following inhalation exposure were found in the available literature. However, epidemiologic studies have shown an increased incidence of lung cancer in humans exposed to coke oven emissions (Lloyd 1971, Redmond et al. 1972, Mazumdar et al. 1975), roofing tar emissions (Hammond et al. 1976), and cigarette smoke (Wynder and Hoffmann 1967, Maclure and MacMahon 1980, Schottenfeld and Fraumeni 1982). Each of these mixtures contains B[a]P as well as other carcinogenic PAHs and other potentially carcinogenic chemicals, such as nitrosamines. It is thus impossible to evaluate the contribution of B[a]P to the total carcinogenicity of these mixtures in humans because of their complexity and the presence of other carcinogens. Reports of this nature provide qualitative evidence of the potential for B[a]P-induced carcinogenicity nonetheless.

Animal. B[a]P has elicited lung tumors in several bioassay systems following inhalation exposure or intratracheal instillation. Its carcinogenic potency is enhanced by coadministration of particulate matter or some gases (IARC 1983).

Few studies have investigated the carcinogenicity of B[a]P alone by the inhalation route of exposure; most of these have obtained negative results (Laskin et al. 1970). A notable exception is the study of Thyssen et al. (1981) that provides clear-cut evidence of a dose-response relationship between inhaled B[a]P and respiratory tract tumorigenesis. The protocol and results of this key study are summarized in Table 4.3. Respiratory tract tumors were induced in the nasal cavity, larynx, and trachea of animals in the two highest dose groups; lung tumors were absent, although there is some evidence that hamster lung tissue can activate B[a]P as well as the other respiratory tract tissues (Dahl et al. 1985). Tumors related to exposure also occurred in the pharynx, esophagus, and forestomach (presumably as a consequence of mucociliary particle clearance) and were papillomas, papillary polyps, and squamous cell carcinomas. Length of survival decreased with increasing B[a]P concentration.

In another experiment, respiratory tract tumors were observed in rats using a combination of B[a]P and the atmospheric irritant sulfur

Table 4.3. Dose-response relationship between inhaled benzo[a]pyrene and respiratory tract tumors in hamsters[a]

Exposure rate (x) (mg/m^3 B[a]P)	Average survival (t) (weeks)	Effective number exposed	Number of respiratory tract tumors observed
0.0	96.4	27	0
2.2	95.2	27	0
9.5	96.4	26	9
46.5	59.5	25	13

[a]Groups of 24 male Syrian golden hamsters each were exposed throughout their lives to B[a]P in a sodium chloride aerosol for 4.5 h/day, 7 days/week for 10 weeks and then 3 h/day thereafter at dose levels of 2.2, 9.5, or 45.6 mg/m^3 air. Animals that died during the first year of the experiment were replaced, which may account for the discrepancy between the authors' statement that there were 24 hamsters per group and their reported "effective number exposed."

Source: Thyssen et al. 1981.

dioxide (SO_2); sulfur dioxide by itself was not carcinogenic (Laskin et al. 1970). Rats were exposed to 10 mg/m^3 B[a]P for 1 h/day for 1 year in the presence or absence of 10 ppm SO_2 for an additional 6 h/day. Squamous cell carcinomas developed in the lungs of 2/21 rats exposed to B[a]P alone and 5/21 rats exposed to both.

In contrast, intratracheal instillation experiments have produced greater yields of B[a]P-induced lung tumors. Vehicles used, and their effects on tumorigenicity, have varied widely. For example, a number of studies have demonstrated the effects of intratracheal instillation of B[a]P-coated Fe_2O_3 particles (Saffiotti et al. 1972, Stenback et al. 1975) and MgO dust (Stenback et al. 1975) in hamsters, although each of these studies failed to include a group receiving B[a]P alone, negating an evaluation of the extent of cocarcinogenic activity of the dusts used (if any). Sellakumar et al. (1976), however, showed that coadministration of Fe_2O_3 and B[a]P by intratracheal instillation in hamsters increased the percentage of respiratory tract tumor-bearing animals from 15 to 71%, as compared to administration of B[a]P alone. In this experiment, administering Fe_2O_3 either prior to or following B[a]P treatment had no effect, supporting the contention that Fe_2O_3 is a cocarcinogen. Harris et al. (1971) reported basal cell hyperplasia of the upper respiratory tract when Fe_2O_3 was administered; the induction of hyperplasia is consistent with one of the proposed mechanisms of action of cocarcinogens. Stenback et al. (1976) and Stenback and Rowland (1979) observed pulmonary interstitial cell proliferation and bronchial epithelial alterations following intratracheal instillation of several dusts in hamsters, including titanium dioxide, aluminum oxide, carbon, ferric oxide, silicon dioxide, manganese dioxide, and agar gelatin. In these experiments, B[a]P alone induced few tumors, while coadministration of B[a]P and dusts elicited a variety of benign and malignant respiratory tract tumors, depending on the dust used. A significant proportion of forestomach tumors were also observed, indicating that ingestion exposure occurred following the mucociliary clearance of particles. Henry et al. (1973) produced tumors in the respiratory tracts of hamsters with a colloidal suspension of B[a]P and gelatin/NaCl; Feron et al. (1973) observed a dose-response relationship with B[a]P and a NaCl solution. In another experiment, coadministration of noncarcinogenic furfural resulted in the earlier appearance of epithelial metaplasia and a shorter latency period for tracheobronchial tumors (Feron 1972). Other experiments with hamsters have failed to demonstrate dose-response relationships, presumably due to excess toxicity-related mortality in higher dose groups (Ketkar et al. 1979, 1978). Dose-response relationships were demonstrated for B[a]P and lung tumor formation following intratracheal instillation with and without coadministration of carbon black in Wistar rats (Davis et al. 1975). In a preliminary report, intratracheal instillation of B[a]P and ferric oxide induced squamous carcinoma of the lung in subhuman primates (lesser bush babies, *Galago crassicaudatus*) (Crocker et al. 1970).

Deutsch-Wenzel et al. (1983) tested B[a]P for carcinogenicity by direct injection of a single dose (0.1-1.0 mg) in a trioctanoin/beeswax vehicle into the lungs of female Osborne-Mendel rats. Upon injection, the mixture congealed into a pellet, from which B[a]P diffused over time into the surrounding lung tissue. Epidermoid carcinomas and pleomorphic

sarcomas were observed, and dose-response relationships were obtained. The treatment method involved some trauma to the animals. Tumor induction times were difficult to observe, so survival time and the number of tumor-bearing animals were the responses evaluated. Table 4.4 shows the results. The reduced survival rates of the higher dose groups probably reduced the tumor incidences observed.

There are several possible reasons why inhalation bioassays of B[a]P have failed to produce lung tumors in contrast to intratracheal instillation or injection:

1. Sufficient doses of B[a]P may not have been deposited and retained following inhalation exposure (Harris and Autrup 1983).

2. Elution of B[a]P from carrier particles or wax may be slow, maximizing exposure duration in the case of intratracheal instillation or injection.

3. Mucociliary clearance mechanisms may be impaired by toxicity resulting from direct instillation, thus increasing exposure duration.

4. Direct instillation or injection involves some trauma and necrotic activity, which can result in regenerative hyperplasia. Increasing the number of proliferating cells (as in the case of hyperplasia) can increase the number of cells at risk of B[a]P-induced mutagenic and potentially carcinogenic events (Hirakawa et al. 1979).

5. B[a]P is only a moderately potent respiratory tract carcinogen.

The inhalation study of Thyssen et al. (1981) is the least likely to be confounded by artifacts of intratracheal instillation or injection procedures and can be extrapolated more directly to human routes of exposure.

4.3.5.3 Oral

Human. No studies on the carcinogenicity of B[a]P in humans following oral exposure were found in the available literature.

Animal. B[a]P ingestion has been associated with tumor development in both mice and rats. Dietary B[a]P elicited papillomas and carcinomas in the forestomach of male and female Swiss mice in a series of experiments in which doses of 0-250 ppm B[a]P in the diet were consumed for 1-197 days and animals were observed for 70-300 days (Neal and Rigdon 1967). The details and results of this key study are depicted in Table 4.5. The lack of a consistent protocol in these experiments and other factors, such as variable age of first exposure, a duration of exposure that only lasted ~1/7 of a lifetime, and an observation period that was <1/5 of a lifetime, make it difficult to reliably quantitate a dose-response relation. Furthermore, tumors were reported as combined papillomas and carcinomas, so that no distinction between these benign and malignant tumors can be made. The same authors found an association between dietary B[a]P at concentrations of 0, 250, and 1000 ppm

Table 4.4. Tumor dose-response relationships for benzo[a]pyrene injected into rat lungs[a]

Compound	Dose (mg)	Number of animals	Median survival time (weeks) (95% confidence interval)	Number of animals bearing epidermoid carcinomas/number of animals bearing pleomorphic sarcomas	Tumor incidence (%)
B[a]P	0.1	35	111 (95-120)	4/6	28.6
B[a]P	0.3	35	77 (68-99)	21/2	65.7
B[a]P	1.0	35	54 (46-64)	33/0	94.3
BW-TC[b]		35	104 (91-121)	0/0	0.0
Untreated control		35	118 (104-133)	0/0	0.0

[a]Single doses of B[a]P were injected into the left lung of female Osborne-Mendel rats in a vehicle of molten trioctanoin/beeswax, which congealed and permitted gradual diffusion of B[a]P into lung tissue over time.

[b]Beeswax and trioctanoin (vehicle).

Source: Deutsch-Wenzel et al. (1983).

Table 4.5. Forestomach tumors in mice fed benzo[a]pyrene[a]

Age first exposed (days)	Concentration of B[a]P in food (mg/g)	Number of days fed B[a]P	Age killed (days)	Number with forestomach tumors/ number of mice
	0.0		300	0/289
30	0.001	110	140	0/25
30	0.01	110	140	0/24
116	0.02	110	226	1/23
33-67	0.03	110	143-177	0/37
33-101	0.04	110	143-211	1/40
31-71	0.045	110	143-183	4/40
17-22	0.05	107-197	124-219	24/34
20-24	0.10	98-122	118-146	19/23
18-20	0.25	70-165	88-185	66/73
49	0.25	1	155	0/10
56	0.25	2	162	1/9
49	0.25	4	155	1/10
62	0.25	5	168	4/9
49	0.25	7	155	3/10
91	0.25	30	198	26/26
74	0.10	7	182	0/10
48	0.10	30	156	12/18
98-180	5.0	1	209-294	17/33

[a]Male and female Swiss mice received B[a]P in the diet for varying lengths of time. The sizes of the treatment groups were apparently the same as the numbers of mice reported in this table; treatment-related effects on survival thus cannot be evaluated.

Source: Adapted from Neal and Rigdon (1967).

administered to mice for different lengths of time and the development of leukemia and forestomach and lung tumors (Rigdon and Neal 1966, 1969). The results of these experiments are shown in Table 4.6. Tumor incidence was related to both dose and length of exposure (except in the case of leukemia). These studies have the same limitations as the Neal and Rigdon (1967) study. The Neal and Rigdon (1967) study provides the best dose-response information available for the oral route of exposure, despite the irregular protocol employed, although the relevance of forestomach tumors in rodents to human cancer is the subject of some controversy.

Mammary tumors have been induced by intragastric doses of B[a]P in female LEW/Mai rats (McCormick et al. 1981). Rats receiving a single dose of 50 mg B[a]P had a 77% incidence of mammary tumors after 90 weeks, whereas rats receiving 8 weekly doses of 6.25 mg had an incidence of 67%. The control rats had a high spontaneous mammary tumor rate of 30%, indicating that B[a]P can increase the rate at which spontaneous tumors develop, which is thought in some cases to occur via mechanisms other than direct mutation/initiation, possibly by affecting oncogene expression (Goldsworthy and Pitot 1985).

Intragastric doses of B[a]P have also been shown to elicit pulmonary adenomas and forestomach papillomas in female ICR/Ha, A/J, and A/HeJ mice (Sparnins et al. 1986, Wattenberg and Leong 1970, Wattenberg and Bueding 1986). As parts of experiments designed to evaluate the effectiveness of various inhibitors of carcinogenesis, B[a]P was administered by gavage to mice in the presence or absence of suspected inhibitors. For example, A/HeJ mice received two doses of 3 mg B[a]P in 0.25 mL sesame oil 2 h apart, which was repeated twice at approximately 2-week intervals (Wattenberg and Leong 1970); the pulmonary tumor count was found to rise from 0.3 ± 0.5 per mouse in the control group to 16.6 ± 7.7 in the treated group at 30 weeks of age. Of A/J mice receiving 2 mg B[a]P in 0.2 mL corn oil three times at 2-week intervals, 100% developed forestomach tumors (Sparnins et al. 1986); no controls were included, however.

4.3.5.4 Dermal

Human. No studies on the carcinogenicity of B[a]P in humans following dermal exposure were found in the available literature. As with inhalation exposure, however, there are reports of skin cancer among individuals exposed dermally to mixtures of PAHs containing B[a]P. The earliest of these is the report of Pott (1775) of scrotal cancer among chimney sweeps. More recently, skin cancer among those exposed dermally to shale oils has been reported (Purde and Etlin 1980). These reports provide only qualitative evidence of the carcinogenic potential of B[a]P in humans, however, because of the presence of other putative carcinogens in the mixtures.

Animal. B[a]P is a moderately potent experimental skin carcinogen, and it is often used as a positive control in bioassays of other agents. B[a]P was first reported to induce skin tumors in mice in 1933 (Cook et al. 1933, Cook 1933), although mixtures of PAHs that include B[a]P (such as coal tar) were shown to be dermal carcinogens in animals as early as

Table 4.6. Tumor incidence in mice fed benzo[a]pyrene[a]

Dose (ppm)	Duration of treatment (days)	Tumor type	Tumor incidence[a]
0	38-210+	Forestomach papilloma/carcinoma	2/175 (1)
		Lung adenoma	33/151 (19)
		Leukemia	0/175 (0)
250	80-140	Forestomach papilloma/carcinoma	69/108 (64)
		Lung adenoma	52/108 (48)
		Leukemia	40/108 (37)
250	72-99	Stomach papilloma/carcinoma	12/52 (23)
		Lung adenoma	26/52 (50)
250	147-196	Stomach papilloma/carcinoma	9/13 (69)
		Lung adenoma	10/13 (77)
1000	73-83	Stomach papilloma/carcinoma	5/9 (56)
		Lung adenoma	7/9 (78)
1000	127-187	Stomach papilloma/carcinoma	13/13 (100)
		Lung adenoma	3/13 (23)

[a]Male and female Swiss mice received B[a]P in the diet for varying lengths of time. The sizes of the treatment groups were apparently the same as the numbers of mice reported in this table; treatment-related effects on survival thus cannot be evaluated. In each case, the duration of the treatment was equal to the duration of the study.

[b]Data within parentheses indicate percentages.

Source: Adapted from Rigdon and Neal 1966, 1969.

1918 (Yamagiwa and Ichikawa 1918). B[a]P is active both as a "complete" carcinogen and as an initiator using initiation/promotion protocols. In its role as a positive control, B[a]P is usually administered at a single dose level, so that quantitative evaluation of dose-response relationships is not possible. For this reason, this discussion will be limited to key experiments employing more than one dose level.

In mice, the tumorigenic dose of B[a]P is dependent on the solvent used for delivery and on the strain of mice (IARC 1983). For example, Habs et al. (1980) tested B[a]P in acetone in order to determine its dose-response relationships as a carcinogen when topically applied, using a syringe, to the interscapular region of groups of 40 female NMRI mice twice weekly throughout their lifetimes. Table 4.7 lists the doses used and results obtained. A clear-cut dose-response relationship was seen for B[a]P and the induction of tumors, although the authors do not specify whether papillomas were considered to be tumors as well as carcinomas (however, this protocol usually produces only the latter). This strain of mice has a high (~70%) background incidence rate of systemic tumors, so an evaluation of the effects of B[a]P on any organ other than the site of administration was not possible.

Bingham and Falk (1969) applied graded concentrations of B[a]P topically to the backs of C3H/He mice (sex unspecified) three times per week for 50 weeks and quantitated local tumors. B[a]P was dissolved in decalin or a solution of *n*-dodecane and decalin (50:50 by weight), and 50 mg by weight of solution was administered at each dosing; however, the method of application was not specified. Table 4.8 shows the results of this experiment. Sample sizes were small and no decalin solvent controls were included; however, decalin is not considered to be carcinogenic. Use of the *n*-dodecane and decalin solvent mixture enhanced the potency of B[a]P significantly at lower doses in comparison with decalin alone.

Hoffmann and Wynder (1966) tested B[a]P for activity as a carcinogen or as a tumor initiator on mouse skin. For the carcinogenicity evaluations, female Ha/ICR/mil Swiss albino mice received three weekly topical applications of 0.05 or 0.1% solutions in dioxane for 1 year. The number of animals with papillomas observed at each dose is shown in Table 4.9. No tumors were observed in the dioxane vehicle controls. For the initiation/promotion experiments, ten doses of the B[a]P were applied in dioxane 2 days apart to the backs of mice for a total dose of 0.25 mg per mouse and followed by 2.5% croton oil in acetone. The frequency and duration of croton oil administration were unclear. Twenty-four of 30 animals (80%) developed tumors in the treated group, while 2 of 30 control animals (7%; croton oil alone) developed tumors. B[a]P was applied to mouse skin in both of these experiments using a brush; as a result, accurate dose quantitation is not possible.

As part of a study of the carcinogenicity of tobacco and its constituents, B[a]P was tested as a complete carcinogen on the skin of mice (Wynder and Hoffmann 1959). Groups of 20 to 30 female Swiss mice received concentrations of 0.001 to 0.01% of the test substances dissolved in acetone three times a week applied to their backs with a brush throughout their lifetimes. Table 4.10 shows the results of this experiment. No solvent control group was reported; however, no

Table 4.7. Benzo[a]pyrene-induced skin tumor rates in mice[a]

Compound	Applied dose (μg/animal)	Number of tumor-bearing animals/ total number of animals	Tumor incidence (%)
B[a]P	1.7	8/34	23.5
	2.8	24/35	68.6
	4.6	22/36	61.1
Acetone		0/35	0.0

[a]B[a]P in acetone was applied to the interscapular region of groups of 40 female NMRI mice twice weekly throughout their lives.

Source: Adapted from Habs et al. (1980).

Table 4.8. Tumor incidence following dermal exposure of mice to benzo[a]pyrene[a]

Vehicle	Dose		Tumor incidence[d]	
	Percent concentration[b]	mg/kg/day[c]	Malignant	Benign
Decalin	0.02	4.8	5/12 (42)	1/12 (8)
Decalin	0.002	0.48	0/20 (0)	0/20 (0)
Decalin	0.0002	0.048	0/21 (0)	0/21 (0)
Decalin	0.00002	0.0048	0/18 (0)	0/18 (0)
n-Dodecane + decalin[e]	0.02	5.4	10/16 (63)	5/16 (31)
n-Dodecane + decalin	0.002	0.54	7/26 (27)	2/26 (8)
n-Dodecane + decalin	0.0002	0.054	3/23 (13)	3/23 (13)
n-Dodecane + decalin	0.00002	0.0054	5/24 (21)	0/24 (0)
n-Dodecane + decalin	0.000002	0.00054	0/24 (0)	0/24 (0)
n-Dodecane + decalin	0	0	0/30 (0)	0/30 (0)

[a]Solutions of B[a]P were applied to the backs of C3H/He mice three times per week for 50 weeks. Approximately 50 mg of solution was applied at each dosing by an unspecified method.

[b]As determined by authors.

[c]Calculated by assuming that the density of decalin is 0.9 and the density of *n*-dodecane and decalin is 0.8, and adjusting for intermittent exposure by multiplying by 3/7.

[d]Data within parentheses indicate percentages.

[e]50:50 by weight.

Source: Bingham and Falk (1969).

Table 4.9. Carcinogenic activity of benzo[a]pyrene on mouse skin—I[a]

Compound	Dose (percent concentration)[b]	Number of tumor-bearing animals/ number of animals	Tumor incidence (%)
B[a]P	0.05	17/20	85
	0.01	19/20	95
Dioxane		0/20	0

[a]B[a]P in dioxane was applied to the backs of groups of 20 female Ha/ICR/mil Swiss mice three times weekly for one year.

[b]Equivalent to 50 and 10 mg B[a]P per dose, respectively (D. Hoffmann, personal communication).

Source: Hoffmann and Wynder (1966).

Table 4.10. Carcinogenic activity of benzo[a]pyrene on mouse skin—II[a]

Dose (percent concentration)[b]	Incidence of papillomas[c,d]	Incidence of carcinomas[c,d]
0.001	13/24 (54)	1/24 (4)
0.005	22/22 (100)	19/22 (86)
0.01	19/20 (95)	19/20 (95)

[a]B[a]P in acetone was applied to the backs of groups of 20 to 30 female Swiss mice three times weekly throughout their lives.

[b]Equivalent to 1, 5, and 10 mg B[a]P per dose, respectively (D. Hoffmann, personal communication).

[c]These numbers differ from those reported by the authors, who did not account for survival.

[d]Data within parentheses indicate percentages.

Source: Wynder and Hoffmann (1959).

papillomas or carcinomas were obtained for several other PAHs tested in the same experiment. A solvent control group would most likely have been negative as well. Again, dose quantitation is difficult due to the method of application. Dose-response relationships for B[a]P and skin tumors in mice were also demonstrated by Wynder et al. (1957, 1960).

Some of the dermal carcinogenicity experiments described in this section may have underestimated the potency of B[a]P because the ability of this compound to induce the enzymes responsible for its metabolic detoxication can reduce its carcinogenicity (Slaga and diGiovanni 1984). Levin et al. (1976) showed that doses of 0.1 nmol B[a]P (25 mg) administered to the backs of female C57Bl/6J mice as infrequently as once every 2 weeks produced a 94% tumor incidence after 60 weeks of treatment. More frequent administration would have been expected to reduce tumor incidence (Slaga and diGiovanni 1984, Weibel 1980).

B[a]P has also produced skin tumors in rats, rabbits, and guinea pigs (IARC 1973), although mice appear to be the most sensitive species.

4.3.5.5 General discussion

The most sensitive (occurs at the lowest doses) and well-studied end point of B[a]P-induced intermediate- and long-term toxicity is cancer. B[a]P has been shown to cause cancer in laboratory animals by all routes of exposure by which humans can expect to be exposed (inhalation, oral, dermal). In addition, B[a]P has elicited tumors in animals by several experimental routes of exposure such as intraperitoneal, intrapulmonary, and subcutaneous injection, as well as transplacentally (IARC 1973, 1983).

A series of steps is involved between exposure to B[a]P and tumor development; these involve metabolic activation and genotoxicity, as described in previous sections. Target tissues for B[a]P-induced carcinogenesis possess the ability to metabolically activate B[a]P to its reactive epoxide derivative. Covalent binding of reactive metabolites of B[a]P to DNA can occur and results in the formation of DNA adducts. This step appears to be essential for the production of B[a]P-induced neoplasia (Gelboin 1980, Weinstein et al. 1978).

B[a]P metabolites have been found to bind to DNA in every tissue that has been examined, regardless of species, dose, or route of administration. The physical nature of the adducts formed, the levels at which they occur, and the extent to which they persist unrepaired appear to be similar in various tissues, whether or not those tissues are likely to develop tumors (Stowers and Anderson 1985). Thus, the formation of B[a]P-DNA adducts is a necessary but not sufficient step for B[a]P-induced carcinogenesis; another step is also required.

B[a]P-induced mutation can result when a DNA adduct remains unrepaired and cell proliferation occurs. Mutations that result at sites critical to the regulation of cell differentiation or growth control may lead to malignancy. Marshall et al. (1984) have shown that reaction of B[a]P diol epoxide in vitro can lead to the activation of a transforming oncogene which, when introduced into the DNA of mammalian cells, can lead to mutation and transformation. The difference between the oncogene before and after activation is that of a single base-pair substitution.

Tissues that have higher rates of cell turnover, such as the skin and lung, appear to be target tissues for B[a]P-induced tumor formation, while those with slower rates, such as the liver, are not. The rate of cell proliferation can have an important influence on the rate at which mutation occurs and may account for the differences in susceptibility among tissues. For example, B[a]P does not usually cause liver tumors in rats. Performing partial hepatectomy on rats leads to a high rate of hepatic cell turnover. If partial hepatectomy is performed prior to B[a]P administration, tumors will occur in that organ (Hirakawa et al. 1979).

B[a]P is thus a moderately potent tumor initiator; its potency is related to the extent to which it is metabolized to its reactive epoxide metabolite, the extent to which that metabolite reacts with DNA, and the rate at which cell proliferation occurs in a potential target tissue.

4.4 INTERACTIONS WITH OTHER CHEMICALS

Most human exposures to B[a]P are not to the pure compound but to particle-bound B[a]P; the presence of particles is likely to affect its pharmacokinetics and carcinogenicity. Sun et al. (1982) showed that when B[a]P was particle-bound, it was cleared from hamster lungs much more slowly than a pure B[a]P aerosol, thus increasing the length of time the lungs were exposed and increasing the dose to the gastrointestinal tract as a result of mucociliary clearance. Respirable B[a]P-containing particulates such as diesel exhaust, when coated with the phospholipid component of a pulmonary surfactant, are genotoxic (Wallace et al. 1987). Dusts can increase the rates of pulmonary cell proliferation (Harris et al. 1971, Stenback et al. 1976, Stenback and Rowland 1979), which in turn increases the susceptibility of these cells to an initiation event in the presence of a carcinogen. Coadministration of B[a]P and particles greatly increases respiratory tract tumor yields in experimental animals (Stenback et al. 1976, Stenback and Rowland 1979). The effects of particles on B[a]P's potential human carcinogenicity is likely to be similar.

Human exposure to B[a]P in the environment occurs seldom, if ever, to B[a]P alone but to B[a]P as a component of complex mixtures of PAHs and other chemicals. Interactions between B[a]P and other mixture components are likely to occur. In particular, interactions may play a large part in carcinogenesis resulting from experimental exposure to PAHs. For example, Mahlum et al. (1984) have shown that different temperature-range distillates of coal liquids have different skin-tumor-initiating activities in mice, despite the fact that they contain similar levels of known carcinogenic PAHs. This difference is believed to be due to the modifying effects of the spectrum of noncarcinogenic PAHs obtained at different temperatures. Most of the PAH components of coal liquid fractions obtained at different temperatures will vary both qualitatively and quantitatively, and consequently their abilities to modify carcinogenesis will vary accordingly. Other experiments have shown that most PAH mixtures are considerably less potent than B[a]P alone. For example, various kinds of combustion emissions and B[a]P were tested for potency as tumor initiators on the skin of SENCAR mice (Slaga et al. 1980). Table 4.11 shows that the PAH mixtures were much less potent as tumor initiators than B[a]P. The authors calculated relative

Table 4.11. Relative tumor-initiating potency of various emission extracts and benzo[a]pyrene

Substance[a]	Relative potency[b] [based on papillomas/(mouse-mg)]
Benzo[a]pyrene	1.0
Roofing-tar emission extract	0.004
Coke-oven emission extract	0.007
Caterpillar diesel exhaust extract	0[c]
Oldsmobile diesel exhaust extract	0.002
Nissan diesel exhaust extract	0.007
Mustang gasoline exhaust extract	0.002
Cigarette-smoke condensate	0[c]

[a]Material was applied to Sencar mice once as initiator. Phorbol myristate acetate (2 μg), twice a week, was used as promoter. Emission exposures that were used in the relative potency calculations were restricted to the linear portion of the dose-response curve.

[b]As calculated by authors.

[c]These entries refer to potencies that were not significantly different from zero at $P = 0.05$.

Sources: Slaga et al. (1980) and NAS (1983).

potency estimates that ranged from 0.007 for coke oven emissions extract to less than 0.002 for diesel engine exhaust extract, using papillomas per mouse per milligram as the end point. In another study, the tumorigenicity of an automobile emission condensate (AEC), a diesel emission condensate (DEC), a representative mixture of carcinogenic PAHs, and B[a]P were tested for carcinogenicity by chronic application to mouse skin (Misfeld 1980). The results are shown in Table 4.12. Relative potencies were calculated by the authors to be 0.00011, 0.0053, and 0.36 for DEC, AEC, and the PAH mixture, respectively, as compared with B[a]P. The relative roles of the PAH components of each of these mixtures are unknown, however, so that quantitative evaluation is not possible. Since human exposure occurs to mixtures of PAHs, and not individual components, quantitative evaluation of the toxicity of individual PAHs is probably insufficient.

Human exposure to complex mixtures of PAHs has been extensive; some adverse effects are well-documented, particularly carcinogenic effects following long-term exposure. The extent of human exposures to well-defined PAH mixtures that are responsible for producing excess disease is generally not known in quantitative terms. Coke oven emissions and related substances such as coal tar have probably been the most widely studied. Coal tar derivatives were most likely responsible for the first observation of occupational cancer, that of scrotal cancer among London chimney sweeps, made by Pott (1775). More recent mortality studies have demonstrated strong associations between human exposure to coke oven emissions and excess disease; specifically, significant increases in lung and genitourinary cancer mortality have been observed (IARC 1983). The earliest of these reports was made in 1936 by investigators in Japan and England (Kennaway and Kennaway 1936) who were studying lung cancer mortality among persons employed in coal carbonization and gasification processes. Subsequent studies conducted in the United States clearly demonstrated substantial increases in lung and genitourinary system cancer mortality among coke oven workers (Lloyd 1971, Redmond et al. 1972, IARC 1984). Human tumorigenicity has also been reported to result from exposure to creosote. Creosote is a generic term that refers to wood preservatives derived from coal tar, creosote, or coal tar neutral oil and includes extremely complex mixtures of liquid and solid aromatic hydrocarbons. Workers who engaged in activities such as dipping timbers in creosote were reported to have developed malignant and premalignant skin lesions of the face, arms, and scrotum (O'Donovan 1920, Cookson 1924, Henry 1947, Lenson 1956). Many of the individual PAH components of creosote have been shown to be both mutagenic and carcinogenic in laboratory bioassays, supporting the evidence of its human carcinogenicity (IARC 1983).

Exposures to many other complex chemical mixtures that include PAHs, such as the use of tobacco products and exposure to roofing tar emissions and shale oils, have been associated with human disease incidence. Although this discussion falls short of providing a thorough review of the extensive literature available on the experimental and epidemiological observations of the toxicity of PAH mixtures, its purpose has been to provide examples wherein such toxicity has been documented, in order to emphasize that human exposure occurs to multiple PAHs.

Table 4.12. Carcinogenic activity of automobile emission condensate (AEC), diesel emission condensate (DEC), and PAHs on mouse skin

Treatment	Percent mice with tumors	Relative potency[a]
Solvent control	0	
Benzo[a]pyrene		1
3.86 μg	32.8	
7.69 μg	60.9	
15.4 μg	89.1	
AEC[b]		0.0053
290 μg	10.3	
880 μg	44.3	
2,630 μg	83.3	
DEC[b]		0.00011
4,300 μg	0	
8,600 μg	2.6	
17,150 μg	12.7	
Mixture of PAHs		0.36
3.5 μg	1.3	
10.5 μg	38.7	

[a]As calculated by authors.
[b]Obtained with leaded fuel.

Sources: Misfeld (1980) and NAS (1983).

Predicting the toxicity of a complex mixture on the basis of one or several of its components may be misleading because interactions among the components may modify toxicity. For example, both carcinogenic and noncarcinogenic PAHs may compete for the same metabolic activating enzymes and thereby reduce the toxicity of carcinogenic PAHs. Exposure to other PAHs can induce enzyme levels leading to more rapid detoxication of B[a]P, reducing its carcinogenicity (Levin et al. 1976). Interactions between B[a]P and benzo[e]pyrene have been shown to have both synergistic and antagonistic effects on mutagenicity (Hass et al. 1981). Naturally occurring compounds have been found to induce the enzymes that metabolize PAHs, leading to either increased or decreased toxicity. For example, plant flavonoids can induce microsomal monooxygenases and reduce the carcinogenicity of B[a]P (Weibel 1980). Environmental contaminants such as TCDD can also increase microsomal enzyme activity and consequently affect PAH toxicity (Kouri et al. 1978). Interactions can thus play important modulating roles in PAH toxicity that may not be adequately reflected in the identification of significant human exposure levels based on the toxicity of single PAHs, since human exposure occurs to mixtures of PAHs.

5. MANUFACTURE, IMPORT, USE, AND DISPOSAL

5.1 OVERVIEW

B[a]P is on the Toxic Substances Control Act (TSCA) Chemical Inventory (EPA 1979b), which lists chemicals (as defined by TSCA) that have been manufactured, imported, or processed for a commercial purpose in the United States since January 1, 1975. Data from the TSCA inventory indicates that the aggregate production of B[a]P is <1 million lb. B[a]P also occurs in fossil fuels and as a result of the incomplete combustion of fuel and wood. B[a]P is available as a research chemical from some specialty chemical firms. B[a]P and other polycyclic aromatic hydrocarbons are found in coal tar and in the creosote oils and pitches formed from the distillation of coal tars. Coal tar pitch is primarily used as a binder for electrodes. Creosote is primarily used as a wood preservative. Coal tar is also used as a therapeutical treatment for skin diseases (e.g., psoriasis). PAHs are also found in limited amounts in bitumens and asphalt.

5.2 PRODUCTION

The primary current source of B[a]P in air is combustion of wood for residential heating (EPA 1985). The production of B[a]P from this source is a consequence of incomplete combustion and uncontrolled release into the air. As a product of combustion, an estimated 1.8 million lb of B[a]P is released from stationary sources. The sources for 96% of this amount are refuse piles, outcrops, abandoned coal mines, coke manufacture, and residential external combustion of bituminous and anthracite coal.

Crude coal tar is produced as a by-product in the formation of coke from coal. Hot gases and vapors that are released from the conversion of coal to coke are collected in a scrubber that condenses these gases into ammonia, water, crude tar, and other by-products. A typical coke oven produces 80% coke, 12% coke-oven gas, 3% coal tar, and 1% crude benzene. The coal tar is then distilled to yield a number of chemical oils, creosote, and coal tar pitch. The coal tar pitch residue is 40.5% of the crude tar; creosote is ~11.5%. Heavy and light creosote also make up a small percentage of distillate (NIOSH 1977). Coal tar contains ~30 mg/kg B[a]P; coal tar pitch contains ~10 mg/kg B[a]P; and creosote oil contains <0.01 mg/kg B[a]P (EPA 1985).

As of 1981, the world output of crude coal tar was 1.8×10^7 metric tons; 1.4×10^7 metric tons was of coke-oven origin. In 1980, the U.S. production of crude tar was 2.4×10^6 metric tons. Creosote oil production in the United States in 1981 was estimated to be 5.1×10^5 metric tons. The coal tar pitch production in the United States in 1974 was estimated to be 1×10^6 metric tons (McNeil 1983).

Bitumens and asphalt are derived from crude oils. Asphalt is a mixture of bitumen with mineral materials (IARC 1985). Bitumen samples have been reported to contain between 0.1 and 27 mg/kg B[a]P (IARC 1985).

5.3 IMPORT

In 1985, the United States imported a total of almost 12 million gal of creosote oil from the Netherlands, France, West Germany, and other countries and almost 185 million lb of coal tar pitch, blast furnace tar, and oil-gas tar from Canada, Mexico, West Germany, Asian countries, Australia, and other countries (USDOC 1986).

5.4 USE

B[a]P has some use as a research chemical. It is available from some specialty chemical firms in quantities of 100 mg to 1 g (Aldrich Chemical Co. 1986).

Coal tar pitch is removed from the tar still as a residue. The rate of feeding and firing of the still regulates the viscosity of the tar. Coal tar pitch is primarily used as a binder for electrodes in the aluminum reduction process; it is used to bind the carbon electrodes used in the reduction pots (NIOSH 1977). In North America, coal tar pitch is also used as the adhesive in membrane roofs (McNeil 1983).

Almost 99% of creosote produced is sold to wood preservation plants; from 0.1 to 0.2% is sold to individual customers (NIOSH 1977). Creosote is used in the preservation of railroad ties, marine pilings, and telephone and telegraph poles. Some creosote is also consumed as fuel by steel producers (NIOSH 1977).

Coal tar is also used in the clinical treatment of skin disorders (e.g., *eczema*, *dermatitis*, and *psoriasis*). The use of dermatological coal tar preparations is extensive (NIOSH 1977).

Bitumens and asphalt are primarily used for paving roads, waterproofing and roofing, electrical insulation, sound insulation, and pipe coating (IARC 1985).

5.5 DISPOSAL

Following small input of B[a]P from coal-tar creosote, 0.36 mg/L B[a]P has been found in water raw discharge from timber product industries in 1978 (EPA 1985).

Total B[a]P wastewater discharge in 1978 from coke-making operations was reported as 3 metric tons (EPA 1985).

6. ENVIRONMENTAL FATE

6.1 OVERVIEW

B[a]P in the environment is derived from both natural (e.g., volcanoes, wildfires) and man-made sources, but B[a]P originating from man-made sources is quantitatively the most significant. B[a]P is formed during high-temperature pyrolytic processes; consequently, natural and man-induced combustion are the major sources of environmental B[a]P. Virtually all direct releases of B[a]P into the environment are to the air. Small and approximately equal amounts are released to water and land. B[a]P is removed from the atmosphere primarily by photochemical oxidation and dry deposition to land or water. B[a]P that reaches the surface will likely remain and will be partitioned primarily to soil and sediment, where it is very persistent. The dominant degradation process for B[a]P in soil/sediment is biodegradation. Biodegradation is a slow process, with a half-life of 290 days being estimated for B[a]P in soil.

6.2 RELEASES TO THE ENVIRONMENT

Incomplete combustion of carbonaceous material is the major source of B[a]P formation in the environment, and residential heating is the single largest combustion source. The large quantity of B[a]P released during home heating is primarily a consequence of inefficient combustion processes and uncontrolled emissions. Historically, the greatest amount of residential B[a]P releases has been attributed to home combustion of coal (Edwards 1983, Pucknat 1981, Perera 1981, Suess 1976, NAS 1972). However, current trends in energy consumption indicate a diminishing reliance on coal as a residential heating source and an increased reliance on heating oil, electricity, gas, and wood (Census 1981). Of all home heating sources, wood heating is by far the greatest contributor to B[a]P emissions. In fact, Harkov and Greenberg (1985) estimated that over 95% of all B[a]P emissions in New Jersey are from home wood combustion. In a recent assessment of B[a]P sources and release volumes across the United States, EPA (1985) also estimated that home wood combustion is the single largest B[a]P source, contributing 72 metric tons, or 40% of all released volumes. Combustion sources overall are responsible for 154 metric tons, or over 90% of total B[a]P releases. All other sources (e.g., coal tar, creosote, asphalt, and bitumen production and use) individually contribute 2% or less to total B[a]P releases.

Ninety-eight percent of all estimated environmental releases of B[a]P are to air. Of the remaining 2%, approximately equal amounts of B[a]P are released to water and land.

Although they contribute small amounts of B[a]P and other PAHs to the environment on a national scale, hazardous waste sites may

constitute concentrated sources of B[a]P and PAHs on a local scale. For example, abandoned wood treatment plants are sources of high concentrations of creosote; former manufactured-gas plants (town gas sites) are sources of high concentrations of coal tar. Both creosote and coal tar are composed of a variety of PAHs, including B[a]P. PAHs at these sites are likely to occur on the soil and on suspended particulate matter in the air.

6.3 ENVIRONMENTAL FATE

The environmental fate of B[a]P is determined, to a large degree, by the chemical's low water solubility (3.8 μg/L at 20°C) and high propensity for binding to particulate or organic matter. As a result, B[a]P in the atmosphere is associated primarily with particulate matter, especially soot, whereas the majority of B[a]P in aquatic systems is strongly bound to suspended particles or bed sediments. Likewise, B[a]P is strongly sorbed to soils. Dispersion of particle-bound B[a]P is the primary transport process within air, water, and land. B[a]P can leach through soils, but low water solubility and strong sorption to soil limit the relative importance of this intramedia transport process.

Dry deposition of particle-bound B[a]P is the most significant transport process between air and land or water. Approximately 52% of B[a]P released into the atmosphere will reach the surface via dry deposition; wet deposition is less significant by a factor of from 3 to 5 (EPA 1985). Because of a very low vapor pressure, B[a]P that reaches the surface will likely remain, and will be partitioned to soil/sediment. Soil/particle adsorption or biotic uptake are the primary transport processes for the removal of waterborne B[a]P. Desorption into water from soil is very unlikely, and erosion of contaminated soils by surficial runoff is the most probable process for transport of soil-bound B[a]P to aquatic systems.

Information about the fate of particulate B[a]P released to the atmosphere is unclear. It is generally assumed, however, that photochemical oxidation processes play an important role. Atmospheric half-lives on the order of hours or days have been suggested (NAS 1972). B[a]P strongly absorbs solar radiation at wavelengths above 300 nm, and there is sufficient evidence to indicate that B[a]P undergoes photooxidation in solution, as the pure solid, and when adsorbed onto certain solid substrates (e.g., alumina) (NAS 1972). Singlet oxygen has been implicated as the primary oxidant, and endoperoxides (and, ultimately, quinones) as the reaction products (NAS 1972).

It has been inferred that similar processes take place when the compounds are adsorbed on airborne particles. However, the data in support of this view are somewhat limited. Thomas et al. (1968) reported that B[a]P adsorbed on soot was readily photooxidized, with 40% of the B[a]P destroyed within the first 40 min of illumination. Peters and Seifert (1980) reported that B[a]P deposited from liquid solution onto dust-coated glass fiber filters underwent rapid photodegradation when exposed to unfiltered halogen lamp light. However, Korfmacher et al. (1980a,b) found that B[a]P will rapidly photooxidize in liquid solution but is highly resistant when adsorbed on fly ash. Additional research is needed to elucidate the exact fate of atmospheric B[a]P.

Within aquatic systems, B[a]P accumulates in the sediment and is transported with suspended sediment. B[a]P in the water column also accumulates in aquatic organisms. However, many organisms metabolize and excrete B[a]P rapidly, so that bioaccumulation is a short-term process. For example, in bluegill sunfish, an 89% loss of B[a]P was recorded 4 h after exposure (Leversee et al. 1981). Lee et al. (1972) reported rapid elimination of B[a]P in three species of California marine teleosts. Depuration rates in invertebrate species vary more widely. Some species (e.g., hard-shell clams) show little or no depuration, while others (e.g., oysters) eliminate virtually all PAHs following exposure (Eisler 1987).

Aquatic organisms also can assimilate B[a]P and other PAHs from food. For example, crustaceans and fish have been reported to readily assimilate PAHs from contaminated food (Eisler 1987). However, in many cases where assimilation of PAHs has been demonstrated, metabolism and excretion of PAHs were rapid (Eisler 1987). In laboratory aquatic ecosystem studies in which radiolabeled B[a]P was used, Lu et al. (1977) found that B[a]P can be accumulated through the food to high levels in mosquito fish. After 3 days of exposure, the intact parent compound comprised over 50% of the extractable radiolabeled carbon in fish. However, after 33 days of exposure, the intact parent compound comprised only 7% of the total extractable radiolabeled carbon, indicating metabolism of B[a]P. The tendency of fish to metabolize B[a]P may explain why B[a]P is frequently undetected, or only detected in low concentrations in the livers of fish from environments heavily contaminated with B[a]P and other PAHs.

A minimal amount of B[a]P is dissolved and degraded rapidly by direct photolysis. Smith et al. (1978) calculated a half-life of 1.2 h for midday direct photolysis of dissolved B[a]P. Chemical oxidation may be a significant fate process for B[a]P degradation in water when chlorine or ozone (both oxidants) exist in sufficient concentrations (EPA 1979a).

The major fate of sediment-bound B[a]P is biodegradation. In general, biodegradation processes are quite slow; a half-life of 21,000 h has been reported for B[a]P (EPA 1979a). Biodegradation half-lives in contaminated streams can be from 10 to 400 times longer. These long half-lives indicate that B[a]P is relatively persistent in sediments and aquatic systems.

Within terrestrial systems also, biodegradation is the probable fate process. However, this process is very slow and, consequently, B[a]P is very persistent in soils. Bossert and Bartha (1986) reported that 72% of the original amount of B[a]P applied to soils existed after 16 months of incubation with bacteria. Coover and Sims (1987) estimated a half-life of B[a]P in soil of 290 days.

At hazardous waste sites half-lives may be longer, as other contaminants present at the site may be toxic to the degrading microorganisms. Bossert and Bartha (1986) reported reduced biodegradation of B[a]P in soil containing a chemical toxic to microorganisms.

7. POTENTIAL FOR HUMAN EXPOSURE

7.1 OVERVIEW

As the previous discussions indicate, the greatest portion of environmental B[a]P releases are directly into the atmosphere. Consequently, inhalation is the primary route of background human exposure to B[a]P in the environment. Approximately 52% of the B[a]P in the atmosphere returns to the surface via dry deposition. This input, in addition to small direct releases by industry and publicly owned treatment works, leads to B[a]P in soil and water to which humans may be exposed. Humans may also be exposed to B[a]P in food, tobacco smoke, and some occupational environments, and through contact with PAH-containing products (e.g., coal tar, coal tar-based shampoos, asphalt, and creosote-treated wood). At hazardous waste sites, humans will most likely be exposed to B[a]P in the soil and on particulate matter in air.

7.2. LEVELS MONITORED IN THE ENVIRONMENT

7.2.1 Air

B[a]P has been detected in both urban and rural atmospheres, but a concentration of industrial activities and transportation in and around cities has led to a substantial difference between B[a]P concentrations in urban and nonurban areas. B[a]P concentrations reported for urban air are up to 10 to 100 times greater than concentrations in rural areas. Pucknat (1981) summarized 1970 data from the National Air Sampling Network (NASN) and reported B[a]P concentrations in 120 U.S. cities of between 0.2 and 19.3 ng/m^3. Ambient B[a]P concentrations in nonurban areas ranged between 0.1 and 1.2 ng/m^3.

Other investigators (Edwards 1983, Perera 1981, Sawicki 1976) have reported similar ambient air concentrations for U.S. urban and rural areas, using data derived largely from the 1960s and early 1970s. More recent data, however, indicate that ambient levels may be decreasing. Faoro and Manning (1981) analyzed a limited sample of NASN data updated through 1977 and indicated that B[a]P concentrations have shown consistent sizeable declines during the period from 1967 to 1977 at 26 urban sites and 3 background sites studied (data not provided). However, this trend was described based on a limited sample size and, therefore, cannot be regarded as definitive.

In addition to historical trends, seasonal variations in B[a]P air levels also have been demonstrated. Harkov and Greenberg (1985) studied B[a]P emissions during the heating season (November-March) and the non-heating season, and estimated (based on monitoring data) that 97% of the annual B[a]P emissions in New Jersey occurred during the 5-month heating

season. This emission pattern is consistent with reports by other authors (Edwards 1983, Pucknat 1981).

7.2.2 Water

B[a]P has been detected in U.S. groundwaters and in surface waters used as drinking water sources, but minimal data limit the degree to which background levels can be adequately characterized.

EPA (1980) reported B[a]P concentrations in groundwater in one site in Indiana and one site in Ohio to be 4.0 and 0.3 ng/L, respectively. Concentrations of B[a]P in treated surface waters used as drinking water sources ranged between 0.3 and 2.0 ng/L. Untreated water concentrations ranged between 0.6 and 210 ng/L (EPA 1985, 1980; Sorrell 1981).

Because of a high propensity to bind to organic matter, it is unlikely that B[a]P will occur to any appreciable extent in surface water or groundwater at hazardous waste sites or other areas.

7.2.3 Soil

Very few data are available on B[a]P levels in U.S. soils. Blumer (1961) reported concentrations between 40 and 1300 μg/kg in the soil from relatively rural areas of the eastern United States. Soil concentrations in more populated and industrialized areas may be higher. Butler et al. (1984) have demonstrated much higher soil B[a]P concentrations near complex road interchanges than at areas more distant. Typical concentrations of B[a]P in soils of the world are between 100 and 1,000 μg/kg, although values as high as 650,000 μg/kg (10 m from a German soot plant) have been reported (Edwards 1983). Soils near waste sites (e.g., former manufactured-gas plants and creosote wood treatment plants) can be expected to contain B[a]P and other PAHs in the soil.

7.2.4 Food

B[a]P has been detected in unprocessed cereal, potatoes, grain, flour, bread, vegetables, and fruits, and in a variety of processed foods and beverages (Grimmer 1983). EPA (1985) estimated a daily B[a]P intake from food of 50 ng. The method of preparation of certain foods can increase the B[a]P intakes. In meat or fish, the amount of B[a]P present depends to some degree on the method of cooking; time of exposure, distance from the heat source, and the disposal of fat during cooking all influence B[a]P content. Charcoal broiling increases the amount of B[a]P in meat. Lijinsky and Shubik (1965) measured an average of 9 μg/kg B[a]P in charcoal-broiled steak. B[a]P also has been detected in vegetables and fruits grown in B[a]P-contaminated soil near areas with high vehicular traffic (Wang and Meresz 1982). Thus, consumption of food grown near hazardous waste sites and areas of high vehicular traffic may contribute to human exposure to B[a]P.

Humans also may be exposed to B[a]P in aquatic organisms (e.g., fish, clams, and oysters) that are typical components of the diet. PAHs, including B[a]P, have been detected in bivalve mollusks (i.e., clams, oysters, mussels), crabs, and lobsters (Eisler 1987). PAHs also have

been detected in fish, but fish levels are usually low, probably because this group rapidly metabolizes PAHs.

7.2.5 Tobacco Products and Tobacco Smoke

B[a]P has been reported to occur in chewing tobacco (Hoffman et al. 1986) and in mainstream and sidestream tobacco smoke. Concentrations in cigarette mainstream smoke between 5 and 78 ng/cigarette have been reported (IARC 1983). Concentrations in sidestream smoke have been reported to be even higher. Undiluted sidestream smoke of four types of commercial cigarettes contained more B[a]P (44.8 to 67.0 ng/cigarette) than the mainstream smoke of the same cigarette (2.2 to 26.2 ng/cigarette) (Adams et al. 1987).

Today there is an increasing concern about indoor air pollution by environmental tobacco smoke. A report by the U.S. Surgeon General (1986) concluded that environmental tobacco smoke can be a substantial contributor to the level of indoor air pollution concentrations of respirable particles. These higher concentrations of sidestream smoke constituents (e.g., B[a]P), in conjunction with the fact that many people spend many hours in indoor polluted atmospheres, may lead to increased health risks to individuals passively exposed to cigarette smoke.

7.3 OCCUPATIONAL EXPOSURES

B[a]P has been isolated in numerous occupational situations, including coal-tar production and coking plants, coal gasification sites, smoke houses, aluminum production plants, bitumen and asphalt production plants, road and roof tarring operations, and around municipal incinerators. Within these environments, B[a]P occurs with a complex mixture of other PAHs. Thus, exposure to B[a]P alone does not occur. Historically, the highest level of human exposure to B[a]P occurred in industrial situations; B[a]P concentrations ranging from 800 to 23,100 ng/m^3 have been reported to occur in the workroom air of coke oven operations in the United Kingdom (Davies et al. 1986). Similarly high values have been reported by Lindstedt and Solenberg (1982) in Swedish industries.

7.4 POPULATIONS AT HIGH RISK

At highest risk for cancer by B[a]P are those people who are exposed to high levels of B[a]P. Examples of high-risk populations include: workers in certain occupations that have elevated B[a]P concentration in the ambient work environment; smokers and involuntary (passive) smokers who receive elevated B[a]P intake in tobacco smoke; and populations living near industries (e.g., creosote and coal tar manufacturers) that generate B[a]P as a by-product of production.

Individuals in these high-exposure groups may have varying susceptibility to PAH toxicity. Some of the available data on PAH carcinogenicity suggest a relationship between aryl hydrocarbon hydroxylase (AHH) activity and cancer risk. Genetic variation in AHH inducibility has been implicated as a determining factor for susceptibility to lung and laryngeal cancer (EPA 1980). Attempts have been made to demonstrate that persons with lung cancer have higher

inducibility of AHH in cultured lymphocytes. A review by Calabrese (1984) indicates that several studies support this hypothesis, and some genetic data indicate that the human population can be segregated based on this trait (EPA 1980). Thus, individuals that are AHH-inducible may constitute a high-risk population. However, the data regarding genetic susceptibility are not conclusive.

8. ANALYTICAL METHODS

8.1 ENVIRONMENTAL SAMPLES

The procedures used to sample and extract B[a]P in different media are very similar. In air and tobacco smoke, PAHs, including B[a]P, are adsorbed predominantly on particulate matter, and the particulate matter is collected on a filter. In water and soil, PAHs are extracted without filtration.

The extraction of PAHs from the filter can be accomplished by a variety of techniques with or without solvents. The following extraction techniques are the most commonly used: soxhlet, sublimation at elevated temperatures, ultrasonic, and polytron extraction (Sawicki 1976, Swanson and Walling 1981).

A cleanup step is necessary to separate B[a]P and PAHs from other chemicals. Typically, this step involves liquid-liquid extraction of the dry organic particulate extract, followed by adsorption chromatography using silica gel or alumina columns (Sawicki 1976, Riggin and Strup 1984). These adsorbents selectively remove interfering compounds. In addition, thin-layer chromatography can be used as a cleanup method (Sawicki 1976) but may not yield a B[a]P peak free of interference (Tomkins et al. 1985).

The most commonly used analytical methods for determining B[a]P in environmental samples are column gas chromatography (GC) and high-performance liquid chromatography (HPLC). Table 8.1 summarizes common analytical methods, detection limits, and accuracy (percent recovery) for the determination of B[a]P in air, water, soil, cigarette smoke, and food.

Column gas chromatography (GC) is an analytical technique in which components of a sample are separated by differential distribution between a gaseous mobile phase and a solid or liquid stationary phase (EPA 1983). Complete separation of B[a]P from other PAHs is difficult using gas chromatography. When B[a]P is present in the sample with perylene or benzo[e]pyrene, separation of B[a]P is insufficient because of problems in resolution (Sawicki 1976). Following separation in the GC column, sample components are identified and quantified by a detection system [e.g., flame ionization detection (FID) or mass spectrometry (MS)]. These techniques are detailed in NIOSH (1984) and EPA (1983, 1984a).

HPLC is an analytical method in which components are separated based on their polarity (EPA 1983). Reverse-phase HPLC, which is used more widely for the analysis of PAHs, uses a nonpolar stationary phase and a polar mobile phase; hydrophilic components are eluted earlier than

Table 8.1. Methods for analysis of benzo[a]pyrene in environmental media

Media	Sample preparation	Analytical method[a]	Detection limit	Accuracy	References
Air	Ultrasonic extraction with cyclohexane	HPLC	3 ng/m^3 (1500-m^3 sample)	NA[b]	NIOSH 1984 (Method 5506)
	Ultrasonic extraction with benzene, pentane, or dichloromethane	HPLC/FS	5 pg	NA	Andersson et al. 1983
	Soxhlet extraction with benzene-methanol	GC/MS	0.05 ng/m^3	NA	Matsumoto and Kashimoto 1985
	Extraction with solvent	GC/MS	NA	NA	NIOSH 1984 (Method 5515)
	Soxhlet extraction with dichloromethane	TLC/FS	0.1 ng/g suspended particulate matter	NA	Katz 1979
	Soxhlet extraction with petroleum benzene	TLC/QLL	0.05 ng/mL extract	NA	Yanysheva and Kireeva 1979
Water	Extraction with methylene chloride	HPLC/FS	0.023 ng/L	~56%	EPA 1984a (Method 610)
		UV	4 μg/L	76-135%	Riggin and Strup 1984
	Extraction with dichloromethane	HPLC/UV	2.5 pg/L	NA	Ogan et al. 1979
	Extraction with methylene chloride at pH ≤ 2 and pH ≥ 11	GC/MS	2.5 μg/L	~90%	EPA 1984a (Method 625)
		GC/MS	NA	NA	EPA 1986a
	Extraction with methylene chloride at pH 12-13 and pH ≤ 2	GC/MS	10 μg/L	NA	EPA 1984a (Method 1625)
	Extraction with cyclohexane	TLC/FS	0.5-1 ng/L	NA	Borneff and Kunte 1979
	Not specified	TLC/QLL	0.03 ng/L (10-L sample)	NA	Ya Khesina 1979
Soil	Extraction with *n*-pentane	TLC/UV	NA	NA	Butler et al. 1984
	Soxhlet extraction with benzene	TLC/UV	NA	NA	Blumer 1961
	Extraction with methylene chloride	GC/MS	NA	NA	EPA 1986a
Cigarette smoke	Ultrasonic extraction with benzene	HPLC/FS	≤1 ng/cigarette	95%	Tomkins et al. 1985
Food	Extraction with isooctane	TLC/UV	0.2 μg/kg	NA	Howard 1979

[a]Abbreviations: HPLC, high-performance liquid chromatography; TLC, thin-layer chromatography; FS, fluorescence spectroscopy; QLL, quasi-linear luminescence; GC, column gas chromatography; MS, mass spectrometry; UV, ultraviolet absorption spectroscopy.

[b]NA = Not available.

are hydrophobic components. HPLC can separate B[a]P from other PAHs (Sawicki 1976). The detection systems most appropriate for HPLC analysis of B[a]P are UV absorption spectroscopy (UV) and fluorescence spectroscopy (FS) (EPA 1983). Fluorescence spectroscopy is useful for extremely dilute solutions; therefore, pretreatment and cleanup of the sample before HPLC may not be necessary (Das and Thomas 1978).

Thin-layer chromatography (TLC) has also been used to analyze for PAHs. One-dimensional TLC cannot separate B[a]P from other PAHs; however, B[a]P can be separated using a two-dimensional alumina-cellulose acetate TLC (Sawicki 1976). With quasi-linear luminescence methods (QLL), quasi-linear spectra can be obtained for PAHs at liquid nitrogen temperatures (Sawicki 1976).

GC and HPLC are the chromatographic methods routinely used for the determination of 10 to 20 of the major PAHs in air and water samples. Detailed analysis of major and minor PAHs in a complex PAH mixture requires a combination of chromatographic techniques (Wise et al. 1986). GC/MS has a detection limit of >10 pg; HPLC has an approximate detection limit for PAHs of 25 to 50 pg (Santodonato et al. 1981). TLC/FS has been used for analysis of PAHs in air, water, and soil. It is useful for the analysis of one or two compounds and has a detection limit of 1 to 2 ng (Santodonato et al. 1981).

HPLC (5506) or GC/MS (5515) are the methods recommended by NIOSH for analyzing PAHs in workplace air (NIOSH 1984). These methods incorporate a sampling train consisting of a filter and a solid sorbent (NIOSH 1984). The use of a high-volume sampler to sample a large quantity of air allows for detection of small amounts of B[a]P. The analytical methods required by EPA (1984a) for the analysis of B[a]P in water are procedures 610 (HPLC/FS), 625 (GC/MS), and 1625 (GC/MS). These are required test procedures for municipal and industrial wastewater-discharging sites under the Clean Water Act. GC/MS is the method required by the EPA Contract Laboratory Program (CLP) for analysis of B[a]P and other PAHs in water and soil. The Contract Required Quantitation Limit (CRQL) for B[a]P in water is 10 µg/L, and that in soil/sediment is 330 µg/kg (EPA 1986a).

8.2 BIOLOGICAL SAMPLES

The available biological monitoring techniques are useful for detecting whether occupational or environmental exposure to PAHs has occurred, but because there have been no population-based studies to determine normal body levels of PAHs, it is not yet possible to predict environmental exposure from body PAH levels or to predict what health effects are likely to be associated with these levels. In general, techniques that measure PAH or PAH metabolite concentration in the urine are most appropriate for use in determining occupational exposure, since a high level of PAH exposure is necessary to result in the presence of these compounds in the urine. Methods that detect diol epoxide-DNA adducts are more sensitive to low exposure levels and are most appropriate for use in determining environmental exposure. The techniques presently available for determining exposure to PAHs are summarized in Table 8.2 and discussed in detail in this subsection.

Table 8.2. Methods for analysis of PAHs in biological samples

Medium	Technique	Measured parameter	Reference
Tissue	Gas chromatography	PAH concentration	Modica et al. 1982, Bartosek et al. 1984
	Postlabeling of DNA	Diol epoxide-DNA adducts	Randerath et al. 1985, 1986
	High-performance liquid chromatography	Diol epoxide-DNA adducts	Shugart 1985, 1986; Haugen et al. 1986
	Liquid chromatography	Diol epoxide-hemoglobin adducts	Shugart 1985, 1986
Blood	Immunoassay	Antibodies to diol epoxide-DNA adducts	Harris 1985, Harris et al. 1985, Harris et al. 1986
Urine	Gas chromatography	PAH concentration	Clonfero et al. 1986
	High-performance liquid chromatography	PAH concentration	Becher and Bjorseth 1983, Becher et al. 1984

Modica et al. (1982) and Bartosek et al. (1984) examined PAHs (specifically chrysene and benz[a]anthracene) present in blood, mammary, adipose, liver, and brain tissue from rats orally exposed to PAHs, using gas-liquid chromatography and FID. PAHs were determined in all tissues examined. Examples of PAH concentrations in human tissue samples using this technique were not located in the available literature. The detection units for this method were not reported.

In mammalian systems, B[a]P can be converted by specific cellular enzymes to *trans*-B[a]P-7,8-dihydrodiol. This metabolite is further converted to two isomeric diol epoxides (anti- and syn-B[a]PDE). These diol epoxides are capable of binding to DNA (Weinstein et al. 1976). The degree of DNA adduct formation can be used as a measure of dose in target tissues or organs (Phillips et al. 1979; Perera et al. 1982; Rahn et al. 1982; Randerath et al. 1985; Vahakangas et al. 1985; Shugart 1985, 1986). Randerath et al. (1985, 1986) examined PAH-DNA adducts in skin tissue from mice dermally treated with cigarette smoke condensate and placenta, bronchus, and larynx tissue from smokers. In this technique, radioactivity (^{32}P) is incorporated into the DNA removed from the exposed cells and the digested DNA is separated using TLC. Quantitation of the adducts is achieved by scintillation counting. Small amounts of DNA are needed for analysis. In another technique, B[a]PDE-DNA adducts obtained from mice dermally exposed to or subcutaneously injected with B[a]P were isolated and acid hydrolyzed, and the liberated tetrols were analyzed by HPLC/FS (Shugart 1985, 1986).

Shugart (1985, 1986) also reported that there is a dose-response relationship between the amount of B[a]P and the occurrence of B[a]P adducts to hemoglobin in mice exposed dermally or by subcutaneous injection. The B[a]PDE adducts with hemoglobin can be isolated and acid hydrolyzed, and the liberated tetrols can be analyzed by HPLC/FS. Further, Shugart (1985, 1986) reported that the amount of anti-B[a]PDE binding to DNA and hemoglobin at various doses of B[a]P appears to be qualitatively similar. The anti-diol epoxide is the carcinogenic form that interacts with both hemoglobin and DNA in the target tissue (Shugart 1985). Therefore, a measure of the stable hemoglobin adducts in blood may be suitable for estimating carcinogenic risk of B[a]P exposure.

Procedures are currently available that examine the presence of antibodies to DNA adducts in the blood using enzymatic immunoassays (Perera et al. 1982; Santella et al. 1985; Harris 1985; Harris et al. 1985, 1986; Haugen et al. 1986). Perera et al. (1982) injected mice intraperitoneally with B[a]P and reported a dose-related increase in DNA adducts as determined by immunoassay. Harris (1985, Harris et al. 1985) developed a technique for determining human exposure to PAHs by detecting antibodies in sera to diol epoxide-DNA adducts using an immunoassay. The technique was tested on coke oven workers exposed to substantial amounts of B[a]P and other PAHs in the work atmosphere, smokers, and nonsmokers. Antibodies to B[a]P diol epoxide-DNA adducts were quantified by enzyme-linked immunosolvent assay (ELISA). Higher proportions of sera positive for antibodies were found in a group of smokers and in the occupationally exposed group.

The urine of exposed animals or humans has been examined for the presence of B[a]P and B[a]P metabolites. PAHs and their metabolites were extracted from human urine and analyzed using HPLC/FS or GC/MS following occupational exposure or therapeutic coal tar application (Becher and Bjorseth 1983, Becher et al. 1984, Jongeneelen et al. 1985, 1986; Clonfero et al. 1986). Occupationally exposed individuals were found to have a higher concentration of PAHs in the urine than unexposed individuals. However, high environmental concentrations of PAHs in the workplace were not found to be reflected to the same extent in excretion of PAHs in the urine (Becher and Bjorseth 1983, Becher et al. 1984). This was suggested to result from the nonbioavailability of particulate-bound B[a]P, and this method may still be applicable in other exposure situations. Clonfero et al. (1986) reported that B[a]P was found in the urine of individuals dermally treated with therapeutic coal tar, but only high levels of PAHs in the coal tar resulted in a measurable urine concentration. Quantification of the urinary metabolite of B[a]P, 3-hydroxy-benzo[a]pyrene, by HPLC/FS can also be used as an indication of exposure to B[a]P (Jongeneelen et al. 1986). Detection limits for chromatographic techniques used in urine analysis were not reported.

Vo-Dinh et al. (1987) have developed an antibody-based fiber-optic biosensor that can be used to detect B[a]P or other PAHs in sample solutions. In this technique, antibodies to B[a]P are covalently bound to the tip of the sensing probe. A helium-cadmium laser excites the molecules of B[a]P bound to the antibodies, and the resulting fluorescence of these molecules is recorded by a photomultiplier. The intensity of the fluorescence signal is proportional to the amount of antigen bound to the sensor tip. The fiber-optics device can detect 1 femtomole (fmol; one-quadrillionth of a mole) B[a]P in a 5-μL sample drop. This technique can be useful in the assessment of an individual's exposure to B[a]P and other PAHs, provided appropriate antibodies are used.

9. REGULATORY AND ADVISORY STATUS

Regulatory standards and advisory levels have been developed for the carcinogenic PAHs and for B[a]P specifically. The present regulatory (enforceable) standards and advisory (nonenforceable) levels for air and water exposures are presented in Table 9.1 and discussed in detail in this section.

B[a]P has been shown to be carcinogenic in experimental animals and undergoes metabolism to reactive electrophiles capable of binding covalently to DNA and inducing bacterial mutation and DNA damage. IARC (1983) has classified B[a]P in Group 2B, because of sufficient evidence of carcinogenicity in experimental animals. IARC (1985) has also concluded that there is sufficient evidence of carcinogenicity of coal tars, creosote, and coal tar pitches in experimental animals. In addition, IARC (1985) concluded that there is sufficient evidence that occupational exposure to coal tar and coal tar pitch is associated with skin cancer and that there is limited evidence of the carcinogenicity of creosote in occupationally exposed individuals.

Applying the classification criteria for weight of evidence developed by the Carcinogen Assessment Group of EPA, B[a]P is classified by EPA (1984b) in Group B2--probable human carcinogen. This category applies to agents for which there is sufficient evidence of carcinogenicity from animal studies and inadequate evidence of carcinogenicity from epidemiologic studies.

9.1 INTERNATIONAL

The World Health Organization (WHO 1971) set an upper limit of 0.2 μg/L for the total concentration of the PAHs B[a]P, fluoranthene, benzo[g,h,i]perylene, benzo[b]fluoranthene, benzo[k]fluoranthene, and indeno[1,2,3-cd]pyrene in domestic waters. This limit was not chosen on the basis of potential health effects.

9.2 NATIONAL

9.2.1 Regulatory Standards

Coal tar, coal tar pitch, and creosote are considered by NIOSH and EPA to be human carcinogens (NIOSH 1977; EPA 1978, 1981, 1986b). NIOSH reviewed epidemiologic and experimental toxicological evidence and concluded that inhalation exposure to these coal products, which contain a number of PAHs including B[a]P, increases the risk of lung and skin cancer in workers (NIOSH 1977). The Secretary of Labor has taken the position that no safe occupational exposure can be established for a carcinogen.

Table 9.1. Regulatory standards and advisory levels

Regulatory standard or advisory level	Basis	Concentration or risk coefficient	Reference
	Air		
Regulatory standard:			
8-h Time-weighted average permissible exposure limit (PEL)	Benzene-soluble fraction of coal tar pitch volatiles	0.2 mg/m^3	OSHA 1985a
Advisory levels:			
8-h Time-weighted average PEL	B[a]P	0.2 $\mu g/m^3$	OSHA 1985b
8-h Time-weighted average threshold limit value	Benzene-soluble fraction of coal tar pitch volatiles	0.2 mg/m^3	ACGIH 1986
10-h Time-weighted average threshold limit value	Cyclohexane-soluble fraction of coal tar pitch volatiles	0.1 mg/m^3	NIOSH 1977
	Water		
Advisory levels:			
Ambient water quality criterion	Total carcinogenic PAHs	0 (28, 2.8, and 0.28 ng/L)[a]	EPA 1980

[a]The EPA recommended concentration for ambient water is zero. However, because attainment of this level may not be possible to achieve, the EPA estimated concentrations of total carcinogenic PAHs for ambient water corresponding to a 10^{-5}, 10^{-6}, and 10^{-7} upper-bound lifetime excess risk estimate, respectively, are presented.

The current workroom air standard determined by OSHA is an 8-h time-weighted average permissible exposure limit (PEL) of 0.2 mg/m^3 for the benzene-soluble fraction of coal tar pitch volatiles. The PEL was established to minimize exposure to those volatiles believed to be carcinogens; these include B[a]P as well as anthracene, phenanthrene, acridine, chrysene, and pyrene (OSHA 1985a, 1986).

9.2.2 Advisory Levels

9.2.2.1 Air advisory levels

Proposed OSHA permissible exposure limit. In 1974, OSHA established the Standards Advisory Committee on Coke Oven Emissions. The Committee recommended a time-weighted average PEL of 0.2 $\mu g/m^3$ for occupational exposure to B[a]P (OSHA 1985b).

ACGIH time-weighted average threshold limit value. The American Conference of Governmental Industrial Hygienists (ACGIH 1986) recommended a time-weighted average threshold limit value (TLV) for occupational exposure to coal tar pitch volatiles based on an 8-h workday and a 40-h week. The ACGIH time-weighted average TLV of 0.2 mg/m^3 was recommended for the benzene-soluble fraction of coal tar pitch volatiles (including B[a]P as well as anthracene, phenanthrene, acridine, chrysene, and pyrene). The TLV is based upon the ACGIH conclusion that, at concentrations below 0.2 mg/m^3, any increase in the incidence of lung and other tumors caused by occupational exposure to coal tar pitch volatiles should be minimal.

NIOSH time-weighted average threshold limit value. NIOSH examined the epidemiologic and experimental toxicological evidence on coal tar, coal tar pitch, and creosote and concluded that they are carcinogenic to experimental animals and potentially humans (NIOSH 1977). Polynuclear hydrocarbons such as B[a]P have been identified in coal tar products. Because of the carcinogenic potential of these compounds, NIOSH recommended that the permissible exposure limit be set at the lowest concentration detected by the NIOSH-recommended method of environmental monitoring, 0.1 mg/m^3 (NIOSH 1977). NIOSH proposed this time-weighted average threshold limit value to reduce the risk of cancer associated with exposure to coal tar products in the workplace.

9.2.2.2 Water advisory levels

Ambient water quality criterion. EPA (1980) developed an ambient water quality criterion (AWQC) to protect human health from the potential carcinogenic effects caused by exposure to carcinogenic PAHs through ingestion of contaminated water and contaminated aquatic organisms.

Benzo[a]pyrene is a known animal carcinogen. Because there is no recognized safe concentration for a human carcinogen, EPA (1980) recommended that the sum of the concentrations of total carcinogenic PAHs in ambient water be zero. However, EPA (1980) recognized that a zero concentration level may not be possible to attain. The present criterion for total carcinogenic PAHs was developed using the carcinogenicity assay reported by Neal and Rigdon (1967), in which stomach tumors developed in CFW-Swiss mice exposed to doses of

1 to 250 ppm B[a]P in the diet with a statistically higher incidence than in controls. Assuming that an individual consumes 2 L of water and 6.5 g of fish and shellfish each day, the sum of the concentrations of total carcinogenic PAHs corresponding to upper-bound lifetime excess cancer risks of 10^{-5}, 10^{-6}, and 10^{-7} are 28, 2.8, and 0.28 ng/L, respectively.

9.2.2.3 Food advisory levels

No food advisory levels for B[a]P were located in the available literature.

9.2.2.4 Non-media-specific levels

Although EPA previously published inhalation and oral cancer risk estimates for B[a]P based on the studies of Thyssen et al. (1981) and Neal and Rigdon (1967), these numbers are currently under review and have not been included here pending recalculation.

9.2.2.5 Other guidance

Sections 103(a) and 103(b) of the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA) require that persons in charge of vessels or facilities from which a hazardous substance has been released in quantities that are equal to or greater than its reportable quantity (RQ) immediately notify the National Response of the release. Potential carcinogens are grouped into high-, medium-, or low-hazard categories on the basis of biological information available. The reportable quantity for B[a]P is 1 lb (EPA 1987).

9.3 STATE

The State of New York has recommended a guidance level of 0.2 μg/L for the sum of benz[a]anthracene, benzofluoranthene, B[a]P, chrysene, fluoranthene, indeno[1,2,3-cd]pyrene, methylbenz[a]anthracene, and pyrene in ambient water (NYSDEC 1984). (Regulations and advisory guidance from the states were still being compiled at the time of printing.)

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11. GLOSSARY

Acute Exposure--Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Bioconcentration Factor (BCF)--The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same time period.

Carcinogen--A chemical capable of inducing cancer.

Ceiling value (CL)--A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure--Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity--The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity--Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

Frank Effect Level (FEL)--That level of exposure which produces a statistically or biologically significant increase in frequency or severity of unmistakable adverse effects, such as irreversible functional impairment or mortality, in an exposed population when compared with its appropriate control.

EPA Health Advisory--An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)--The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure--Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity--The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In vitro--Isolated from the living organism and artificially maintained, as in a test tube.

In vivo--Occurring within the living organism.

Key Study--An animal or human toxicological study that best illustrates the nature of the adverse effects produced and the doses associated with those effects.

Lethal Concentration(LO) (LC_{LO})--The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration(50) (LC_{50})--A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose(LO) (LD_{LO})--The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose(50) (LD_{50})--The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)--The lowest dose of chemical in a study or group of studies which produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lowest-Observed-Effect Level (LOEL)--The lowest dose of chemical in a study or group of studies which produces statistically or biologically significant increases in frequency or severity of effects between the exposed population and its appropriate control.

Malformations--Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level--An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

Mutagen--A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity--The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)--That dose of chemical at which there are no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

No-Observed-Effect Level (NOEL)--That dose of chemical at which there are no statistically or biologically significant increases in frequency or severity of effects seen between the exposed population and its appropriate control.

Permissible Exposure Limit (PEL)--An allowable exposure level in workplace air averaged over an 8-h shift.

q_1^*--The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1^* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually $\mu g/L$ for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD)--An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)--The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are: (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-h period.

Reproductive Toxicity--The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL)--The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity--This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen--A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)--A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-weighted Average (TWA)--An allowable exposure concentration averaged over a normal 8-h workday or 40-h workweek.

Uncertainty Factor (UF)--A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of humans, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX: PEER REVIEW

A peer review panel was assembled for benzo[a]pyrene. The panel consisted of the following members: Dr. Alexander Wood, Hoffmann-La Roche, Inc.; Dr. Dietrich Hoffmann, American Health Foundation; and Dr. Roger McClellan, Lovelace Institute for Inhalation Toxicology. These experts collectively have knowledge of B[a]P's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in the Superfund Amendments and Reauthorization Act of 1986, Sect. 110.

A joint panel of scientists from ATSDR and EPA has reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with the Agency for Toxic Substances and Disease Registry.