Agency for Toxic Substances and Disease Registry (ATSDR)
Case Studies in Environmental Medicine
Toxicity of Polycyclic Aromatic Hydrocarbons (PAHs)

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Key Concepts	• Because of combustion of fossil fuels and organic waste, PAHs are ubiquitous in the environment • Studies show that certain PAH metabolites interact with DNA and are genotoxic, causing malignancies and heritable genetic damage in humans. • In humans, heavy occupational exposure to mixtures of PAHs entails a substantial risk of lung, skin, or bladder cancer.
About This and Other Case Studies in Environmental Medicine	This educational case study document is one in a series of self-instructional modules designed to increase the primary care provider's knowledge of hazardous substances in the environment and to promote the adoption of medical practices that aid in the evaluation and care of potentially exposed patients. The complete series of Case Studies in Environmental Medicine is located on the ATSDR Web site at http://www.atsdr.cdc.gov/csem/. In addition, the downloadable PDF version of this educational series and other environmental medicine materials provides content in an electronic, printable format, especially for those who may lack adequate Internet service.
How to Apply for and Receive Continuing Education Credit	See Internet address www.atsdr.cdc.gov/csem/conteduc.html for more information about continuing medical education credits, continuing nursing education credits, and other continuing education units.

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How to Use This Course

Introduction	The goal of *Case Studies in Environmental Medicine* (CSEM) is to increase the primary care provider's knowledge of hazardous substances in the environment and to help in evaluation and treating of potentially exposed patients. This CSEM focuses on the toxicity of polycyclic aromatic hydrocarbons.
Available Versions	Two versions of the *Toxicity of Polycyclic Aromatic Hydrocarbons* CSEM are available. • The HTML version http://www.atsdr.cdc.gov/csem/pah/ provides content through the Internet. • The downloadable PDF version provides content in an electronic, printable format, especially for those who may lack adequate Internet service. The HTML version offers interactive exercises and prescriptive feedback to the user.
Instructions	To make the most effective use of this course. • Take the Initial Check to assess your current knowledge about the toxicity of polycyclic aromatic hydrocarbons. • Read the title, learning objectives, text, and key points in each section. • Complete the progress check exercises at the end of each section and check your answers. • Complete and submit your assessment and posttest response online if you wish to obtain continuing education credit. Continuing education certificates can be printed immediately upon completion.
Instructional Format	This course is designed to help you learn efficiently. Topics are clearly labeled so that you can skip sections or quickly scan sections you are already familiar with. This labeling will also allow you to use this training material as a handy reference. To help you identify and absorb important content quickly, each section is structured as follows:

Section Element	Purpose
Title	Serves as a "focus question" that you should be able to answer after completing the section
Learning Objectives	Describes specific content addressed in each section and focuses your attention on important points
Text	Provides the information you need to answer the focus question(s) and achieve the learning objectives
Key Points	Highlights important issues and helps you review
Progress Check	Enables you to test yourself to determine whether you have mastered the learning objectives
Answers	Provide feedback to ensure you understand the content and can locate information in the text

Learning Objectives	Upon completion of the Toxicity of Polycyclic Aromatic Hydrocarbons (PAH) CSEM, you will be able to

Content Area	Objectives
Overview	• explain what PAHs are • describe the properties of PAHs • identify where PAHs are found
Exposure Pathways	• identify routes of exposure to PAHs
Who is at Risk	• identify the populations at high risk for exposure to PAHs
Standards and Regulations	• describe the Occupational Safety and Health Administration's permissible exposure limit (PEL) for PAHs • describe the U.S. Environmental Protection Agency's maximum contaminant level (MCL) for PAHs in drinking water
Biological Fate	• describe the biologic fate of PAHs in the body
Pathogenic Changes	• describe how PAHs are believed to induce pathogenic changes
Health Effects	• describe health effects associated with PAH exposure
Clinical Assessment	• describe typical signs and symptoms of patients with acute PAH exposure • describe typical signs and symptoms of patients with chronic PAH exposure • describe important elements of the exposure history • describe the focus of the physical examination • describe tests used to assist in evaluation of patients exposed to PAHs
Treatment and Management	• identify strategies for managing patients with chronic PAH exposure
Patient Education and Counseling	• describe care advice for the patient exposed to PAHs

Initial Check

Instructions	This Initial Check will help you assess your current knowledge about the toxicity of polycyclic aromatic hydrocarbons (PAH). To take the Initial Check, read the case below, and then answer the questions that follow.
Case Study	**Dyspnea, weight loss, and weakness in a 52-year-old male coal tar manufacturing plant worker** A 52-year-old man comes to your office for a health evaluation, his first in 3 years. While trying to assure you that he is in reasonably good health, he admits that his wife prompted this visit. She is concerned about his weight loss, lack of stamina, and weakness in the shoulders and arms. When you review his chart, you see that he has lost 30 pounds since his last visit. The patient also describes shortness of breath with moderate activity. He is a lifelong nonsmoker and drinks alcohol only occasionally. He is taking no medications. His past medical history is noncontributory. A review of systems reveals that the patient also has a chronic, intermittently productive cough, which has been ongoing for 1 month. The patient has worked at a coal tar manufacturing plant for the past 34 years. He has been a lifelong resident of an urban industrial neighborhood that is approximately 1 mile from where he works. He has been married for 25 years. His wife and adult daughter are in good health. A physical examination shows that his vital signs are normal. An inspection of his skin reveals multiple dry, scaly, hyperpigmented macules involving the forehead, temporoparietal areas, eyelids, and brows, and several hyperkeratotic papillomata on his face, neck, upper chest, forearms, and hands. Palpation of the right supraclavicular area reveals a firm, nontender, fixed lymph node 2 x 3 centimeters (cm) in size. Auscultation discloses intermittent, scattered, right-sided wheezes and dry bibasilar crackles. The remainder of the exam is unremarkable. The patient's laboratory results are remarkable for the following: 1. hemoglobin = 12.9 grams per deciliter (g/dL) (normal = 14–18 g/dL); 2. hematocrit = 36% (normal = 42%–52%); 3. leukocyte count = 2.9 x 10^3 per microliter (µL) (normal = 3.9–11 x 10^3/µL); 4. serum calcium = 12.9 milligrams per deciliter (mg/dL) (normal = 8.5–10.5 mg/dL); 5. alkaline phosphatase = 483 international units per liter (IU/L) (normal = 30–125 IU/L) with concomitant elevation of GGTP (GGT); 6. SGOT (AST) 121 IU/L (normal = 7–45); 7. SGPT (ALT) 129 IU/L (normal = 7–35 IU/L); 8. The chest radiograph reveals a 3.3-cm central, thick-walled, cavitating lesion with irregular, spicular margins in the right upper lobe, and atelectasis and prominence of the right hilar lymphatics.

Initial Check

1. What are likely sources of PAHs for the patient described in the case study?
2. Besides the patient, who in the case study might be at risk for PAH exposure?
3. The patient's daughter, who has lived in his household all of her life, recently gave birth to a daughter. Is the newborn at risk for PAH exposure? Why or why not?
4. How could you document that the work environment of the patient described in the case study contributed to his risk of lung cancer?
5. Before his present employment, the patient in the case study was employed as a laborer on a farm. He says that he was not exposed to pulmonary toxic agents such as asbestos or silica. What is the problem list and the differential diagnosis for this patient?
6. The diagnosis for the patient described in the case study is squamous cell carcinoma of the lung. In general, what can you do to decrease the risk for lung cancer among your patients?
7. Would you consider the patient described in the case study a sentinel case requiring notification of public health agencies? Explain.

Initial Check Answers

1. The patient may have been exposed to coal tar manufacturing pollutants at his work for more than 34 years. Moreover, if his home is in the prevailing downwind direction from the coal tar manufacturing plant, pollutants might contribute to ambient air contamination near his home. However, environmental studies related to air pollution are more complex and must separate out contaminants from indoor cooling/heating systems, environmental tobacco smoke, urban air pollution, and other sources. The patient might have been exposed to PAH mixtures by all three routes: inhalation, ingestion, and direct cutaneous contact.

   More information for this answer can be found in the "What Are Routes of Exposure to PAHs?" and "Who Is at Risk of Exposure to PAHs?" sections.

2. Workers at the coal tar manufacturing plant and residents in the community downwind from the plant might be exposed to PAH mixtures. However, other contributors to environmental ambient air contamination should be kept in mind, including environmental tobacco smoke, indoor cooking and heating practices, and urban air pollution. The patient's family members might be at risk for additional exposure if the patient carried these compounds home on his skin and work clothes.

   More information for this answer can be found in the "What Are Routes of Exposure to PAHs?" and "Who Is at Risk of Exposure to PAHs?" sections.

3. The patient's newborn granddaughter may be at risk for PAH exposure. If the patient's daughter breathed contaminated air in and around the house, then the baby could have been exposed *in utero*. This exposure could have occurred while the patient's daughter was

doing various household chores, such as laundering, dusting, and general cleaning of the contaminated home or her father's work clothing. Based on animal studies, PAH mixtures absorbed into the mother's system might continue to be transferred to the baby via breast milk. The baby might also be breathing contaminated air, thereby increasing her exposure.

More information for this answer can be found in the "Who Is at Risk of Exposure to PAHs?" section.

4. The role of the workplace in the patient's PAH mixture exposure can be determined by area sampling at the work site, individual monitoring, medical surveillance of coworkers, and air sampling within the immediate community. Industrial hygienists would typically perform these activities. Data may be available through sources at the coal tar manufacturing plant and at local, state, or federal agencies.

   More information for this answer can be found in the "Who Is at Risk of Exposure to PAHs" section.

5. The patient's problem list includes weight loss, fatigue, muscle weakness, skin lesions on exposed areas, exertional dyspnea, and a roentgenographically identified cavitating lesion in the right upper lobe with associated lymphadenopathy. The differential diagnosis includes carcinoma of the lung, tuberculosis, fungal lung infection, and lung abscess.

   More information for this answer can be found in the "What Health Effects are Associated with PAH Exposure" and "Clinical Assessment."" sections.

6. The main objective is to educate patients about cancer prevention. You should try to stimulate changes in their work habits and lifestyle that will decrease the risk for cancer. A risk assessment can identify elements in a person's workplace, family history, medical history, and lifestyle that might be controllable risk factors.

   For example, between 75% and 80% of all cases of bronchogenic carcinoma are due to cigarette smoking and are therefore preventable. Of the remaining 20%–25%, many are related to occupation or the environment and could therefore be prevented by appropriate workplace or environmental controls. The incidence of lung cancer might also be decreased through education efforts that focus on

   - smoking prevention,
   - improving working conditions,
   - substitution of less-hazardous materials in work processes and building materials, and
   - increased awareness of personal risk factors.

More information for this answer can be found in the "What Instructions Should Be Given to Patients Exposed to PAHs?" section.

7. In view of the patient's medical, social, occupational, and family history, the workplace and environmental factors emerge as the most likely causal factors in the development of his neoplastic disease. When the potential exists for others to be exposed, serious illness related to occupational or environmental factors should be reported to the appropriate state and federal authorities. For example, OSHA would have responsibility for PAHs in the workplace air at the coal tar manufacturing site. EPA would have responsibility for the level of emissions to the ambient air or water. Inclusion of this case in a tumor registry should also be considered.

   More information for this answer can be found in the "Clinical Assessment" and "How Should Patients Exposed to PAHs be Treated and Managed?" sections.

What Are Polycyclic Aromatic Hydrocarbons (PAHs)?

Learning Objective

Upon completion of this section, you will be able to

- explain what PAHs are, and
- describe the properties of PAHs.

Definition

PAHs are a class of organic compounds produced by incomplete combustion or high-pressure processes. PAHs form when complex organic substances are exposed to high temperatures or pressures.

Often, PAHs consist of three or more fused benzene rings containing only carbon and hydrogen (**Figure 1**). Differences in the configuration of rings may lead to differences in properties.

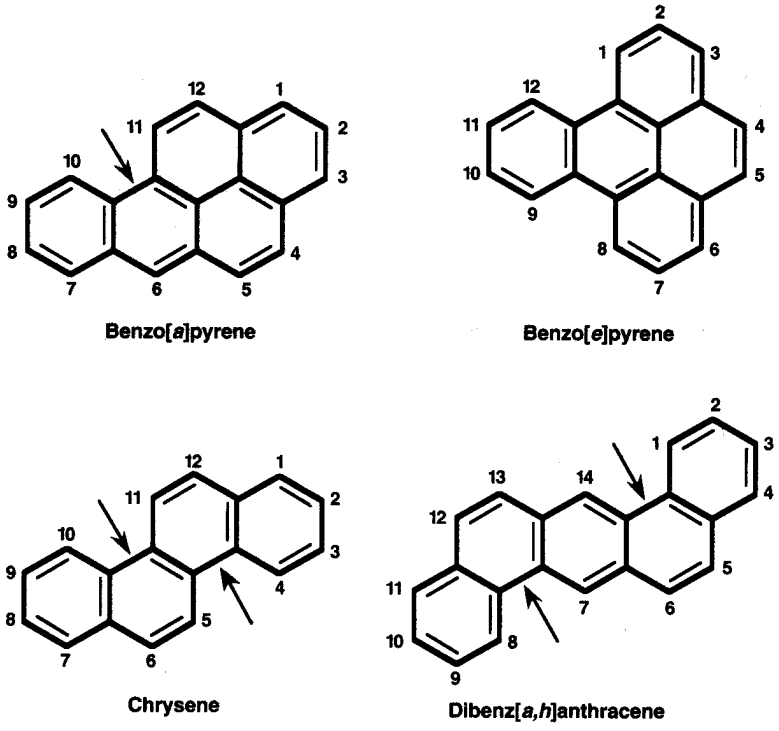

Figure 1. Structural formulas of selected polycyclic aromatic hydrocarbons (PAHs). The arrows indicate bay regions.

Synonyms

PAHs are known by several names:

- polycyclic organic matter (POM),
- polynuclear aromatic hydrocarbons,
- polynuclear aromatics (PNAs), and
- polynuclear hydrocarbons.

The more common PAHs include

- benzo(a)anthracene,

- benzo(a)pyrene,
- benzo(e)pyrene,
- benzo(g,h,i)perylene,
- benzo(k)fluoranthene,
- chrysene,
- coronene,
- dibenz(a,h)acridine,
- dibenz(a,h)anthracene, and
- pyrene.

Properties

PAHs:

- are solids with low volatility at room temperature,
- have relatively high molecular weights,
- are soluble in many organic solvents,
- are relatively insoluble in water, and
- most can be photo-oxidized and degraded to simpler substances.

Key Points

- PAHs are a class of organic compounds produced by incomplete combustion or high-pressure processes.
- Often, PAHs consist of three or more fused benzene rings containing only carbon and hydrogen.
- PAHs are solids with low volatility at room temperature. They are relatively insoluble in water, and most can be photo-oxidized and degraded to simpler substances.

Progress Check

1. Which of the following is (are) true regarding PAHs?

   A. PAHs comprise a class of organic compounds produced by high-pressure processes.
   B. Often, PAHs consist of three or more fused benzene rings containing only hydrogen and carbon.
   C. PAHs comprise a class of organic compounds produced from incomplete combustion.
   D. All of the above.

   To review relevant content, see "Definition" in this section.

2. Which of the following is (are) true regarding PAHs?

   A. They are water-soluble.
   B. They have relatively low molecular weights.
   C. They are solids with low volatility at room temperature.
   D. All of the above.

   To review relevant content, see "Properties" in this section.

Answers

1. The correct true answer is D. PAHs are a class of organic compounds produced from incomplete combustion or high-pressure processes and consist of three or more fused benzene rings containing only hydrogen and carbon.
2. The correct true answer is C. PAHs are solids with low volatility at room temperature. The remaining choices are false because PAHs are relatively insoluble in water and have relatively high molecular weights.

Where Are Polycyclic Aromatic Hydrocarbons (PAHs) Found?

Learning Objective	Upon completion of this section, you will be able to • identify where PAHs are found.
Introduction	PAHs are ubiquitous in the environment and are common byproducts of combustion processes. PAHs are a natural component of most fossil fuels. Although produced naturally by forest fires and volcanoes, most PAHs in ambient air are the result of man-made processes. Such processes include • burning fuels such as coal, wood, petroleum, petroleum products, or oil, • burning refuse, used tires, polypropylene, or polystyrene, • coke production, and • motor vehicle exhaust [Cherng *et al.* 1996; Lewitas 1997]. There are approximately 100 different known PAHs in air, soil, foodstuffs, and water [Zedeck 1980]. Diesel exhaust contains significant amounts of PAHs. Benzo(a)pyrene, a potent carcinogen, is commonly used as an environmental indicator for PAHs.
Industrial Use	PAHs are found in industries that produce or use coal tar, coke, or bitumen (asphalt). Coal tar pitch and creosote, which are complex mixtures of liquid and solid aromatic hydrocarbons produced in coke ovens, contain significant amounts of benzo(a)pyrene and other PAHs. PAHs are produced in • coal gasification plants, • municipal incinerators, • smokehouses, and • some aluminum production facilities.
Environmental Fate	Once emitted to the atmosphere, weight influences the fate of the gaseous PAH mixtures. Heavier PAHs (more than four rings) tend to adsorb to particulate matter, while lighter PAHs (less than four rings) tend to remain gaseous until removed via precipitation [Skupinska *et al.* 2004]. PAH concentrations in water tend to be low (around 100 ng/L) due to their weak solubility. The weak solubility leads to accumulation in sediments and aquatic organisms. PAHs can be absorbed by plants and can accumulate in soil.
Cigarettes	Cigarette smoke contains many PAHs; therefore, cigarette smoking and environmental tobacco smoke are additional sources of PAHs.
Environmental Indicator for PAHs	Benzo(a)pyrene, a potent carcinogen, is generally used as an environmental indicator for PAHs.

Key Points

- PAHs are ubiquitous in the environment.
- Most PAHs in ambient air are the result of man-made processes.
- PAHs are found in industries that produce or use coal tar, coke, or bitumen (asphalt). They are emitted by coal gasification plants, smokehouses, municipal incinerators, and some aluminum production facilities.
- PAHs mostly accumulate in soils.
- Benzo(a)pyrene is commonly used as an environmental indicator for PAHs.

Progress Check

3. Which of the following is true regarding PAHs?

   A. PAHs are found predominantly in water reservoirs.
   B. PAHS are found in relatively few geographic areas worldwide.
   C. PAHS are found in coal gasification plants and some aluminum production facilities.
   D. PAHs mostly result from natural processes.

   To review relevant content, see "Introduction" and "Industrial Use" in this section.

4. Which of the following industries or processes involve PAH production?

   A. Smokehouses.
   B. Municipal incinerators.
   C. Coal tar or coke production or use.
   D. All of the above.

   To review relevant content, see "Industrial Use" in this section.

Answers

3. The correct answer is C. PAHs are found in coal gasification plants and some aluminum production facilities.
4. The correct answer is D. Industries or processes that involve PAH production include smokehouses, municipal incinerators, and coal tar or coke production or use.

What Are the Routes of Exposure for Polycyclic Aromatic Hydrocarbons (PAHs)?

Learning Objective	Upon completion of this section, you will be able to • identify routes of exposure to PAHs.
Introduction	PAH exposure through air, water, soil, and food sources occurs on a regular basis for most people. Routes of exposure include ingestion, inhalation, and dermal contact in both occupational and non-occupational settings. Some exposures may involve more than one route simultaneously, affecting the total absorbed dose (such as dermal and inhalation exposures from contaminated air). All non-workplace sources of exposure such as diet, smoking, and burning of coal and wood should be taken into consideration.
Air	PAH concentrations in air can vary from less than 5 to 200,000 nanograms/cubic meter (ng/m^3) [Cherng *et al.* 1996; Georgiadis and Kyrtopoulos 1999]. Although environmental air levels are lower than those associated with specific occupational exposures, they are of public health concern when spread over large urban populations [Zmirou *et al.* 2000]. The background levels of seventeen of the Agency for Toxic Substances and Disease Registry's toxicological profile priority PAHs in ambient air are reported to be 0.02–1.2 $nanograms/m^3$ in rural areas and 0.15–19.3 ng/m^3 in urban areas [ATSDR 1995]. Cigarette smoking and environmental tobacco smoke are other sources of air exposure. Smoking one cigarette can yield an intake of 20–40 ng of benzo (a) pyrene [Phillips 1996; O'Neill *et al.* 1997]. Smoking one pack of unfiltered cigarettes per day yields 0.7 µg/day benzo(a)pyrene exposure. Smoking a pack of filtered cigarettes per day yields 0.4 µg/day [Sullivan and Krieger 2001]. Environmental tobacco smoke contains a variety of PAHs, such as benzo(a)pyrene, and more than 40 known or suspected human carcinogens. Side-stream smoke (smoke emitted from a burning cigarette between puffs) contains PAHs and other cytotoxic substances in quantities much higher than those found in mainstream smoke (exhaled smoke of smoker) [Jinot and Bayard 1996; Nelson 2001].
Water	PAHs can leach from soil into water. Water contamination also occurs from industrial effluents and accidental spills during oil shipment at sea. Concentrations of benzo(a)pyrene in drinking water are generally lower than those in untreated water and about 100-fold lower than the U.S. Environmental Protection Agency's (EPA) drinking water standard. (EPA's maximum contaminant level [MCL] for benzo(a)pyrene in drinking water is 0.2 parts per billion [ppb].)
Soil	Soil contains measurable amounts of PAHs, primarily from airborne fallout. Documented levels of PAHs in soil near oil refineries have been as high as 200,000 micrograms per kilogram (µg/kg) of dried soil. Levels in soil samples obtained near cities and areas with heavy traffic were typically less than 2,000 µg/kg [IARC 1973].

Foodstuffs	In non-occupational settings, up to 70% of PAH exposure for a non-smoking person can be associated with diet [Skupinska *et al.* 2004]. PAH concentrations in foodstuffs vary. Charring meat or barbecuing food over a charcoal, wood, or other type of fire greatly increases the concentration of PAHs. For example, the PAH level for charring meat can be as high as 10–20 µg/kg [Phillips 1999]. Charbroiled and smoked meats and fish contain more PAHs than do uncooked products, with up to 2.0 µg/kg of benzo(a)pyrene detected in smoked fish. Tea, roasted peanuts, coffee, refined vegetable oil, cereals, spinach, and many other foodstuffs contain PAHs. Some crops, such as wheat, rye, and lentils, may synthesize PAHs or absorb them via water, air, or soil [Grimmer 1968; Menzie *et al.* 1992; Shabad and Cohan 1972; IARC 1973].
Other Sources of Exposure	PAHs are found in prescription and nonprescription coal tar products used to treat dermatologic disorders such as psoriasis and dandruff [Van Schooten 1996]. PAHs and their metabolites are excreted in breast milk, and they readily cross the placenta. Anthracene laxative use has been associated with melanosis of the colon and rectum [Badiali *et al.* 1985].
Background Exposures	In the Third National Report on Human Exposure to Environmental Chemicals [CDC 2005], urinary levels of hydroxylated metabolites of PAHs were measured in a subsample of the National Health and Nutrition Examination Survey (NHANES) among participants aged 6 years and older during 1999–2002. Participants were selected within the specified age range to be a representative sample of the U.S. population. Measurements of the 22 metabolites reflect exposure to PAHs that occurred a few days prior to the urine samples being taken. Pyrene is commonly found in PAH mixtures, and its urinary metabolite, 1-hydroxypyrene, has been used as an indicator of exposure to PAH chemicals [Becher and Bjorseth 1983; Granella and Clonfero 1993; Popp 1997; Santella *et al.* 1993, CDC 2005]. The American Conference of Governmental Industrial Hygienists recommends measurement of 1-hydroxypyrene in the end-of-shift, end-of-work-week urine samples as a biological exposure index (BEI) for assessment of exposure to mixtures containing PAHs [ACGIH 2005; Heikkila *et al.* 1995]. The geometric mean of urine concentrations (in nanograms/grams creatinine) of 1-hydroxypyrene for the U.S. population aged 6 years and older for survey years 1999–2000 was 74.2, and in survey years 2001–2002 it was 46.4 [CDC 2005]. The geometric mean levels of 1-hydroxypyrene in a NHANES 2001–2002 subsample is similar to that of other general populations residing in an urban setting [Goen *et al.* 1995; Chuang *et al.* 1999; Heudorf and Angerer 2001; Roggi *et al.* 1997; Yang *et al.* 2003]. Higher levels have been noted for residents of industrialized urban areas than in rural or suburban settings [Adonis *et al.* 2003; Kanoh *et al.* 1993; Kuo *et al.* 2004]. Many-fold higher levels can be found in workers from certain occupations [Jacob and Seidel 2002], including aluminum smelting [Alexandrie *et al.* 2000]; diesel engine

	mechanics [Adonis *et al.* 2003; Kuusimaki *et al.* 2004]; taxi, bus, and truck drivers [Chuang *et al.* 2003; Hansen *et al.* 2004; Kuusimaki *et al.* 2004]; painters [Lee *et al.* 2003], boilermakers [Mukherjee *et al.* 2004]; toll booth operators [Tsai *et al.* 2004]; traffic police [Merlo *et al.* 1998] and coke oven plant workers [Lu *et al.* 2002; Serdar *et al.* 2003; Siwinska *et al.* 2004]. Tobacco smoking leads to higher levels in smokers [Chuang *et al.* 2003; Adonis *et al.* 2003; Heudorf and Angerer 2001b] as well as in the non-smoking children of smokers [Tsai *et al.* 2003]. Coal stove exposure or consumption of broiled, fried, or grilled meat contribute to higher levels of 1-hydroxypyrene [Siwinska *et al.* 1999; Scheepers *et al.* 2002; Yang *et al.* 2003; [CDC 2005].
Key Points	• PAH exposure occurs on a regular basis for most people. • In non-occupational settings, most PAH exposures for a non-smoking person can be associated with diet • Routes of exposure include inhalation, ingestion, and dermal • Exposure may also occur via placental transfer, breast milk, and coal tar-containing products.
Progress Check	5. In non-occupational settings, PAH exposure in a non-smoking individual mostly comes from which of the following? A. Foodstuff ingestion. B. Inhalation route. C. Dermal route. D. Water. *To review relevant content, see "Foodstuffs" in this section.* 6. Exposure to PAHs may occur as a result of which of the following? A. Eating roasted peanuts. B. Eating charbroiled meats. C. Inhaling second hand tobacco smoke. D. All of the above. *To review relevant content, see "Air" and "Foodstuffs" in this section.*

Answers

5. The correct answer is A. In non-occupational settings, the majority of PAH exposure in a non-smoking individual comes from foodstuff ingestion.
6. The correct answer is D. Exposure to PAHs may occur as a result of eating roasted peanuts, eating charbroiled meats, or inhaling secondhand tobacco smoke.

Who Is at Risk of Exposure to Polycyclic Aromatic Hydrocarbons (PAHs)?

Learning Objective	Upon completion of this section, you will be able to • identify the populations at high risk for exposure to PAHs.
Introduction	Persons working with coal and coal products have a greater likelihood of exposure to PAHs. Awareness of historical occupational and environmental exposures can aid the clinician in not only assessing potential sources of exposure but also in recognizing those populations who may be at higher risk of exposure.
Historical Occupational Exposures	Percival Pott, an English surgeon, was the first to report a connection between occupational exposure and cancer. In 1775, he described an unusually high incidence of scrotal cancer among London chimney sweeps and suggested this was due to their exposure to soot and ash. Since then, other coal tar-related cancers have been induced in laboratory animals and found in humans [Kennaway 1995; Kjaerheim 1999]. For example, the PAH benzo(a)pyrene, which was isolated from coal tar in the 1930s, was determined to be carcinogenic when applied to the skin of test animals. In 1947, the relationship between lung cancer and working conditions of gas industry workers and those working with coal tar was established [Kenneway 1995]. An increased incidence of cancers, particularly of the lung, was shown in epidemiologic studies of gas workers [Doll *et al.* 1965, 1972]. Several epidemiologic studies have shown increased cancer mortality in workers exposed to PAH mixtures. Exposure to other potentially carcinogenic substances often occurred in these studies [Lloyd 1971; Mazumdar *et al.* 1975; Redmond *et al.* 1972; Redmond and Strobino 1976; Hammond *et al.* 1976].
Current Occupational Exposures	Workers in industries or trades using or producing coal or coal products are at highest risk for PAH exposure. Those workers include, but are not limited to • aluminum workers, • asphalt workers, • carbon black workers, • chimney sweeps, • coal-gas workers, • coke oven workers, • fishermen (coal tar on nets), • graphite electrode workers, • machinists, • mechanics (auto and diesel engine), • printers, • road (pavement) workers, • roofers, • steel foundry workers, • tire and rubber manufacturing workers, and • workers exposed to creosote, such as

	○ carpenters, ○ farmers, ○ railroad workers, ○ tunnel construction workers, and ○ utility workers. A small increased risk of cancer in workers exposed to diesel exhaust has been suggested by some epidemiologic studies [Bhatia *et al.* 1998; Boffetta *et al.* 1988, 1990, 1997; Garshick *et al.* 1987, 1988; Steenland *et al.* 1990, 1992]. Exposure is almost always to mixtures that pose a challenge in developing conclusions [Samet 1995].
Historical Environmental Exposures	Historically, in locations where gas for lighting and heating was manufactured from coal or oil, large amounts of PAHs existed and may still exist as waste deposits. Before World War II, more than 1,000 coal gasification plants are estimated to have existed throughout the midwestern and eastern United States [Environmental Research and Technology 1984]. These plants began to phase out in the early 1950s when the use of interstate natural gas pipelines became more prominent.
Susceptible Populations	Fetuses may be at risk for PAH exposure. PAH and its metabolites have been shown to cross the placenta in various animal studies [ATSDR 1995]. Because PAHs are excreted in breast milk, nursing infants of exposed mothers can be secondarily exposed.
Key Points	• PAH and metabolites cross the placenta and are excreted in breast milk. • Occupations that entail exposure to PAH include workers exposed to coal and coal products.
Progress Check	7. Which of the following groups of workers is (are) at most risk of heavy exposure to PAHs on the job? A. Workers exposed to creosote. B. Steel foundry workers. C. Roofers. D. All of the above. *To review relevant content, see "Current Occupational Exposures" in this section.* 8. Which of the following is true regarding PAH exposure? A. Those most at risk are workers in the auto emission testing industry. B. Health endpoints can often be directly traced to a specific PAH metabolite. C. PAHs cross the placenta. D. None of the above. *To review relevant content, see "Current Occupational Exposures" and "Susceptible Populations" in this section.*

Answers

7. The correct answer is D. Steel foundry workers, roofers, and workers exposed to creosote have jobs that put them at risk of heavy exposure to PAHs.
8. 8.The correct answer is C. PAHs do cross the placenta. Persons working with coal and coal products have a greater likelihood of exposure to PAHs than workers in the auto emission testing industry. Exposures are typically to mixtures of PAHs, making it difficult to attribute a health end point to a specific PAH metabolite.

What Are the Standards and Regulations for Polycyclic Aromatic Hydrocarbons (PAH) Exposure?

Learning Objectives

Upon completion of this section, you will be able to

- describe the Occupational Safety and Health Administration's (OSHA) Permissible Exposure Level (PEL) for PAH, and
- describe the U.S. Environmental Protection Agency's (EPA) Maximum Contaminant Level (MCL) for PAH in drinking water.

Introduction

U.S. government agencies have established standards that are relevant to PAHs exposures in the workplace and the environment. There is

- a standard relating to PAH in the workplace, and
- a standard for PAH in drinking water.

Workplace

OSHA has not established a substance-specific standard for occupational exposure to PAHs. Exposures are regulated under OSHA's Air Contaminants Standard for substances termed coal tar pitch volatiles (CTPVs) and coke oven emissions. Employees exposed to CTPVs in the coke oven industry are covered by the coke oven emissions standard.

The OSHA coke oven emissions standard requires employers to control employee exposure to coke oven emissions by the use of engineering controls and work practices. Wherever the engineering and work practice controls that can be instituted are not sufficient to reduce employee exposures to or below the permissible exposure limit, the employer shall nonetheless use them to reduce exposures to the lowest level achievable by these controls and shall supplement them by the use of respiratory protection. The OSHA standard also includes elements of medical surveillance for workers exposed to coke oven emissions.

Air

The OSHA PEL for PAHs in the workplace is 0.2 milligram/cubic meter (mg/m^3).

The OSHA-mandated PAH workroom air standard is an 8–hour time-weighted average (TWA) permissible exposure limit (PEL) of 0.2 mg/m^3, measured as the benzene-soluble fraction of coal tar pitch volatiles. The OSHA standard for coke oven emissions is 0.15 mg/m^3. The National Institute for Occupational Safety and Health (NIOSH) has recommended that the workplace exposure limit for PAHs be set at the lowest detectable concentration, which was 0.1 mg/m^3 for coal tar pitch volatile agents at the time of the recommendation. Table 1 summarizes relevant exposure criteria for PAHs.

Workplace Standards

Table 1. Standards and Regulations for Polycyclic Aromatic Hydrocarbons (PAHs)

Agency	Focus	Level	Comments
American Conference of Governmental Industrial Hygienists	Air: workplace	0.2 milligrams per cubic meter (mg/m^3) for benzene-soluble coal tar pitch fraction	Advisory: TLV* (8-hour TWA†)
National Institute for Occupational Safety and Health	Air: workplace	0.1 mg/m^3 for coal tar pitch volatile agents	Advisory: REL‡ (8-hour TWA)
Occupational Safety and Health Administration	Air: workplace	0.2 mg/m^3 for benzene-soluble coal tar pitch fraction	Regulation: (benzene soluble fraction of coal tar volatiles) PEL§ (8-hour workday)
U.S. Environmental Protection Agency	Water	0.0001 milligrams per liter (mg/L)	MCL¶ for benz(a)anthracene
		0.0002 mg/L	MCL for benzo(a)pyrene, benzo(b)fluoranthene, benzo(k)fluoranthene, chrysene
		0.0003 mg/L	MCL for dibenz(a,h)anthracene
		0.0004 mg/L	MCL for indenol(1,2,3-c,d)pyrene

*TLV: threshold limit value.

†TWA (time-weighted average): concentration for a normal 8-hour workday and a 40-hour workweek to which nearly all workers may be repeatedly exposed.

‡REL (recommended exposure limit): recommended airborne exposure limit for coal tar pitch volatiles (cyclohexane-extractable fraction) averaged over a 10-hour work shift.

§PEL (permissible exposure limit): the legal airborne permissible exposure limit (PEL) for coal tar pitch volatiles (benzene soluble fraction) averaged over an 8-hour work shift.

¶MCL: maximum contaminant level.

Environ-mental Standards	***Water*** The maximum contaminant level goal for benzo(a)pyrene in drinking water is 0.2 parts per billion (ppb). In 1980, EPA developed ambient water quality criteria to protect human health from the carcinogenic effects of PAH exposure. The recommendation was a goal of zero (nondetectable level for carcinogenic PAHs in ambient water). EPA, as a regulatory agency, sets a maximum contaminant level (MCL) for benzo(a)pyrene, the most carcinogenic PAH, at 0.2 ppb. EPA also sets MCLs for five other carcinogenic PAHs (see Table 1). For more information on EPA rules and regulations regarding PAH, visit EPA's Web site at www.epa.gov. ***Food*** The U.S. Food and Drug Administration has not established standards governing the PAH content of foodstuffs.
Key Points	• OSHA's PEL for PAH in the workplace is 0.2 mg/m^3 for benzene-soluble coal tar pitch fraction of air (8-hour TWA). • OSHA requires workers to be trained in the proper use of appropriate personal protective equipment (PPE) and safety. • Workers must receive medical surveillance if exposed above the PEL. • EPA's maximum contaminant level (MCL) for PAH in drinking water is 0.2 ppb of drinking water.

Progress Check

9. Which of the following is true regarding OSHA's role in PAH exposure limits?

   A. OSHA is a regulatory agency that has a permissible exposure level (PEL) established for PAHs in the workplace.
   B. OSHA requires all workers to be provided with appropriate personal protection equipment (PPE) and receive safety training.
   C. OSHA requires workers to receive medical surveillance if exposed above the permissible exposure limit PEL.
   D. All of the above.

   To review relevant content, see "Workplace Standards" in this section.

10. Which of the following is true regarding EPA's role in PAH exposure limits?

    A. The maximum contaminant levels (MCLs) for PAHs are set to protect human health against the carcinogenic effects of PAH.
    B. EPA regulates PAH levels in foodstuffs.
    C. EPA is a regulatory agency that has established MCLs for several PAHs in air.
    D. MCLs are based on an 8–hour time weighted average.

    To review relevant content, see "Environmental Standards" in this section.

Answers

9. The correct answer is D. OSHA is a regulatory agency which has established a PEL established for PAHs in the workplace. OSHA requires all workers to be provided with appropriate PPE and receive safety training. OSHA requires workers to receive medical surveillance if exposed above the PEL.
10. The correct answer is A. The MCLs for PAHs are set to protect human health against the carcinogenic effects of PAHs. The FDA, not EPA, regulates contaminant levels in foodstuffs and currently has no standard set for PAHs in foodstuffs. EPA is a regulatory agency that has established MCLs for several PAHs in water, not air. OSHA's PELs are based on an 8–hour time-weighted average, not EPA's MCLs.

What Is the Biologic Fate of PAHs in the Body?

Learning Objective

Upon completion of this section, you will be able to

- describe the biologic fate of the PAHs in the body.

Introduction

Once PAHs enter the body, several things occur:

- PAHs are metabolized in a number of organs and excreted in bile and urine
- PAHs are excreted in breast milk and stored to a limited degree in adipose tissue.

Not much data for humans exists regarding the metabolic fate of PAHs. However, information on absorption, distribution, and elimination of these substances is available from animal studies.

Pyrene is commonly found in PAH mixtures, and its urinary metabolite, 1-hydroxypyrene, has been used as an indicator of exposure to PAH chemicals [Becher and Bjorseth 1983; Granella and Clonfero 1993; Popp 1997; Santella *et al.* 1993, CDC 2005]. The ACGIH recommends measurement of 1-hydroxypyrene in the end-of-shift, end-of-work-week urine samples as a biological exposure index (BEI) for assessment of exposure to mixtures containing PAHs.

Measurements of 22 PAH hydroxylated urinary metabolites were taken as part of the Third National Report on Human Exposure to Environmental Chemicals from a subsample of the National Health and Nutrition Examination Survey (NHANES) from participants aged 6 years and older during 1999–2002. These data provide physicians with a reference range so that they can determine whether people have been exposed to higher levels of PAHs than are found in the general population [CDC 2005].

Absorption

PAHs are absorbed through ingestion, inhalation, and dermal contact, according to animal study data. The percent absorbed varies in these studies for several reasons, including the vehicle (transport medium) in which the PAHs are found [Kawamura *et al.* 1988]. In general, PAHs not bound to particulate matter may be absorbed in the lungs better than the same dose found on the surface of airborne particulate matter [Cresia *et al.* 1976; Seto 1993].

Distribution

Once absorbed, PAHs

- enter the lymph,
- circulate in the blood, and
- are metabolized primarily in the liver and kidney.

PAHs differ with respect to distribution patterns and lipophilic properties [Busbee *et al.* 1990]. Because of their lipophilic nature, PAHs can accumulate in breast milk and adipose tissue. However, biliary and urinary excretion of PAHs is relatively efficient because of the wide distribution of enzymes that transform PAHs into polar metabolites.

Metabolism and Excretion	PAHs are predominantly metabolized via CYP enzymes (enzymes in the P-450 mixed-function oxidase system) in the liver [Kapitulnik *et al.* 1977; Keifer *et al.* 1988; Monteith *et al.* 1987]. In addition to the liver and kidneys, metabolism of PAHs occurs in the adrenal glands, testes, thyroid, lungs, skin, sebaceous glands, and small intestines [ATSDR 1995]. PAHs are transformed initially to epoxides, which are converted to dihydrodiol derivatives and phenols. Glucuronide and sulfate conjugates of these metabolites are excreted in the bile and urine. Glutathione conjugates are further metabolized to mercapturic acids in the kidney and are excreted in the urine. The hydroxylated metabolites of the PAHs are excreted in human urine both as free hydroxylated metabolites and as hydroxylated metabolites conjugated to glucuronic acid and sulfate [CDC 2005]. A commonly measured urinary metabolite is 1-hydroxypyrene [Becher and Bjorseth 1983; Granella and Clonfero 1993; Popp 1997; Santella 1993]. Metabolism is a prerequisite for hepatobiliary excretion and elimination through the feces, regardless of route of entry. Excretion half-lives in feces and urine have been reported in animal studies as 22 hours and 28 hours, respectively [Becher and Bjorseth 1983].
Key Points	• Absorption by route varies in animal studies. • PAH distribution patterns vary due to differences in lipophilic properties. • Metabolism via CYP liver enzymes (enzymes in the P-450 mixed-function oxidase system) is the predominant mechanism of PAH metabolism. • PAHs are transformed to epoxides, then to dihydrodiol derivatives and phenols. • Excretion occurs via the bile or urine after metabolite conjugation to glucuronides and sulfates. • 1- Hydroxypyrene is a commonly measured urine metabolite.

Progress Check

11. Which of the following is true regarding PAHs?

    A. PAHs are mostly excreted unchanged in the feces.
    B. PAHs are stored in adipose tissue to a large extent.
    C. PAHs have varied distribution patterns.
    D. PAHs become lodged and are retained in lung tissue.

    To review relevant content, see "Absorption", "Distribution", and "Metabolism and Excretion" in this section.

12. Which of the following is true of PAHs?

    A. All PAH metabolites are formed via CYP liver enzymes (enzymes in the P-450 mixed function oxidase system).
    B. PAHs can accumulate in breast milk and adipose tissue.
    C. Most PAHs have similar distribution patterns and lipophilic properties.
    D. PAHs bound to particulate matter are better absorbed in the lungs than are unbound PAHs.

    To review relevant content, see "Absorption", "Distribution", and "Metabolism and Excretion" in this section.

Answers

11. The correct answer is C. PAHs have varied distribution patterns due to differences in lipophilic properties. Because of their lipophilic nature, PAHs can accumulate in breast milk and adipose tissue. However, biliary and urinary excretion of PAHs is relatively efficient because of the wide distribution of enzymes that transform PAHs into polar metabolites.
12. The correct answer is B. PAHs can accumulate in breast milk and adipose tissue. Not all PAH metabolites are formed via CYP liver enzymes (enzymes in the P-450 mixed function oxidase system). PAHs do differ in their distribution patterns and lipophilic properties. Unbound PAHs are better absorbed in the lungs, not bound PAHs.

How Do PAHs Induce Pathogenic Change?

Learning Objective	Upon completion of this section, you will be able to • describe how PAHs are believed to induce pathogenic changes.
Introduction	A key factor in PAH toxicity is the formation of reactive metabolites. Not all PAHs are of the same toxicity because of differences in structure that affect metabolism. Another factor to consider is the biologic effective dose, or the amount of toxics that actually reaches the cells or target sites where interaction and adverse effects can occur. CYP1A1, the primary cytochrome P-450 isoenzyme that biologically activates benzo (a) pyrene, may be induced by other substances [Kemena *et al.* 1988; Robinson *et al.* 1975]. The mechanism of PAH-induced carcinogenesis is believed to be via the binding of PAH metabolites to deoxyribonucleic acid (DNA).
Carcinogenicity	Some parent PAHs are weak carcinogens that require metabolism to become more potent carcinogens. Diol epoxides—PAH intermediate metabolites—are mutagenic and affect normal cell replication when they react with DNA to form adducts. A theory to explain the variability in the potency of different diol epoxides, "the bay theory," predicts that an epoxide will be highly reactive and mutagenic if it is in the "bay" region of the PAH molecule (**Figure 1**) [Jerina *et al.* 1976 and 1980; Weis 1998]. The bay region is the space between the aromatic rings of the PAH molecule. PAH-induced carcinogenesis can result when a PAH-DNA adduct forms at a site critical to the regulation of cell differentiation or growth. A mutation occurs during cell replication if the aberration remains unrepaired. Cells affected most significantly by acute PAH exposure appear to be those with rapid replicative turnover, such as those in bone marrow, skin, and lung tissue. Tissues with slower turnover rates, such as liver tissue, are less susceptible. Benzo(a)pyrene diol epoxide adducts bind covalently to several guanine positions of the bronchial epithelial cell DNA p53 gene, where cancer mutations are known to occur from exposure to cigarette smoke. This is one possible genotoxic mechanism of cancer causation by tobacco [Denissenko 1996].
Genetic Susceptibility	CYP1A1 inducible persons might be at greater risk for the effects of PAHs. Persons with a high degree of CYP1A1 inducibility may be more susceptible to PAH health risks. Genetic variation in CYP1A1 inducibility has been implicated as a determining factor for susceptibility to lung and laryngeal cancer.

	CYP1A1, the primary cytochrome P-450 isoenzyme that biologically activates benzo (a) pyrene, may be induced by other substances [Kemena *et al.* 1988; Robinson *et al.* 1975]. Glutathione transferase deficiencies may result in elevated cancer risk. Several studies have focused on breast cancer risk and metabolism of PAHs [Ambrosone *et al.* 1995; Calaf and Russo 1993; Davis *et al.* 1993; Hecht *et al.* 1994].
Oncogene Activation	Several animal studies have implicated the *ras* oncogene in PAH tumor induction [Chakravarti *et al.* 1995; DiGiovanni *et al.* 1993; Ronai *et al.* 1994].
Key Points	• The formation of reactive metabolites and the biologically effective dose are key to PAH toxicity. • Diol epoxides—PAH intermediate metabolites—are mutagenic and affect normal cell replication when they react with DNA to form adducts. • The location of epoxides in the bay region of a PAH predicts reactivity and mutagenicity. • DNA adducts, as markers of exposure used in research, can be measured in various biologic media. • The ability of CYP1A1 to biologically activate PAHs may be heritable and thus point to genetically susceptible populations at risk of PAH carcinogenesis.
Progress Check	13. The mechanism of PAH-induced carcinogenesis is believed to be which of the following? A. Binding of PAH metabolites to DNA. B. Generation of active oxygen species. C. Cell-mediated inflammatory mechanisms. D. All of the above. *To review relevant content, see "Carcinogenicity" in this section.* 14. Which of the following is (are) true regarding PAHs? A. Tissues with rapid cell turnover are most vulnerable to the carcinogenic effects from some PAHs. B. The degree to which CYP1A1 biologically activates PAHs may be heritable. C. The location of epoxides in the bay region of a PAH predicts reactivity and mutagenicity. D. All of the above are true. *To review relevant content, see "Carcinogenicity" and "Genetic Susceptibility" in this section.*

Answers

13. The correct answer is A. The mechanism of PAH induced carcinogenesis is believed to be the binding of PAH metabolites to DNA.
14. The correct answer is D. All of the statements are true. Tissues with rapid cell turnover are most vulnerable to the carcinogenic effects from some PAHs; the degree to which CYP1A1 biologically activates PAHs may be heritable; and the location of epoxides in the bay region of a PAH predicts reactivity and mutagenicity.

What Health Effects Are Associated With PAH Exposure?

Learning Objective

Upon completion of this section, you will be able to

- describe health effects associated with PAH exposure.

Introduction

The most significant endpoint of PAH toxicity is cancer.

PAHs generally have a low degree of acute toxicity to humans. Some studies have shown noncarcinogenic effects that are based on PAH exposure dose [Gupta *et al.* 1991].

After chronic exposure, the non-carcinogenic effects of PAHs involve primarily the

- pulmonary,
- gastrointestinal,
- renal, and dermatologic systems.

Many PAHs are only slightly mutagenic or even nonmutagenic in vitro; however, their metabolites or derivatives can be potent mutagens.

Carcinogenicity

The carcinogenicity of certain PAHs is well established in laboratory animals. Researchers have reported increased incidences of skin, lung, bladder, liver, and stomach cancers, as well as injection-site sarcomas, in animals. Animal studies show that certain PAHs also can affect the hematopoietic and immune systems and can produce reproductive, neurologic, and developmental effects [Blanton 1986, 1988; Dasgupta and Lahiri 1992; Hahon and Booth 1986; Malmgren *et al.* 1952; Philips *et al.* 1973; Szczeklik *et al.* 1994; Yasuhira 1964; Zhao 1990].

It is difficult to ascribe observed health effects in epidemiological studies to specific PAHs because most exposures are to PAH mixtures.

Increased incidences of lung, skin, and bladder cancers are associated with occupational exposure to PAHs. Epidemiologic reports of PAH-exposed workers have noted increased incidences of skin, lung, bladder, and gastrointestinal cancers. These reports, however, provide only qualitative evidence of the carcinogenic potential of PAHs in humans because of the presence of multiple PAH compounds and other suspected carcinogens. Some of these reports also indicate the lack of quantitative monitoring data [Hammond *et al.* 1976; Lloyd 1971; Mazumdar 1975; Redmond *et al.* 1972; Redmond and Strobino 1976].

The earliest human PAH-related epidemiologic study was reported in 1936 by investigators in Japan and England who studied lung cancer mortality among workers in coal carbonization and gasification processes. Subsequent U.S. studies among coke oven workers confirmed an excess of lung cancer mortality, with the suggestion of excessive genitourinary system cancer mortality. Later experimental studies showed that PAHs in soot were probably responsible for the increased incidence of scrotal cancer noted by Percival Pott among London chimney sweeps in his 1775 treatise [Zedeck 1980].

Research	Continued research regarding the mutagenic and carcinogenic effects from chronic exposure to PAHs and metabolites is needed. The following table indicates the carcinogenic classifications of selected PAHs by specific agencies.

Agency	PAH Compound(s)	Carcinogenic Classification
U.S. Department of Health and Human Services (HHS)	• benz(a)anthracene, • benzo(b)fluoranthene, • benzo(a)pyrene, • dibenz(a,h)anthracene, and • indeno(1,2,3-c,d)pyrene.	Known animal carcinogens
International Agency for Research on Cancer (IARC)	• benz(a)anthracene and • benzo(a)pyrene.	Probably carcinogenic to humans
	• benzo(a)fluoranthene, • benzo(k)fluoranthene, and • ideno(1,2,3-c,d)pyrene.	Possibly carcinogenic to humans
	• anthracene, • benzo(g,h,i)perylene, • benzo(e)pyrene, • chrysene, • fluoranthene, • fluorene, • phenanthrene, and • pyrene.	Not classifiable as to their carcinogenicity to humans
U.S. Environmental Protection Agency (EPA)	• benz(a)anthracene, • benzo(a)pyrene, • benzo(b)fluoranthene, • benzo(k)fluoranthene, • chrysene, • dibenz(a,h)anthracene, and • indeno(1,2,3-c,d)pyrene.	Probable human carcinogens
	• acenaphthylene, • anthracene, • benzo(g,h,i)perylene, • fluoranthene, • fluorene, • phenanthrene, and pyrene.	Not classifiable as to human carcinogenicity

Key Points

- PAHs generally have a low degree of acute toxicity to humans.
- The most significant endpoint of PAH toxicity is cancer.
- Increased incidences of lung, skin, and bladder cancers are associated with occupational exposure to PAHs. Data for other sites is much less persuasive.
- It is difficult to ascribe observed health effects in epidemiological studies to specific PAHs because most exposures are to PAH mixtures.
- Animal studies show that certain PAHs affect the hematopoietic, immune, reproductive, and neurologic systems and cause developmental effects.

Progress Check

15. Which of the following is (are) true?

    A. PAHs generally have a high degree of acute toxicity in humans.
    B. PAHs have been associated with increased incidences of lung, skin, and bladder cancers from occupational exposures.
    C. Specific PAHs can easily be linked to observed health effects in epidemiologic studies.
    D. All of the above.

    To review relevant content, see "Introduction" and "Carcinogenicity" in this section.

16. According to IARC and EPA, which of the following PAHs are probable human carcinogens?

    A. Benzo(a)pyrene.
    B. Benz(a)anthracene.
    C. Anthracene.
    D. Both A and B.

    To review relevant content, see "Carcinogenicity" in this section.

Answers

15. The correct answer is B. PAHs have been associated with increased incidences of lung, skin, and bladder cancers from occupational exposures. PAHs, however, do not have a high degree of acute toxicity in humans. It also is difficult to ascribe observed health effects in epidemiological studies to specific PAHs because most exposures are to PAH mixtures.
16. The correct answer is D. According to IARC and EPA, both benzo(a)pyrene and benz(a)anthracene are probable human carcinogens. Anthracene is not classifiable as to its carcinogenicity to humans by either agency.

Clinical Assessment

Learning Objectives	Upon completion of this section, you will be able to • describe typical signs and symptoms of patients with acute PAH exposure, • describe typical signs and symptoms of patients with chronic PAH exposure, • describe important elements of the exposure history, • describe the focus of the physical examination, and • describe tests used to assist in evaluation of patients exposed to PAHs.
Introduction	In addition to the standard clinical approaches to patient evaluation, clinicians should take an appropriate PAH exposure history. They should know what to look for during the physical exam and how to test for PAH exposure.
Signs and Symptoms—Acute Exposure	Acute effects attributed to PAH exposure, such as headache, nausea, respiratory and dermal irritation, are probably caused by other agents. Since PAHs have low acute toxicity, other more acutely toxic agents probably cause the acute symptoms attributed to PAHs. Hydrogen sulfide in roofing tars and sulfur dioxide in foundries are examples of concomitant, acutely toxic contaminants. Naphthalene, the most abundant constituent of coal tar, is a skin irritant, and its vapors may cause headache, nausea, vomiting, and diaphoresis [Rom 1998].
Signs and Symptoms—Chronic Exposure	Effects reported from occupational exposure to PAHs include • chronic bronchitis, • chronic cough irritation, • bronchogenic cancer, • dermatitis, • cutaneous photosensitization, and • pilosebaceous reactions. Reported health effects associated with chronic exposure to coal tar and its by-products (*e.g.*, PAHs). • Skin: erythema, burns, and warts on sun-exposed areas with progression to cancer. The toxic effects of coal tar are enhanced by exposure to ultraviolet light. • Eyes: irritation and photosensitivity. • Respiratory system: cough, bronchitis, and bronchogenic cancer. • Gastrointestinal system: leukoplakia, buccal-pharyngeal cancer, and cancer of the lip. • Hematopoietic system: leukemia (inconclusive) and lymphoma. • Genitourinary system: hematuria and kidney and bladder cancers.

Exposure History	Exposure is most often determined based on the patient exposure history. A relevant patient history might include the following information: • occupational history, • occupation of the spouse and other household members, • use of medications, including coal tar-containing dermatologic preparations, • diet, especially charbroiled meats, • alcohol consumption; and • smoking habits. Hobbies and recreational activities might reveal additional evidence of exposure to PAH-containing mixtures. In general, risk increases with total dose. For more information on the exposure history, see the *Taking an Exposure History* CSEM at www.atsdr.cdc.gov/csem/exphistory/
Physical Examination	Physical examination is important. Physical examination should include a review of all systems, with the knowledge that cancer is the most significant endpoint of chronic PAH toxicity. If PAH exposure is suspected, the clinician should be alert to malignant transformation of actinic skin lesions. The buccal mucosa and oropharynx should be inspected for malignant changes. Inspection of sun-exposed areas for evidence of hyperpigmentation in response to sunlight is advised.
Direct Biological Measurement	Direct biologic measurement of PAHs is neither cost-effective nor clinically useful. Direct measurement refers to testing directly for the parent compound (or specific PAHs exposed to), not the metabolites. Although researchers have examined PAHs directly in the blood and tissues of experimental animals, these methods have not been widely used for human samples. The high costs of testing and limited knowledge of the significance of background levels in humans limit the clinical usefulness of such tests.
Indirect Biological Measurement	The most common tests for determining exposure to PAHs involve examining tissues, blood, and urine for the presence of metabolites. Pyrene is commonly found in PAH mixtures, and its urinary metabolite, 1-hydroxypyrene, has been used as an indicator of exposure to PAH chemicals [Becher and Bjorseth 1983; Granella and Clonfero 1993; Popp 1997; Santella *et al. 1*993, CDC 2005]. The ACGIH recommends measurement of 1-hydroxypyrene in the end-of-shift, end-of-work-week urine samples as a biological exposure index (BEI) for assessment of exposure to mixtures containing PAHs. This practice may help identify workplaces requiring improved industrial hygiene measures [ACGIH

2005; Heikkila *et al.* 1995].

In the Third National Report on Human Exposure to Environmental Chemicals, urinary levels of hydroxylated metabolites of PAHs were measured in a subsample of the National Health and Nutrition Examination Survey (NHANES) participants aged 6 years and older during 1999–2002. The geometric mean for 1-hydroxypyrene (ng/g of creatinine) for the U.S. population aged 6 years and older during 1999–2002 was 74.2, with a 95% confidence interval of (61.6–89.3).

Note that finding a measurable amount of one or more metabolites in the urine does not mean that the levels of the PAH metabolites cause an adverse health effect. Whether levels of PAH metabolites at the levels reported are cause for health concern is not known, and more research is needed. These data provide physicians with a reference range so that they can determine whether people have been exposed to higher levels of PAHs than are found in the general population. As well, the data help scientists plan and conduct research on exposure to PAHs and health effects.

Deoxyribonucleic acid (DNA) adducts may be used as an indicator of exposure in research settings and can be measured in a variety of biologic media [Popp 1997; Ross *et al.* 1991; Santella *et al.* 1993; Weyand and La Voie 1988]. For example, tissue in culture can be labeled with radioactive phosphorus and analyzed by thin-layer chromatography and scintillation to identify and quantify the DNA adducts formed. Also, an immunoassay technique, ELISA, has been developed to detect antibodies to the PAH-DNA adducts in blood. These tests are not readily available for routine clinical use.

PAH diol epoxides form adducts with hemoglobin in the red blood cells. These adducts can be quantified by use of fluorescence spectroscopy. This technique is limited in its potential usefulness, however, because of individual differences in PAH metabolism and the limited specificity of the technique itself.

In general, indirect biologic monitoring can be useful in determining whether exposure to PAHs has occurred. However, it is not clinically useful for evaluating individual patients because normal or toxic levels have not been determined. Arterial blood gases, a chest radiograph, and other monitoring might be indicated. Individual variability, confounding effects of drugs or cigarettes, and nonspecificity of techniques are likely to complicate the interpretation of the results, especially in low-level environmental exposures.

Employees exposed to CTPVs in the coke oven industry are covered by the coke oven emissions standard. This OSHA standard includes elements of medical surveillance for workers exposed to coke oven emissions. It should be noted that OSHA recommended surveillance set at the time of the standard might not necessarily be consistent with current evidenced based medical practice.

Key Points	• Acute effects attributed to PAH exposure are probably caused by other agents. • Exposure is most often determined based on the patient exposure history. • Pertinent exposure history should include past and current occupational, recreational, hobbies, dietary, and smoking assessments. • Physical examination is important, including a review of all systems. • Direct biologic measurement of PAHs is neither cost-effective nor clinically useful. • A commonly measured urinary metabolite used to assess PAH exposure is 1-hydroxypyrene. • DNA adducts may be used as an indicator of exposure in research settings and can be measured in a variety of biologic media.
Progress Check	17. Which of the following is (are) true regarding the evaluation of a patient exposed to PAHs? A. Urinary 1-hydroxypyrene levels are used as prognostic indicators. B. Direct biologic measurement of PAHs is clinically useful. C. Exposure is most often determined based on the patient exposure history. D. All of the above. *To review relevant content, see "Exposure History", "Direct Biological Measurement" and "Indirect Biological Measurement" in this section.* 18. Key features of the physical examination of PAH-exposed patients include which of the following? A. Inspection of the buccal mucosa and oropharynx. B. Inspection of skin, especially sun-exposed areas. C. Auscultation of the lungs. D. All of the above. *To review relevant content, see "Physical Examination" in this section.*

Answers

17. The correct answer is C. Exposure is most often determined based on the patient exposure history. Urinary 1-hydroxypyrene levels are used as exposure indicators, not prognostic indicators. Direct biologic measurement of PAHs is not clinically useful.
18. The correct answer is D. Physical examination of PAH-exposed patients includes a complete review of systems for carcinogenic endpoints, which includes the inspection of the buccal mucosa and oropharynx, inspection of skin (especially sun-exposed areas), and auscultation of the lungs.

How Should Patients Exposed to PAHs Be Treated and Managed?

Learning Objectives	Upon completion of this section, you will be able to • identify strategies for managing patients with acute high dose PAH exposure, and • identify strategies for managing patients with chronic low level PAH exposure.
Introduction	The management and treatment focus of individuals exposed to PAHs differs for high dose acute and low dose chronic exposures. Decontamination and supportive measures are the primary objectives after acute high dose PAH exposure. Treatment of chronic PAH toxicity is symptomatic and supportive. Health education and risk communication are important aspects of patient care. Some clinicians recommend periodic pulmonary function tests and chest x-rays for PAH-exposed individuals (inhalation exposures).
Acute High Dose Exposure	Decontamination and supportive measures are the primary objectives after acute high dose PAH exposure. Acute symptoms are generally from co-exposures to other substances. Contaminated clothing should be removed from the victim as soon as possible. The victim's skin should be decontaminated by gently scrubbing with soap and water. Ocular contamination should be treated with irrigation and a complete eye examination. Supportive care should be administered as clinically necessary.
Chronic Exposure and Toxicity	Effective risk communication and education for patients at risk for PAH-related disease is an important part of patient care. Persons exposed to potentially significant levels of PAHs should be aware of the increased risk for bronchogenic cancer and the additive effect of cigarette smoke and other toxic agents. Periodic evaluations of healthy patients who have been significantly exposed to PAHs, even in the absence of symptoms, may facilitate early diagnosis and intervention if a malignancy develops. The OSHA coke oven emissions standard includes elements of medical surveillance for workers exposed to coke oven emissions. It should be noted that OSHA recommended surveillance (set at the time of the standard) might not necessarily be consistent with current evidenced based medical practice.
Risk Communication in Patient Care	Because estimation of additional risk due to PAH exposure is often impossible, the challenge to the clinician is to maintain a balance between appropriate concern and undue alarm. Predicting the carcinogenicity of a complex chemical mixture based on one or several of its components is difficult because of possible interactions among the components. Effective risk communication takes this into account and can be important in prevention or management of disease.

Key Points	• Decontamination and supportive measures are the primary objectives after acute high dose PAH exposure. • Treatment of chronic PAH toxicity is generally symptomatic and supportive. • Effective risk communication and health education are important aspects of patient care. • Periodic evaluations of healthy patients who have been significantly exposed to PAHs, even in the absence of symptoms, is recommended by some clinicians to facilitate early diagnosis and intervention if a malignancy develops.
Progress Check	19. Primary strategies for managing patients with acute high dose exposure to PAH include(s) which of the following? A. Removal of contaminated clothing. B. Cleansing of skin with soap and water. C. Supportive care as clinically indicated. D. All of the above. *To review relevant content, see "Acute High Dose Exposure" in this section.* 20. When managing patients with chronic low-level exposure to PAH, strategies aimed at reducing patient risk of overexposure to PAHs and PAH related disease include (s) which of the following? A. Smoking cessation. B. Patient health education. C. Periodic evaluations for those significantly exposed. D. All of the above. *To review relevant content, see "Risk Communication in Patient Care" in this section.*

Answers

19. The correct answer is D. Since symptoms from acute PAH exposures are mainly from co-exposure to other substances, the primary strategies for managing patients with acute high dose exposure to PAH include removal of contaminated clothing, decontamination of skin with soap and water, and supportive care as clinically indicated.
20. The correct answer is D. When managing patients with chronic low level exposure to PAH, strategies aimed at reducing patient risk of overexposure to PAHs and PAH related disease include smoking cessation, patient health education, and periodic evaluations for those significantly exposed.

What Instructions Should Be Given to Patients to Prevent Overexposure to PAHs?

Learning Objective

Upon completion of this section, you will be able to

- describe care advice the clinician can provide to patients to prevent overexposure to PAHs.

Introduction

By utilizing effective risk communication techniques, the clinician can promote patient behaviors that may reduce the risk of PAH overexposure and PAH related disease. The clinician can provide advice on

- self-care, so that patients can minimize risk of PAH overexposure and
- when to follow-up with a health care provider.

ATSDR has developed patient education care instruction sheets for use in clinical settings; a list of these can be found at:

www.atsdr.cdc.gov/emes/health_professionals/instruction_sheets.html

Self-Care Advice

Self-care advice creates awareness and suggests actionable behaviors that may reduce the risk of PAH overexposure and PAH related disease.

Sample Advice	Rationale
Stop smoking and avoid exposure to smoke.	Smoking and exposure to second hand smoke increase the risk of lung cancer. Cigarette smoke contains PAHs and other carcinogenic substances. Exposure to PAHs by smoking or second hand smoke may increase the risk of overexposure to PAHs and PAH related disease.
Minimize dietary PAH exposures.	The FDA has not published PAH "safe levels" for foodstuffs. However, given that PAHs in food increase the exposure dose and risk of adverse health effects, efforts to minimize dietary contributions would be prudent. Foods that may contain PAHs include • charbroiled, chargrilled, and smoked meats and fish, • tea, • roasted peanuts, • coffee, • refined vegetable oil, • cereals, • spinach, • wheat, • rye, and • lentils.

Minimize hobby, recreational, and home/outdoor PAH exposures.	Awareness of potential PAH exposure through hobbies, recreational, and home/outdoor scenarios and taking action to minimize or avoid exposure may decrease the risk of PAH overexposure. Wearing gloves when working with cutting oils (as well as other PAH-containing substances encountered in hobbies, recreational, and home/outdoor scenarios) and avoiding outdoor burning practices are some examples of behaviors that would decrease total PAH exposure dose.

Advice on when to Follow up with a Health Care Provider

Patients should be advised to consult their physician if they develop signs or symptoms to include

- a new cough or chronic cough with or without hemoptysis,
- unexplained weight loss,
- shortness of breath, and
- other applicable health changes associated with cancer or other serious health condition such as increased fatigue and weakness, recurring respiratory infections, etc.

Key Points

- The clinician can promote patient behaviors that may reduce the risk of PAH overexposure and PAH related disease by providing advice on
    - self-care, so that patients can minimize risk of PAH overexposure and
    - when to follow-up with a health care provider.

Progress Check

21. Clinicians can help their patients reduce the risk of overexposure to PAHs and PAH related disease by

    A. Offering information and assistance with smoking cessation.
    B. Providing information on PAH related health effects.
    C. Providing information on behaviors that can reduce the risk of PAH overexposure and PAH related disease.
    D. All of the above.

    To review relevant content, see "Self Care Advice" in this section.

Answers

21. The correct answer is D. Clinicians can help their patients reduce the risk of overexposure to PAHs and PAH related disease by offering information and assistance with smoking cessation, providing information on PAH related health effects, and providing information on behaviors that can reduce the risk of PAH overexposure and PAH related disease.

Sources of Additional Information

Polycyclic Aromatic Hydrocarbons (PAHs) Specific Information

Please refer to the following Web resources for more information on the adverse effects of PAH toxicity, the treatment of PAH-associated diseases, and management of persons exposed to PAHs.

- Agency for Toxic Substances and Disease Registry
  www.atsdr.cdc.gov
  - For chemical, emergency situations
    - **CDC Emergency Response: 770-488-7100 and request the ATSDR Duty Officer**
  - For chemical, non- emergency situations
    - CDC-INFO (www.bt.cdc.gov/coca/800cdcinfo.asp)
    - 800-CDC-INFO (800-232-4636) TTY 888-232-6348 - 24 Hours/Day
    - E-mail: cdcinfo@cdc.gov

      PLEASE NOTE
      ATSDR cannot respond to questions about individual medical cases, provide second opinions or make specific recommendations regarding therapy. Those issues should be addressed directly with your health care provider.
  - Toxicological Profile for Polycyclic Aromatic Hydrocarbons
    www.atsdr.cdc.gov/toxprofiles/tp69.html
  - ToxFAQs™ for Polycyclic Aromatic Hydrocarbons
    www.atsdr.cdc.gov/tfacts69.html
  - Agency for Toxic Substances and Disease Registry Toxic Substances and Your Health - Polycyclic Aromatic Hydrocarbons (www.atsdr.cdc.gov/substances/PAHs/

Clinical Resources

- American College of Occupational and Environmental Medicine (ACOEM) www.acoem.org
    - ACOEM is the nation's largest medical society dedicated to promoting the health of workers through preventive medicine, clinical care, research, and education.
    - Its members are a dynamic group of physicians encompassing specialists in a variety of medical practices is united via the College to develop positions and policies on vital issues relevant to the practice of preventive medicine both within and outside of the workplace.
- American College of Medical Toxicologists (ACMT) www.acmt.net
    - ACMT is a professional, nonprofit association of physicians with recognized expertise in medical toxicology.
    - The College is dedicated to advancing the science and practice of medical toxicology through a variety of activities.
- Association of Occupational and Environmental Clinics www.aoec.org
    - The Association of Occupational and Environmental Clinics (AOEC) is a network of more than 60 clinics and more than 250 individuals committed to improving the practice of occupational and environmental medicine through information sharing and collaborative research.
- Pediatric Environmental Health Specialty Units (PEHSUs) www.pehsu.net
    - Each PEHSU is based at an academic center and is a collaboration between the pediatric clinic and the (AOEC) occupational and environmental clinic at each site.
    - The PEHSU's have been developed to provide education and consultation for health professionals, public health professionals and others about the topic of children's environmental health.
    - The PEHSU staff is available for consultation about potential pediatric environmental health concerns affecting both the child and the family. Health care professionals may contact their regional PEHSU site for clinical advice.
- Poison Control Center
    - The American Association of Poison Control Centers may be contacted for questions about poisons and poisonings. The web site provides information about poison centers and poison prevention. AAPC does not provide information about treatment or diagnosis of poisoning or research information for student papers.
    - American Association of Poison Control Centers (1-800-222-1222 or www.aapcc.org).

General Environmental Health Information

Please refer to the following Web resources for general information on environmental health.

- Agency for Toxic Substances and Disease Registry www.atsdr.cdc.gov/
    - To view the complete library of CSEMs www.atsdr.cdc.gov/csem/.
    - Taking an Exposure History CSEM www.atsdr.cdc.gov/csem/exphistory/
- Centers for Disease Control and Prevention (CDC) www.cdc.gov
    - CDC works to protect public health and the safety of people, by providing information to enhance health decisions, and promotes health through partnerships with state health departments and other organizations.
    - The CDC focuses national attention on developing and applying disease prevention and control (especially infectious diseases), environmental health, occupational safety and health, health promotion, prevention and education activities designed to improve the health of the people of the United States.
- National Center for Environmental Health (NCEH) www.cdc.gov/nceh/
    - NCEH works to prevent illness, disability, and death from interactions between people and the environment. It is especially committed to safeguarding the health of populations that are particularly vulnerable to certain environmental hazards - children, the elderly, and people with disabilities.
    - NCEH seeks to achieve its mission through science, service, and leadership.
- National Institute of Health (NIH) www.nih.gov
    - A part of the U.S. Department of Health and Human Services, NIH is the primary Federal agency for conducting and supporting medical research.
- National Institute of Occupational Safety and Health (NIOSH) www.cdc.gov/niosh/
    - NIOSH is in the U.S. Department of Health and Human Services and is an agency established to help assure safe and healthful working conditions for working men and women by providing research, information, education, and training in the field of occupational safety and health.

- U.S. Department of Labor, Occupational Safety and Health Administration (OSHA) www.osha.gov

  - The mission of OSHA is to assure safe and healthful working conditions for working men and women

- U.S. Environmental Protection Agency www.epa.gov

  - EPA leads the nation's environmental science, research, education and assessment efforts.
  - The mission of the Environmental Protection Agency is to protect human health and the environment.
  - Since 1970, EPA has been working for a cleaner, healthier environment for the American people

Assessment and Posttest

Introduction	ATSDR seeks feedback on this course so we can asses its usefulness and effectiveness. We ask you to complete the assessment questionnaire online for this purpose. In addition, if you complete the assessment and posttest online, you can receive continuing education credits as follows.

Accrediting Organization	Credits Offered
Accreditation Council for Continuing Medical Education (ACCME)	**CME**: The Centers for Disease Control and Prevention is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The Centers for Disease Control and Prevention designates this educational activity for a maximum of **2** AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity.
American Nurses Credentialing Center (ANCC), Commission on Accreditation	**CNE**: The Centers for Disease Control and Prevention is accredited as a provider of Continuing Nursing Education by the American Nurses Credentialing Center's Commission on Accreditation. This activity provides **2** contact hours.
National Commission for Health Education Credentialing, Inc. (NCHEC)	**CHES**: The Centers for Disease Control and Prevention is a designated provider of continuing education contact hours (CECH) in health education by the National Commission for Health Education Credentialing, Inc. This program is a designated event for the Certified Health Education Specialist (CHES) to receive **2** Category I contact hours in health education, CDC provider number GA0082.
International Association for Continuing Education and Training (IACET)	**CEU**: The CDC has been approved as an Authorized Provider by the International Association for Continuing Education and Training (IACET), 1760 Old Meadow Road, Suite 500, McLean, VA 22102. The CDC is authorized by IACET to offer **0.2** IACET CEU's for this program.

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Instructions	To complete the assessment and posttest, go to www2.cdc.gov/atsdrce/ and follow the instructions on that page. You can immediately print your continuing education certificate from your personal transcript online. No fees are charged.

Posttest

There may be more than one correct answer per question.

1. Other names for PAHs include which of the following?

   A. Polynuclear aromatics (PNAs).
   B. Polynuclear hydrocarbons.
   C. Polynuclear aromatic hydrocarbons.
   D. Polycyclic organic matter (POM).

2. Which of the following statements regarding PAHs is (are) true?

   A. Heavier PAHs (more than 4 rings) tend to adsorb to particulate matter.
   B. Lighter PAHs (less than 4 rings) tend to remain gaseous until removed via precipitation.
   C. PAH concentration in water tends to be low (around 100 ng/l) due to their weak solubility.
   D. PAHs can be absorbed by plants.
   E. PAHs mostly accumulate in soil.

3. Potential sources of PAH exposure include

   A. Passive inhalation of cigarette smoke.
   B. Motor vehicle exhaust.
   C. Alcoholic beverages.
   D. Inhalation of paint vapors in poorly ventilated area.
   E. Wood stoves for home heating.

4. Which of the following statements regarding PAHs are **FALSE**?

   A. PAHs are found only in a small number of industrial settings.
   B. PAHs mostly accumulate in soils.
   C. Benzo[a]pyrene is generally used as an environmental indicator for PAHs.
   D. Most PAHs in ambient air are the result of man-made processes.

5. In non-occupational settings, the majority of PAH exposure in a nonsmoking individual comes from which of the following?

   A. Foodstuff ingestion.
   B. Inhalation route.
   C. Dermal route.
   D. Water.

6. Persons with potentially increased PAH exposure include

   A. Hunters.
   B. Coke oven workers.
   C. Roofing asphalt applicators.
   D. Chimney sweeps.

E. Breastfeeding mothers.

7. Which of the following statements are true about PAHs?

A. Exposure is most often determined based on patient history.
B. Direct assays in the body are not clinically useful.
C. Exposure can cause pancreatitis.
D. Acute exposure can cause convulsions or unexplained loss of consciousness.
E. The prognosis for most acutely exposed patients is poor.

8. Which of the following statements regarding OSHA's standards for PAHs is/are **FALSE**?

A. OSHA requires workers who are exposed to PAH above the PEL to be under medical surveillance.
B. OSHA requires all workers to be trained in proper use of appropriate personal protective equipment and safety.
C. Purchase of personal protective equipment is the responsibility of individual employees.
D. The OSHA PEL is a legally enforceable standard.

9. Which of the following statements regarding PAHs in water is/are true?

A. The EPA maximum contaminant level is a legally enforceable standard.
B. The maximum contaminant level is an 8-hour time-weighted average.
C. EPA has set maximum contaminant levels for PAHs in foodstuffs.
D. EPA developed ambient water quality criteria to protect human health from the carcinogenic effects of PAH exposure.

10. Which of the following regarding the biologic fate of PAHs in the body are true?

A. PAHs are metabolized in a number of organs and excreted in bile and urine.
B. Information on the absorption, distribution, and elimination of PAHs in the human body is derived primarily from animal studies.
C. Generally, PAHs bound to airborne particulate matter are not absorbed as well in the lungs as the same dose of PAHs that are unbound to particulate matter.
D. The liver P-450 mixed-function oxidase system is the predominant mechanism of PAH metabolism.
E. 1-Hydroxypryrene is a commonly measured urine metabolite for PAH exposure.

11. The following signs and symptoms can be found in patients

chronically exposed to PAHs

A. Chloracne.
B. Bronchitis.
C. Vertigo.
D. Exotropia.
E. Cutaneous photosensitization.

12. The mechanism of PAH-induced carcinogenesis is believed to be which of the following?

A. Covalent binding of PAH metabolites to DNA.
B. Generation of active oxygen species.
C. Cell-mediated inflammatory mechanisms.
D. All of the above.

13. Reported health effects associated with chronic exposure to coal tar and its by-products (*e.g.*, PAH) include

A. Warts on sun-exposed areas of the skin, with progression to cancer.
B. Irritation of the eyes.
C. Bronchogenic cancer.
D. Leukoplakia.
E. Lymphoma.

14. In the treatment of patients with PAH exposure, which of the following is/are true?

A. Education and future avoidance of exposure are important.
B. Continued use of tobacco products should be discouraged.
C. Treatment of acute exposure is largely symptomatic.
D. The specific PAH should be determined so that an antidote can be prescribed.
E. A fat biopsy is integral to medical surveillance of PAH-exposed patients.

15. Which of the following should be included in the differential diagnosis of a patient suffering from the chronic effects of PAH exposure?

A. Pancytopenia.
B. Hepatic angiosarcoma.
C. Pancreatitis.
D. Tuberculosis.
E. Lung abscess.

16. Regarding PAH distribution, metabolism, and excretion, which are true?

A. The liver and kidney are both involved in metabolism.

	B. Binding of PAH metabolites to DNA is believed to be the mechanism of PAH-induced carcinogenesis. C. Metabolized PAHs cannot be eliminated by hepatobiliary excretion. D. Excretion is through bile and urine. E. Calcium EDTA chelation enhances PAH excretion. 17. Which of the following statements is (are) true? A. Management of a worker exposed to PAHs includes bone marrow aspiration. B. PAH metabolites can cross the placental barrier. C. Acutely exposed skin should be decontaminated by gently scrubbing with a 10% iodine solution. D. Hair analysis can reveal past PAH exposure. E. The bay region theory attempts to explain why PAHs are found in bay waters. 18. What steps can patients take to reduce the risk of overexposure to PAHs? A. Minimize hobby and recreational PAH exposures. B. Avoid exposure to all forms of smoke. C. Stop smoking. D. Minimize dietary PAH exposure. E. All of the above.
Relevant Content	To review content relevant to the post-test questions, see:

Question	Location of Relevant Content
1	What are PAHs?
2	What are PAHs? Where are PAHs found?
3	Where are PAHs found?
4	Where are PAHs found?
5	What are routes of exposure for PAHs?
6	Who is at risk of PAH exposure?
7	Clinical Assessment
8	What are standards and regulations for PAH exposure?
9	What are standards and regulations for PAH exposure?
10	What is the biologic fate of PAHs in the body?
11	Clinical assessment
12	How do PAHs induce pathogenic changes?

13	What health effects are associated with PAH exposure?
14	How should patients exposed to PAHs be treated and managed?
15	Clinical assessment
16	What is the biologic fate of PAHs? How do PAHs induce pathogenic changes?
17	What are routes of exposure for PAHs?
18	What instructions should be given to patients exposed to PAHs?

Literature Cited

References

[ACGIH] American Conference of Governmental Industrial Hygienists. 2005. Polycyclic aromatic hydrocarbons (PAHs) biologic exposure indices (BEI) Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

Adonis M, Martinez V, Riquelme R, Ancic P, Gonzalez G, Tapia R, *et al.* 2003. Susceptibility and exposure biomarkers in people exposed to PAHs from diesel exhaust. Toxicol Lett 144(1):3–15.

[ATSDR] Agency for Toxic Substances and Disease Registry. 1995. Toxicological profile for polycyclic aromatic hydrocarbons (PAHs) (update). Atlanta, GA: US Department of Health and Human Services.

Alexandrie AK, Warholm M, Carstensen U, Axmon A, Hagmar L, Levin JO, *et al.* 2000. CYP1A1 and GSTM1 polymorphisms affect urinary 1-hydroxypyrene levels after PAH exposure. Carcinogenesis 21(4): 669–76.

Ambrosone CB, Freudenheim JL, Graham S, Marshall JR, Vena JE, Brasure JR, *et al.* 1995. Cytochrome P4501A1 and glutathione S-transferase (M1) genetic polymorphisms and post menopausal breast cancer risk. Cancer Res 55(16):3483–5.

Armstrong B, Hutchinson E, Unwin J, Fletcher T. 2004. Lung cancer risk after exposure to polycyclic aromatic hydrocarbons: a review and meta-analysis. Environ Health Perspect 112(9): 970–8.

Bach PB, Kelley MJ, Tate RC, McCrory DC. 2003. Screening for lung cancer: a review of the current literature. Chest 123(1 Suppl):72S–82S.

Bach PB, Niewoehner DE, Black WC; 2003. American College of Chest Physicians. Screening for lung cancer: the guidelines. Chest 123(1 Suppl):83S–88S.

Badiali D, Marcheggiano A, Pallone F, Paoluzi P, Bausano G, Iannoni C, *et al.* 1985. Melanosis of the rectum in patients with chronic constipation. Dis Colon Rectum 28(4):241–5.

Bartsch H, Nair U, Risch A, Rojas M, Wikman H, Alexandrov K. 2000. Genetic polymorphism of *CYP* genes, alone or in combination, as a risk modifier of tobacco-related cancers. Cancer Epidemiol Biomarkers Prev 9:3–28.

Becher G, Bjorseth A. 1983. Determination of exposure to polycyclic aromatic hydrocarbons by analysis of human urine. Cancer Lett 17:301–11.

Bhatia R, Lopipeto P, Smith AH. 1998. Diesel exhaust exposure and lung

cancer. Epidemiology 9:84–91.

Blanton RJ, Lyte M, Myers MJ, Bick PH. 1986. Immunomodulation by polyaromatic hydrocarbons in mice and murine cells. Cancer Res 46(6):2735–9.

Blanton RH, Myers MJ, Bick PH. 1988. Modulation of immunocompetent cell populations by benzo(a)pyrene. Toxicol Appl Pharmacol 93:267–74.

Boffetta P, Harris RE, Wynder EL. 1990. Case-control study on occupational exposure to diesel exhaust and lung cancer risk. Am J Ind Med 17:577–591.

Boffetta P, Jourenkova N, Gustavsson P. 1997. Cancer risk from occupational and environmental exposure to polycyclic aromatic hydrocarbons. Cancer Causes Control 8(3):444–72.

Boffetta P, Stellman SD, Garfinkel L. 1988. Diesel exhaust exposure and mortality among males in the American Cancer Society prospective study. Am J Ind Med 14:403–15.

Busbee DL, Normal JO, Ziprin RL. 1990. Comparative uptake, vascular transport and cellular internalization of aflatoxin B1 and benzo[a]pyrene. Arch Toxicol 64(4):285–90.

Calaf G, Russo J. 1993. Transformation of human breast epithelial cells by chemical carcinogens. Carcinogenesis 14(3):483–92.

[CDC] Centers for Disease Control and Prevention. Third National Report on Human Exposure to Environmental Chemicals. Atlanta GA [updated 2005 July; accessed 2009 June]. Available from:http://www.cdc.gov/ExposureReport/pdf/thirdreport.pdf

Chakravarti V, Pelling JC, Cavalieri EL, Rogan EG. 1995. Relating aromatic hydrocarbon-induced DNA adducts and c-H-ras mutations in mouse skin papillomas. Proc Natl Acad Sci USA 92(22):10422–6.

Cherng SH, Lin ST, Lee H. 1996. Modulatory effects of polycyclic aromatic hydrocarbons on the mutagenicity of 1-nitropyrene: a structure-activity relationship study. Mut Res 367(4):177–85.

Chuang JC, Callahan PJ, Lyu CW, Wilson NK. 1999. Polycyclic aromatic hydrocarbon exposures of children in low-income families. J Expo Anal Environ Epidemiol;9(2):85–98.

Chuang CY, Lee CC, Chang YK, Sung FC. 2003. Oxidative DNA damage estimated by urinary 8-hydroxydeoxyguanosine; influence of taxi driving, smoking and areca chewing. Chemosphere;52(7):1163–71.

Cresia DA, Poggenburg JK, Nettesheim P. 1976. Elution of benzo[a]pyrene

from carbon particles in the respiratory tract of mice. J Toxicol Environ Health 1:967–75.

Dasgupta PS, Lahiri T. 1992. Alteration of brain catecholamines during growth of benzo[a]pyrene induced murine fibrosarcoma. Neoplasm 39(3):163–5.

Davis DL, Bradlow HL, Wolff M, Woodruff T, Hoel DG. 1993. Medical xenoestrogens as preventable causes of breast cancer. Environ Health Perspect 101(5):372–7.

Denissenko MF. 1996. Preferential formation of benzo(a)pyrene adducts at lung cancer mutational hotspots in P53. Science 274:430–2.

DiGiovanni J, Bletran L, Rupp A, Harvey RG, Gill RD. 1993. Further analysis of c-Ha-ras mutations in papillomas initiated by several polycyclic aromatic hydrocarbons and papillomas from uninitiated, promoter-treated skin in SENCAR mice. Mol Carcinog 8(4):272–9.

Doll R, Fisher REW, Gammon EJ, Gunn W, Hughes GO, Tyrer FH, *et al.* 1965. Mortality of gas workers with special reference to cancers of the lung and bladder, chronic bronchitis and pneumoconiosis. Br J Ind Med 22(1):1–12.

Doll R, Vessey MP, Beasley RWR, Buckley AR, Fear EC, Fisher REW, *et al.* 1972. Mortality of gas workers—final report of a prospective study. Br J Ind Med 29(4):394–406.

Environmental Research and Technology Inc, Koppers Company Inc (for the Utility Solid Waste Activities Group, Superfund Committee, Washington, DC).1984. Handbook on manufactured gas plant sites. Pittsburgh, PA: Edison Electric Institute.

[EPA] US Environmental Protection Agency. 1984. Health effects assessment for polycyclic aromatic hydrocarbons (PAH). Cincinnati, OH: Environmental Protection Agency. EPA Report No. 540/1–86–013.

[EPA] US Environmental Protection Agency. 1985. An exposure and risk assessment for benzo[a]pyrene and other polycyclic aromatic hydrocarbons. Vol IV. Washington, DC: US Environmental Protection Agency. EPA Report No. 4–85–020–V4.

Garshick E, Schenker MB, Munoz A, Segal M, Smith TJ, Woskie SR, *et al.* 1987. A case-control study of lung cancer and diesel exhaust exposure in railroad workers. Am Rev Respir Dis 135(6):1242–8.

Garshick E, Schenker MB, Munoz A, Segal M, Smith TJ, Woskie SR, *et al.* 1988. A retrospective cohort study of lung cancer and diesel exhaust exposure in railroad workers. Am Rev Respir Dis 137(4):820–5.

Georgiadis P, Kyrtopoulos SA. 1999. Molecular epidemiological approaches to the study of the genotoxic effects of urban air pollution. Mut Res 428(1–2):91–8.

Goen T, Gundel J, Schaller KH, Angerer J. 1995. The elimination of 1-hydroxypyrene in the urine of the general population and workers with different occupational exposures to PAH. Sci Total Environ;163(1-3):195–201.

Granella M, Clonfero E. 1993. Urinary excretion of 1-pyrenol in automotive repair workers. Int Arch Occup Environ Health 65:241–5.

Grimmer G. 1968. Carcinogenic hydrocarbons in the human environment. Dtsch Apoth Ztg 108:529.

Gupta P, Banerjee DK, Bhargava SK, Kaul R, Shanker VR. 1991. Prevalence of impaired lung function in rubber manufacturing factory workers exposed to benzo[a]pyrene and respirable particulate matter. Indoor Environ 2:26–31.

Hahon N, Booth JA. 1986. Coinhibition of viral interferon induction by benzo[a]pyrene and chrysotile asbestos. Environ Res 40(1):103–9.

Hammond EC, Selikoff IJ, Lawther PL, Seidman H. 1976. Inhalation of benzpyrene and cancer in man. Ann N Y Acad Sci 271:116–24.

Hansen AM, Wallin H, Binderup ML, Dybdahl M, Autrup H, Loft S, *et al.* 2004. Urinary 1-hydroxypyrene and mutagenicity in bus drivers and mail carriers exposed to urban air pollution in Denmark. Mutat Res;557(1):7–17.

Harris CC, Newman MJ, Weston A, Mann DL. 1986. Identification of human antibodies to polycyclic aromatic hydrocarbon-DNA adducts. Clin Res 34:690A.

Haugen A, Becher G, Benestad C, Vahakangas K, Trivers GE, Newman MJ, *et al.* 1986. Determination of polycyclic aromatic hydrocarbons in the urine, benzo[a]pyrene diol epoxide-DNA adducts in lymphocyte DNA, and antibodies to the adducts in sera from coke oven workers exposed to measured amounts of polycyclic aromatic hydrocarbons in the work atmosphere. Cancer Res 46:4178–83.

Hecht SS. 1999. Tobacco smoke carcinogens and lung cancer. J Natl Cancer Inst 91:1194–210.

Hecht SS. 2002. Human urinary carcinogen metabolites: biomarkers for investigating tobacco and cancer. Carcinogenesis 23:907–22.

Hecht SS, el-Bayoumy K, Rivenson A, Amin S. 1994. Potent mammary carcinogenicity in female Cd rats of a fjord region diol-epoxide of

benzo[c]phenanthrene compared to a bay region diol-epoxide of benzo[a]pyrene. Cancer Res 54(1):21–4.

Heikkila P, Luotamo M, Pyy L, Riihimaki V. 1995. Urinary 1-naphthol and 1-pyrenol as indicators of exposure to coal tar products. Int Arch Occup Environ Health 67(3):211–7.

Heudorf U, Angerer J. 2001. Urinary monohydroxylated phenanthrenes and hydroxypyrene—the effects of smoking habits and changes induced by smoking on monooxygenase-mediated metabolism. Int Arch Occup Environ Health. 74(3):177–83.

Hoffman D., Schmeltz I., Hecht SS, Wynder EL. 1978. Tobacco carcinogenesis. In Gelboin, HS, and Ts'o, POP, editors. Polycyclic hydrocarbons and cancer. New York: Academic Press. Vol. 1. pp 85–117.

[IARC] International Agency for Research on Cancer. 1973. Certain polycyclic aromatic hydrocarbons and heterocyclic compounds. Monograph on the evaluation of carcinogenic risks of the chemical to man. Vol. 3. Lyon, France: World Health Organization.

[IPCS] International Programme on Chemical Safety. 1998 Environmental health criteria 202. Selected non-heterocyclic polycyclic aromatic hydrocarbons. Geneva: World Health Organization.

Jacob J, Seidel A. 2002. Biomonitoring of polycyclic aromatic hydrocarbons in human urine. J Chromatogr B;778(1–2):31–47.

Jerina DM, Lehr RE, Yagi, *et al.* 1976. Mutagenicity of B(a)P derivatives and the description of a quantum mechanical model which predicts the ease of carbonium ion formation from diol epoxides. In: deSerres FJ, Foutes JR, Bend JR, *et al.* eds. In vitro metabolic activation in mutagenesis testing. Amsterdam, The Netherlands: Elsevier/North Holland. 159–178.

Jerina DM, Sayer JM, Thakker DR, *et al.* 1980. Carcinogenicity of polycylic aromatic hydrocarbons: The bay-region theory. In: Pullman B, Ts'O POP, Gelboin H, eds. Carcinogenesis: Fundamental mechanisms and environmental effects. Hingham, MA: D. Reidel Publishing Co, 1–12.

Jinot J, Bayard S. 1996. Respiratory health effects of exposure to environmental tobacco smoke. Rev Environ Health 11(3):89–100.

Jongeneelen FJ, Bos RP, Anzion RBM, Theuws JL, Henderson PT. 1986. Biological monitoring of polycyclic aromatic hydrocarbons: metabolites in urine. Scand J Work Environ Health 12:137–43.

Kapitulnick J, Levin W, Morecki R, Dansette PM, Jerina DM, Conney AH. 1977. Hydration of arene and alkene oxides by epoxide hydrase in human

liver microsomes. Clin Pharmacol Ther 21(2):158–65.

Kanoh T, Fukuda M, Onozuka H, Kinouchi T, Ohnishi Y. 1993. Urinary 1-hydroxypyrene as a marker of exposure to polycyclic aromatic hydrocarbons in environment. Environ Res 62(2):230–41.

Kawamura Y, Kamata E, Ogawa Y, *et al.* 1988. The effect of various foods on the intestinal absorption of benzo(a)pyrene in rats. J Food Hyg Soc Jpn 29(1):21–5.

Kemena A, Norpoth KH, Jacob J. 1988. Differential induction of the monooxygenase isoenzymes in mouse liver microsomes by polycyclic aromatic hydrocarbons. In: Cooke M, Dennis AF, editors. Polynuclear aromatic hydrocarbons: a decade of progress. Proceedings of the tenth international symposium. Columbus, OH: Battelle Press. p. 449–60.

Kennaway E. 1995. The identification of a carcinogenic compound in coal-tar. Br Med J 2:749–52.

Kiefer F, Cumpelik O, Wiebel FJ. 1988. Metabolism and cytotoxicity of benzo[a]pyrene in the human lung tumour cell line NCI-H322. Xenobiotica 18:747–55.

Kjaerheim K. 1999. Occupational cancer research in the Nordic countries. Environ Health Perspect 107(Suppl 2):233–8.

Kuo CT, Chen HW, Chen JL. Determination of 1-hydroxypyrene in children urine using column-switching liquid chromatography and fluorescence detection. J Chromatogr B 2004;805(2):187-93.

Kuusimaki L, Peltonen Y, Mutanen P, Peltonen K, Savela K. Urinary hydroxy-metabolites of naphthalene, phenanthrene and pyrene as markers of exposure to diesel exhaust. Int Arch Occup Environ Health 2004;77(1):23-30.

Lee KH, Ichiba M, Zhang J, Tomokuni K, Hong YC, Ha M, *et al.* 2003. Multiple biomarkers study in painters in a shipyard in Korea. Mutat Res 540(1):89–98.

Lee ML, Novotny M, Bartle KD. 1976. Gas chromatography/mass spectrometric and nuclear magnetic resonance determination of polynuclear aromatic hydrocarbons in airborne particulates. Anal Chem 48(11):1566–72.

Lee ML, Novotny M, Bartle KD. 1981. Analytical chemistry of polycyclic aromatic hydrocarbons. New York, NJ: Academic Press.

Levin W, Wood A, Chang RL, Ryan D, Thomas P, Yagi H, *et al.* 1982. Oxidative metabolism of polycyclic aromatic hydrocarbons to ultimate

carcinogens. Drug Metab Rev 13:555–80.

Lewtas J, Walsh D, Williams R, Dobias L. 1997. Air pollution exposure-DNA adduct dosimetry in humans and rodents: evidence for non-linearity at high doses. Mut Res 378(1–2):51–63.

Lloyd JW. 1971. Long-term mortality study of steelworkers: V. Respiratory cancer in coke plant workers. J Occup Med 13(2):53–68.

Lu PL, Chen ML, Mao IF. 2002. Urinary 1-hydroxypyrene levels in workers exposed to coke oven emissions at various locations in a coke oven plant. Arch Environ Health 57(3):255–61.

Malmgren RA, Bennison BE, McKinley TW Jr. 1952. Reduced antibody titers in mice treated with carcinogenic and cancer chemotherapeutic agents. Proc Soc Exp Biol Med 79:484–8.

Mazumdar S, Redmond C, Sollecito W, Sussman N. 1975. An epidemiological study of exposure to coal tar pitch volatiles among coke oven workers. J Air Pollut Cont Assoc 25:382–9.

Menzie CA, Potocki BB, Santodonato J. 1992. Exposure to carcinogenic PAHs in the environment. Environ. Sci. Technol. 26:1278–83.

Merlo F, Andreassen A, Weston A, Pan CF, Haugen A, Valerio F, *et al.* 1998. Urinary excretion of 1-hydroxypyrene as a marker for exposure to urban air levels of polycyclic aromatic hydrocarbons. Cancer Epidemiol Biomarkers Prev 7(2):147–55.

Monteith DK, Novotny A, Michalopoulos G, Strom SC. 1987. Metabolism of benzo[a]pyrene in primary cultures of human hepatocytes: dose-response over a four-log range. Carcinogenesis 8(7):983–8.

Mukherjee S, Palmer LJ, Kim JY, Aeschliman DB, Houk RS, Woodin MA, *et al.* 2004. Smoking status and occupational exposure affects oxidative DNA injury in boilermakers exposed to metal fume and residual oil fly ash. Cancer Epidemiol Biomarkers Prev 13(3):454–60.

Nelson E. 2001. The miseries of passive smoking. Hum Exp Toxicol 20:61–83.

O'Neill P. 1997. Chemia środowiska [Chemistry of the environment]. Warsaw, PL: Wydawnictwo Naukowe PWN.

Phillips DH. 1996. DNA adducts in human tissues: biomarkers of exposure to carcinogens in tobacco smoke. Environ Health Persp 104(Suppl 3):453–8.

Phillips DH. 1999. Polycyclic aromatic hydrocarbons in the diet. Mut Res

443(1-2):139–47.

Philips FS, Steinberg SS, Marquardt H. 1973. In vivo cytotoxicity of polycyclic hydrocarbons. In: Loomis TA, editor. Pharmacology and the future of man: vol 2. Toxicological problems. Proceedings of the fifth international congress on pharmacology, San Francisco, CA, July 23-28, 1972. New York, NY: Karger. p. 75–88.

Popp W. 1997. DNA single strand breakage, DNA adducts, and sister chromatid exchange in lymphocytes and phenanthrene and pyrene metabolites in urine of coke oven workers. Occup Environ Med 54:176–83.

Redmond CK, Ciocco A, Lloyd JW, Rush HW. 1972. Long-term mortality study of steelworkers: VI. Mortality from malignant neoplasms among coke oven workers. J Occup Med 14:621–29.

Redmond CK, Strobino BR, Cypress RH. 1976. Cancer experience among coke byproduct workers. Ann N Y Acad Sci 271:102–15.

Robinson JR, Felton JS, Levitt RC, Thorgeirsson SS, Nebert DW. 1975. Relationship between "aromatic hydrocarbon responsiveness" and the survival times in mice treated with various drugs and environmental compounds. Mol Pharmacol 11(6):850–65.

Roggi C, Minoia C, Sciarra GF, Apostoli P, Maccarini L, Magnaghi S, *et al.* 1997. Urinary 1-hydroxypyrene as a marker of exposure to pyrene: an epidemiological survey on a general population group. Sci Total Environ;199(3):247–54.

Rom WN. 1998. Polycyclic aromatic hydrocarbons. In: Rom W, ed. Environmental and occupational medicine. 3rd ed. Philadelphia, PA: Lippincott-Raven. p. 1261–7.

Ronai ZA, Gradia S, el-Bayoumy K, Amin S, Hecht SS. 1994. Contrasting incidence of ras mutations in rat mammary and mouse skin tumors. Carcinogenesis 15(10):2113–6.

Ross J, Nelson G, Erexson G, Kligerman A, Earley K, Gupta RC, et. al. 1991. DNA adducts in rat lung, liver and peripheral blood lymphocytes produced by i.p. administration of benzo[a]pyrene metabolites and derivatives. Carcinogenesis 12(10):1953–5.

Samet JM. 1995. What can we expect from epidemiologic studies of chemical mixtures? Toxicology 105:307–14.

Santella RM, Hemminki K, Tang D-L, Paik M, Ottman R, Young TL, *et al.* 1993. Polycyclic aromatic hydrocarbon-DNA adducts in white blood cells and urinary 1-hydroxypyrene in foundry workers. Cancer Epidemiol

Biomarkers Prev 2(1):59–62.

Scheepers PT, Coggon D, Knudsen LE, Anzion R, Autrup H, Bogovski S, *et al.* 2002. Biomarkers for occupational diesel exhaust exposure monitoring (BIOMODEM)—a study in underground mining. Toxicol Lett 134(1-3):305–17.

Serdar B, Waidyanatha S, Zheng Y, Rappaport SM. 2003. Simultaneous determination of urinary 1- and 2-naphthols, 3-and 9-phenanthrols, and 1-pyrenol in coke oven workers. Biomarkers 8(2):93–109.

Seto H. 1993. Determination of polycyclic aromatic hydrocarbons in the lung. Arch Environ Contam Toxicol 24:498–503.

Shabad LM, Cohan YL. 1972. Contents of benzo[a]pyrene in some crops. Arch Geschwulstforsch 40:237–43.

Siwinska E, Mielzynska D, Bubak A, Smolik E. 1999. The effect of coal stoves and environmental tobacco smoke on the level of urinary 1-hydroxypyrene. Mutat Res 445(2):147–53.

Siwinska E, Mielzynska D, Kapka L. 2004. Association between urinary 1-hydroxypyrene and genotoxic effects in coke oven workers. Occup Environ Med 61(3):e10.

Skupinska K, Misiewicz I, Kasprzycka-Guttman T. 2004. Polycyclic aromatic hydrocarbons: physiochemical properties, environmental appearance and impact on living organisms. Acta Pol Pharm 61(3):233–40.

Steenland K, Silverman DT, Hornung RW. 1990. Case-control study of lung cancer and truck driving in the Teamsters Union. Am J Public Health 80:670–74.

Steenland K, Silverman DT, Zebst D. 1992. Exposure to diesel exhaust in the trucking industry and possible relationships with lung cancer. Am J Ind Med 21:887–90.

Sullivan JB, Krieger GR, eds. 2001. Clinical environmental health and toxic exposures. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins. p. 1241.

Szczeklik A, Szczeklik J, Galuszcka Z, Musial J, Kolarzyk E, Tarqosz D. 1994. Humoral immunosuppression in men exposed to polycyclic aromatic hydrocarbons and related carcinogens in polluted environments. Environ Health Perspect 102(3):302–4.

Tsai HT, Wu MT, Hauser R, Rodrigues E, Ho CK, Liu CL, *et al.* 2003. Exposure to environmental tobacco smoke and urinary 1-hydroxypyrene

levels in preschool children. Kaohsiung J Med Sci 19(3):97–104.

Tsai PJ, Shih TS, Chen HL, Lee WJ, Lai CH, Liou SH. 2004. Urinary 1-hydroxypyrene as an indicator for assessing the exposures of booth attendants of a highway toll station to polycyclic aromatic hydrocarbons. Environ Sci Technol 38(1):56–61.

Van Rooij JGM, Van Lieshout EMA, Bodelier-Bade MM, Jongeneelen FJ. 1993. Effect of the reduction of skin contamination on the internal dose of creosote workers exposed to polycyclic aromatic hydrocarbons. Scan J Work Environ Health 19(3):200–7.

Van Schooten F-J. 1996. Coal tar therapy: is it carcinogenic? Drug Safety 6 :374–7.

Weis LM. 1998. Bay or baylike regions of polycyclic aromatic hydrocarbons were potent inhibitors of gap junctional intercellular communication. Environ Health Perspect 106:17–22.

Weyand EH, La Voie EJ. 1988. Comparison of PAH: DNA adduct formation and tumor initiating activity in newborn mice. Proc Annu Meet Am Assoc Cancer Res 29:A390(abst).

Yang M, Kim S, Lee E, Cheong HK, Chang SS, Kang D, *et al.* 2003. Sources of polycyclic aromatic hydrocarbon exposure in nonoccupationally exposed Koreans. Environ Mol Mutagen;42(4):250–7.

Yasuhira K. 1964. Damage to the thymus and other lymphoid tissues from 3-methylcholanthrene, and subsequent thymoma production, in mice. Cancer Res 24:558–69.

Zedeck MS. 1980. Polycyclic aromatic hydrocarbons: a review. J Environ Pathol Toxicol 3:537–67.

Zhao XL. 1990. Effects of benzo[a]pyrene on the humoral immunity of mice exposed by single intraperitoneal injection. Zhonghua Yu Fang Yi Xue Za Zhi [Chin J Prevent Med] 24(4):220–2.

Zmirou D, Masclet P, Boudet C, Dor F, Dechenaux J. 2000. Personal exposure to atmospheric polycyclic aromatic hydrocarbons in a general adult population and lung cancer risk assessment. J Occup Environ Med 42:121–6.