

**Public Health Goal for
BENZO(A)PYRENE
in Drinking Water**

**Prepared by
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PREFACE

Drinking Water Public Health Goal of the Office of Environmental Health Hazard Assessment

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. The PHG describes concentrations of contaminants at which adverse health effects would not be expected to occur, even over a lifetime of exposure. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires OEHHA to adopt PHGs that meet the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which scientific evidence indicates that no known or anticipated adverse effects on health will occur, plus an adequate margin-of-safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of scientific ambiguity, OEHHA shall use criteria most protective of public health and shall incorporate uncertainty factors of noncarcinogenic substances for which scientific research indicates a safe dose-response threshold.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed periodically and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. For this reason PHGs are only one part of the information used by DHS for establishing drinking water standards. PHGs established by

OEHHA exert no regulatory burden and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are developed for technical assistance to DHS, but may also benefit federal, state and local public health officials. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of environmental waters where additional concerns of bioaccumulation in fish and shellfish may pertain. Often environmental water contaminant criteria are more stringent than drinking water PHGs, to account for human exposures to a single chemical in multiple environmental media and from bioconcentration by plants and animals in the food chain.

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SUMMARY

A Public Health Goal (PHG) of 4 ppt is developed for benzo(a)pyrene (BaP) in drinking water. The PHG is based on carcinogenic effects observed in experimental animals. The 1967 study by Neal and Rigdon cited in the development of the PHG demonstrated gastric tumors in mice administered BaP in the diet. For the calculation of the PHG, cancer potency estimates were made based upon the recommended practices of the U.S. Environmental Protection Agency (U.S. EPA) for cancer risk assessment in which the linearized multistage (LMS) model is fit to the experimental data in order to establish the lower 95% confidence bound on the dose associated with a 10% increased risk of cancer (LED₁₀). An assumption of linearity was made for doses below this and outside of the range of observation in order to generate a cancer slope factor (CSF). Interspecies extrapolation was also done using the guidance provided by U.S. EPA. For the calculation of the PHG, theoretical excess individual cancer risk from exposure to BaP was limited to the *de minimis* level of 10⁻⁶. On the basis of the cancer risk calculations, a PHG of 4 ppt is developed. The PHG is considered to contain an adequate margin of safety for the potential noncarcinogenic adverse effects including adverse effects on the skin, and the hematological, gastrointestinal, immunological and reproductive and developmental systems.

INTRODUCTION

BaP is one of the polycyclic aromatic hydrocarbons (PAHs) formed when gasoline, garbage or any animal or plant materials burn incompletely. It was first isolated from coal tar. BaP and PAHs are ubiquitous environmental contaminants. People may be exposed to BaP from air, water, soil, cigarette and other plant product smoke, food and some work environments through inhalation, ingestion and skin contact.

Exposure to PAHs may cause harmful health effects. When humans are exposed to BaP at high concentrations for relatively short periods of time, BaP may cause red blood cell damage leading to anemia and suppressed immune system. Mixtures of PAHs including BaP such as coal tar were shown to be dermal carcinogens in animals as early as 1918. BaP has caused tumors in laboratory animals when administered in the diet, when applied to their skin or when inhaled for a long period of time. Humans exposed to mixtures of PAHs and other compounds at high concentrations over long periods of time can also develop cancer. Mice administered high levels of BaP in the diet during pregnancy had difficulty reproducing and so did their offspring. The offspring from pregnant mice administered BaP in the diet also exhibited birth defects and decreased body weights. Animal studies have also shown that BaP can affect the skin, the digestive system, body fluids and the immune system. A detailed description of the toxicology database for BaP is included later in this document.

This document represents an update on an earlier health risk assessment of BaP from the Office of Environmental Health Hazard Assessment (OEHHA, 1994) which provided part of the technical support to list BaP as a toxic air contaminant and as a Proposition 65 carcinogen, and to establish the California Maximum Contaminant Level (MCL) which is the enforceable primary drinking water standard. The majority of the evaluation is based on U.S. EPA's Drinking Water Criteria Document for PAHs (U.S. EPA, 1991a), and the Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profiles for BaP (ATSDR, 1990a) and PAHs (ATSDR, 1990b; 1995) with additional updated literature.

CHEMICAL PROFILE

Chemical Identity

BaP is a five-ring PAH. The chemical formula, structure, synonyms and identification numbers are listed in Table 1 and are adopted from two ATSDR documents (1990a; 1995).

Sources and Uses

BaP is the most well-studied PAH. PAHs, also known as polynuclear aromatic hydrocarbons, are a class of compounds which possess two or more annellated rings. They are not manufactured commercially in the United States (U.S.) but are ubiquitous in the environment. PAHs are formed during the incomplete burning of coal, oil, gas, wood, garbage, complex petroleum products, products of coal liquefaction processes or other organic substances such as tobacco or any plant materials and charbroiled meat or any animal materials. PAHs can be synthetic or occur naturally. BaP is not produced commercially in the U.S. in quantities greater than research levels and the commercial production is not a significant source of BaP in the environment. There is no known use for BaP except as a research chemical.

The principal natural sources of BaP are forest fires, volcanic eruptions, peat fires and burning of crude oil and shale oil, while anthropogenic sources include the incomplete combustion of fossil fuels, coke oven emissions, aluminum smelters, coal combustion and conversion industries, incinerators, vehicle exhausts and cigarette, cigar and marijuana smoke. BaP is usually found in smoke and soot, combines with dust particles in the air and is carried into water and soil and onto crops. It is found in the coal tar pitch that industry uses to join electrical parts together. It is also found in creosote, a substance used to preserve wood. BaP is one of the alternate PAHs which have an equally distributed electronic density and, therefore, are metabolized to ultimate carcinogens (ATSDR, 1990a; 1990b; 1995).

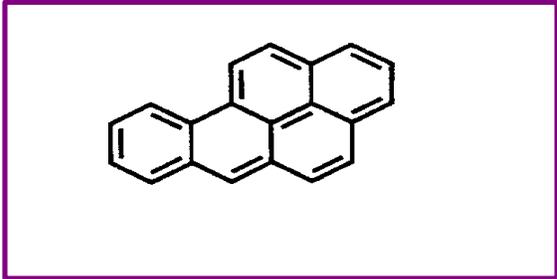
Physical and Chemical Properties

Important physical and chemical properties of BaP are given in Table 2. BaP is only slightly soluble in water and is poorly volatile.

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

The estimated annual U.S. emissions of BaP is 500 tons (ATSDR, 1990a). Most of the direct releases of BaP to the environment are first to the atmosphere from both natural and anthropogenic sources. Emissions from human activities predominate. In air, BaP is predominantly sorbed to particulates but also appears as a gaseous vapor. The low solubility, low vapor pressure, and high K_{ow} of BaP result in its partitioning mainly between soil (82%) and sediment (17%), with approximately 1% partitioning into water and less than 1% into air, suspended sediment and biota. BaP is identified as one of the eleven most persistent toxic chemicals in the Great Lakes, the largest inland body of fresh water on this planet (Hicks, 1996).

Table 1. Chemical Identity of Benzo(a)pyrene (ATSDR, 1990a; 1995; IARC, 1983)

Chemical name	Benzo(a)pyrene
Synonyms¹	Benzo(d,e,f)chrysene; 3,4-benzopyrene; 3,4-benzpyrene; 3,4-benzylpyrene; 3,4-benz(a)pyrene; 3,4-bp; 6,7-benzopyrene; benzpyrene; benz(a)pyrene; BP; B(a)P; benzo(alpha)pyrene; B α P; BaP; b(a)p; bp
Registered trade name	No data
Chemical formula	C ₂₀ H ₁₂ (IARC, 1983)
Wiswesser line notation	L D6 B6666 2AB TJ (HSDB, 1997)
Chemical structure	
Identification numbers	
Chemical Abstracts Service (CAS) Registry No:	50-32-8
NIOSH Registry of Toxic Effects of Chemical Substances (RTECS) [®] No:	DJ3675000
U.S. EPA Hazardous Waste No:	U022
Oil and Hazardous Materials/ Technical Assistance Data System (OHM/TADS) No:	8200129
Hazardous Substances Data Bank (HSDB) No.:	2554
National Cancer Institute (NCI) No.:	Not available

¹Confusion exists in the literature concerning the naming of this compound, mainly because two different systems (Richter and IUPAC) of numbering the pyrene ring structure have been used. The International Agency for Research on Cancer reference does not acknowledge that this confusion exists and that the nomenclature of some of the synonyms listed is incorrect.

Table 2. Physical and Chemical Properties of BaP (ATSDR, 1990a; 1995; U.S. EPA, 1991a)

Property	Value	References
Molecular weight	252.3 g/mol	IARC (1983)
Color	Pale yellow; fluoresces yellow-green in ultraviolet light	IARC (1983) Weast (1987)
Physical state	Solid, plates or needles (recrystallized from benzene/ligroin)	Weast (1987)
Odor	Faint aromatic odor	ATSDR (1995)
Odor threshold	No data	
Melting point	179-179.3 ⁰ C	Weast (1987)
Boiling point	310-312 ⁰ C (at 10 mm Hg) 495 ⁰ C (at 760 mm Hg)	Weast (1987) Aldrich (1996)
Flash point	Unknown	
Flammability limits	Unknown	
Autoignition temperature	Unknown	
Solubility		
Water	3.8 X 10 ⁻⁶ g/L(25 ⁰ C) 2.3 X 10 ⁻³ mg/L	U.S. EPA (1982) ATSDR (1995)
Organic solvents	Sparingly soluble in ethanol and methanol; soluble in benzene, toluene, xylene, acetone, DMSO, and ether	IARC (1983)
Biological fluids	Unknown	
Specific Gravity	1.351	U.S. EPA (1991a)
Density	1.351 g/cm ³	U.S. EPA (1991a)
Partition coefficients		
Octanol-water (K _{ow})	1.15 X 10 ⁻⁶	U.S. EPA (1982)
Log K _{ow}	6.06 (25 ⁰ C)	U.S. EPA (1982)
Soil-organic carbon-water (K _{oc})	5.5 X 10 ⁻⁶	U.S. EPA (1982)
Log K _{oc}	6.74 (25 ⁰ C)	U.S. EPA (1982)
Vapor pressure	5.6 X 10 ⁻⁹ mm Hg (20 ⁰ C) 7.47 X 10 ⁻⁷ mm Hg (25 ⁰ C)	U.S. EPA (1982) WHO (1996)
Henry's law constant	4.9 X 10 ⁻⁷ atm·m ³ /mol	U.S. EPA (1982)
Conversion factors ¹	1 ppm = 10.32 mg/m ³	Verschueren (1983)

¹ Calculated based on the ideal gas law, PV= nRT at 25⁰C: ppm = mg/m³ x 24.45 x 1,000/mol. weight.

BaP may bioconcentrate in aquatic organisms that can not metabolize it including plankton, oysters and some fish. The bioconcentration factors (BCFs) have been reported in the range from 0 in mosquito fish to 9 in clams and to 134,248 in cladoceran water fleas for various periods of exposure. Some levels of accumulation of BaP in aquatic species have been recorded. However, most fish and shellfish can metabolize BaP and the elimination of BaP takes only days. Biomagnification in food chains has not been reported (U.S. EPA, 1980; ATSDR, 1995). Nevertheless, food is the major source of human exposure to BaP which predominantly originates from environmental pollution, food packaging, cooking and processing (Santodonato *et al.*, 1981; de Vos *et al.*, 1990; Buckley *et al.*, 1995).

The most important degradation processes for BaP in water are photooxidation, chemical oxidation and biodegradation by aquatic microorganisms. BaP in water is oxidized by chlorination and ozonation. BaP in air is degraded through photolysis, reaction with nitrogen oxides, hydroxides, ozone, sulfur oxides and peroxyacetyl nitrate with estimated half-lives of approximately 40 minutes to seven days when adsorbed to particles and exposed to sunlight. Microbial metabolism and breakdown by sunlight are the major degradation processes for BaP in soil. The estimated half-life of BaP in soil is about 229 to 309 days. Bioremediation is emerging as a practical alternative to traditional disposal techniques (ATSDR, 1995).

Air

In 1970, ambient BaP concentrations in 120 U.S. cities were between 0.2 and 19.3 ng/m³ while BaP concentrations in non-urban areas ranged from 0.1 to 1.2 ng/m³. Airborne BaP in New York City was recorded at levels up to 50 ng/m³ in 1972 (ATSDR, 1995). The annual average concentration of BaP in London has decreased from 26 to 39 ng/m³ in 1962 to less than 1 ng/m³ in 1997 (Williams and Maynard, 1997). In polluted Lahore, Pakistan, the 1992 yearly average of BaP was 9 ng/m³ (Smith *et al.*, 1996). The inhaled BaP intake from air was estimated as 10 to 44 ng/day (Santodonato *et al.*, 1981).

In addition to certain industrial activities, traffic exhaust is a major source of BaP in cities, especially for nonsmokers (Pastorelli *et al.*, 1996; Zheng *et al.*, 1997). In Moscow, BaP content varied from 1 ng/m³ in parks and forests to 10 ng/m³ in the city center and 20 to 30 ng/m³ in the area adjacent to large factories and crossroads with heavy traffic (Khesina *et al.*, 1996). BaP concentrations were 4.4 ng/m³ in air from a street at Central Copenhagen with only diesel buses and petrol cars, and 1.3 to 1.4 ng/m³ in a nearby city park during January to March, 1992 and March, 1993 (Nielsen, 1996). The traffic to rural ratio of BaP varied between 7.07 and 17.6 in the fine particle mode, and between 5.32 and 16.9 in the coarse particle mode in a southern Taiwan study (Sheu *et al.*, 1996). In diesel exhaust BaP was detected at 680 ng/g particulate in Sweden (Soontjens *et al.*, 1997). BaP was detected in burning biomass while conditions during the burning affected the types and the amounts of PAHs produced (Jenkins *et al.*, 1996).

In 1988, BaP was measured at 1.3 ng/m³ in urban southern Guangzhou City, Guangdong Province, China (Simoneit *et al.*, 1991). BaP was 0.25 to 17.26 ng/m³ in Beicun countryside of Datong City, an industrialized area with twice the usual liver and lung cancer mortality, versus 0.1 to 4.6 ng/m³ in rural areas 30 kilometers north of Datong City, ShanXi Province, China (Han *et al.*, 1995). In Xuan Wei, YunNan Province, a high lung cancer rate area in China, women burning smoky coal without a chimney were exposed to 383 ng/m³ BaP; those burning smoky coal with a chimney were exposed to 184 ng/m³; and women burning wood or natural gas in Beijing had no

detectable exposure (Mumford *et al.*, 1993; 1995). The BaP contribution from kitchens using the characteristic Chinese cooking process can be significant (Zheng *et al.*, 1997). Exposure to complex PAH and other toxic emissions from cookstoves in developing countries may pose health risks (Zhang and Smith, 1996).

In four New Jersey areas, BaP levels in 1985 ranged from 0.11 to 0.23 ng/m³ in urban areas and from 0.04 to 0.06 ng/m³ in rural areas during summer, and from 0.69 to 1.63 ng/m³ urban and from 0.17 to 0.32 ng/m³ rural during winter. At 27 New Jersey sites, urban BaP was 0.6 ng/m³ and rural was 0.3 ng/m³ (ATSDR, 1995). It was estimated that 97% of the annual BaP emissions in New Jersey occurred during the November to March five-month heating season (ATSDR, 1990a). The largest primary source contributors to fine particle mass concentrations in Los Angeles included diesel engine exhaust, paved road dust and gasoline-powered vehicle exhaust, plus emissions from food cooking and wood smoke, with smaller contributions from tire dust, plant fragments, natural gas combustion aerosol and cigarette smoke (Schauer *et al.*, 1996). BaP appeared to be associated primarily with the fine aerosol fraction (Allen *et al.*, 1996).

BaP concentrations from 800 to 23,100 ng/m³ have been reported in the work room air of coke oven operations in the U.K. and in Sweden (ATSDR, 1995). A level of 900 ng/m³ BaP has been detected in a Norwegian electrode paste plant (Ovrebo *et al.*, 1994), from 170 to 4,880 ng/m³ BaP has been measured in a Swiss carbon anode plant (Petry *et al.*, 1996), and from 2 to 60 ng/m³ BaP has been determined in an American iron foundry (Santella *et al.*, 1993). The personal air samples of Estonian cookery workers in an oil shale processing plant had a mean BaP concentration of 5,700 ng/m³ with 18% of the samples exceeding 10,000 ng/m³, in addition to skin contamination of about 1.2 ng/cm² (Kuljukka *et al.*, 1996). Iron and steel workers in Anshan, Anhwei Province, China, were exposed to a range from 840 to greater than 3,200 ng/m³ BaP (Xu *et al.*, 1996). Exposure to eight-hour time-weighted average (TWA) concentrations from 16 to 45 ng/m³ of BaP was reported in Dutch fire-fighting trainers (Feunekes *et al.*, 1997).

Soil

Atmospheric deposition after local and long-term transport is believed to be the major source of BaP in soil since BaP has low mobility in soil. Approximately 52% of the BaP in air returns to surface soil and water via dry deposition. Typical concentrations of BaP in soils of the world are between 100 and 1,000 µg/kg; values as high as 650,000 µg/kg near a German soot plant and up to 500,000 µg/kg near oil refineries have been reported (ATSDR, 1990a). The background concentration of BaP is about 2 to 1,300 µg/kg in rural soil, about 4.6 to 900 µg/kg in agricultural soil, and about 165 to 220 µg/kg in urban soil (ATSDR, 1995). BaP has been detected in sludge ranging from 3 to 1,330 µg/kg, and in freeze-dried sewage sludge ranging from 540 to 13,300 µg/kg (U.S. EPA, 1991a). The soil half-life for BaP ranges from 0.16 years to 1.5 years (Borgert *et al.*, 1995).

Water

BaP, a lipophilic carcinogen, has relative low water solubility. Atmospheric deposition is believed to be the major source of BaP in surface water, with smaller amounts contributed by refinery effluents, municipal waste water, urban runoff and rivers. BaP in raw water tends to adsorb onto particulates and can be removed by filtration before reaching the tap. Contamination of raw water supplies from natural and anthropogenic sources, and leachate from coal tar and asphalt linings in

water storage tanks and distribution lines contribute the major sources of BaP in drinking water. BaP in tap water is mainly caused by the presence of PAH-containing materials in water storage and distribution systems. Granular activated charcoal is the U.S. EPA-approved treatment method for removing BaP and other PAHs in drinking water. It was estimated that one to two tons of BaP were released from municipal sewage effluents and 0.1 to 0.4 tons of BaP were released from petroleum refinery waste water in the U.S. in 1977 (ATSDR, 1990a). BaP was detected in the water soluble fraction of partially combusted crude oil in Kuwait after the 1991 Gulf War (Gundersen *et al.*, 1996). BaP in the ground water from five U.S. wood treatment facilities was reported to have an average concentration of 57,000 ppt (ATSDR, 1995). Mean concentrations of BaP in the Great Lakes have been between 0.03 and 0.7 ppt in water (Environment Canada, 1991).

BaP has been detected in surface water ranging from 0.2 to 13,000 ppt, tap water ranging from 0.2 to 1,000 ppt, rain water ranging from 2.2 to 7.3 ppt, subterranean water ranging from 0.4 to 7 ppt and waste water ranging from 0.001 to 6,000 ppb (U.S. EPA, 1991a), in two ground water sites at 0.3 and 4 ppt, respectively, in treated surface water used as drinking water ranging from 0.3 to 2 ppt and in untreated water ranging from 0.6 to 210 ppt (ATSDR, 1990a). Of the 6,074 sites sampled from 10 states including California, 0.26% had detectable BaP but all were below the MCL of 0.2 ppb (U.S. EPA, 1997b). BaP levels of less than 1 ppt were found in six American drinking water systems (NRC, 1982), and in several American studies including multiple cities, levels ranged from 0.1 to 2.1 ppt with an average of about 1 ppt (HSDB, 1997).

BaP was detected in the source drinking water collected from stomach cancer prevalent areas of Zanhuang County, HoPei Province, China, at 1.48 to 3.05 ppt (Zhang *et al.*, 1995). BaP concentrations averaging 2 and 3 ppt and maximizing at 15 ppt in tap water were reported in European water distribution systems (HSDB, 1997). BaP ranged from 0.01 to 0.95 ppt in Austrian mineral water and from 0.05 to 2.2 ppt in drinking water (Tiefenbacher *et al.*, 1982). The oral BaP intake from water was estimated as 1 ng/day (Santodonato *et al.*, 1981).

Food and Other Sources

Humans may also be exposed to BaP in food, tobacco and other plant smoke, and some occupational environments, and through contacts with BaP-containing products such as coal tar, coal tar-based shampoo, asphalt and creosote-treated wood. BaP has been detected in grains, fruits, vegetables and seafood. It was estimated at an average of 9,000 ng/kg BaP in charcoal-broiled steak (ATSDR, 1990a; 1995). U.S. EPA (1985) estimated a daily BaP intake from food of 50 ng. A daily median total ingested dose of 176 ng of BaP was also estimated, based on a urinary biomarker study of 14 adult human volunteers in New Jersey over 14 consecutive days, exceeding the inhalation dose by 16-fold for the winter dose of 11 ng/day and 122-fold for the summer/fall dose of 2.3 ng/day (Buckley *et al.*, 1995).

The daily oral PAH intake from food *per capita* was estimated as 1,600 to 16,000 ng including 30% carcinogenic PAHs, and 160 to 1,600 ng/day was estimated as the BaP intake from food (Santodonato *et al.*, 1981). A matching study in the Netherlands estimated the oral PAH intake from food *per capita* as 1,100 to 22,500 ng/day with BaP ranging from 30 to 350 ng/day (Vaessen *et al.*, 1988). The daily BaP intake from European total diets was estimated in the range of 120 to 290 ng (de Vos *et al.*, 1990). Similar estimates for BaP intake from food included 50 ng/day in Japan, 250 ng/day in the U.K. and 3,400 ng/day in Austria (Pfannhauser, 1991).

Food is a significant source of BaP in Europe due to PAHs in oils, fats and cereals which represent a high percent of the European diets (Guillen *et al.*, 1996). Legislation in Germany, Austria and Poland in 1987 established a maximum limit of 500 ng/kg for BaP in smoked meat. The German food industries recommended in 1990 a limit of BaP in refined fats and oils of below 5,000 ng/kg, even though levels as high as 68,600 ng/kg had been found in rape seed oil. In Brazil, mean levels of BaP in oils from sunflower, rice, palm, soybean and corn were 200, 1,800, 2,100, 2,200 and 10,800 ng/kg, respectively. BaP levels in garlic and rape seed oil were below the detection limit of 500 ng/kg (Pupin and Toledo, 1996).

In Germany, BaP measured in 27 smoked fish products ranged from 200 to 4,100 ng/kg (ppt) with a mean of 1,200 ng/kg, and the total carcinogenic PAHs averaged 9,000 ng/kg (Karl and Leinemann, 1996). BaP ranged from 10 to 19,110 ng/kg in various Austrian food including fruits, vegetables, smoked meat and fish products, oils, fats, grilled meats and spices (Tiefenbacher *et al.*, 1982), and from 100 to 1,300 ng/kg in various Dutch food including breads, biscuits, rice, wheat products, potatoes, fruits, vegetables, meat and fish products, milk and dairy products, poultry and eggs, oils, fats, nuts and drinks (de Vos *et al.*, 1990). In Spain, mean BaP content of 15 smoke sausage samples was around 20 ng/kg, and all but two samples had BaP below the 30 ng/kg limit imposed in the European legislation for smoking-flavor agents (Garcia Falcon *et al.*, 1996).

Cigarette smoke was reported to contain approximately 5 to 80 ng BaP per cigarette in the mainstream smoke while much higher concentrations of approximately 25 to 200 ng BaP per cigarette was in the sidestream smoke. The BaP in a cigarette smoke-polluted environment can be from 400 to 760,000 ng/m³. Cigar and pipe smoke can contain from 18 to 51 ng/g and 85 ng/g of BaP, respectively. BaP has also been detected at the Gulf War zone, in areas with leaked or spilled crude oil, incineration emissions and ashes, pulp mill and other industrial effluents and indoor air (ATSDR, 1990a; 1995). BaP in 28 pine needle samples from the U.K. ranged from 0.49 to 7.9 ng/g dry weight (Tremolada *et al.*, 1996).

METABOLISM AND PHARMACOKINETICS

Absorption

Metabolism of BaP has been studied extensively both *in vitro* and *in vivo* and has been reviewed and summarized (OEHHA, 1994; ATSDR, 1995). A median ingested dose of 176 ng/day was estimated for BaP (Buckley *et al.*, 1995). Absorption of BaP following ingestion is low in humans but is affected by the vehicle of administration and increases in the presence of oils in the gastrointestinal tract of some animals. Acidity and supplementary food materials in the digestive tract also affect the mobilization of PAHs (Hack and Selenka, 1996). Based on occupational studies, inhaled BaP is absorbed by humans. *In vivo* and *in vitro* dermal absorption of BaP in rat, guinea pig, human and tissue-cultured skin has been reported (Moody *et al.*, 1995). Skin absorption of BaP from soil spiked with petroleum crude oil was demonstrated (Yang *et al.*, 1989). Swimmers and bathers, especially sunburned ones, with prolonged skin exposure to a water body contaminated with BaP and other chemicals such as the Great Lakes may absorb toxicologically significant amounts of the chemicals (Moody and Chu, 1995).

Metabolism

BaP is metabolized initially by the microsomal cytochrome P₄₅₀ systems to several arene oxides. The arene oxides undergo hydration to dihydrodiols by epoxide hydrase and be further epoxidized to diol epoxides or react covalently with glutathione. Some of these intermediate metabolites are ultimate carcinogens. The intermediate metabolites can be conjugated to glucuronides and sulfate esters or form glutathione conjugates. The metabolites are more soluble in water than BaP and can then be excreted (ATSDR, 1995).

Five volunteers between 21 to 41 years of age ingested specially prepared diets high in PAHs, specifically BaP from grilled beef, for two to three days for a BaP intake of approximately 7 to 20 µg/day. A 100 to 250-fold increase in ingested BaP corresponded to a 6 to 12-fold increase in the elimination of 1-hydroxypyrene, one of the BaP metabolites in the excreta (Buckley and Lioy, 1992).

Distribution and Excretion

BaP is widely distributed in tissues of animals with some levels of placental transfer. BaP tends to be stored in fat, kidney and liver. The free BaP and its metabolism products, including epoxide intermediates, dihydrodiols, phenols, quinones and their various combinations of conjugates, can be excreted. Excretion of BaP appears to be mainly through feces, some through urine and the levels vary in different animals. The mechanism of action of BaP involves covalent binding of its metabolites to DNA. The bay region diol epoxide intermediates are considered as the ultimate carcinogens for alternate PAHs including BaP. Once the reactive bay region diol epoxide is formed, it may covalently bind to DNA and other cellular macromolecules and presumably initiate mutagenesis and carcinogenesis (ATSDR, 1995).

TOXICOLOGY

The various health effects in all tested species, the duration of exposure, selected no-observed-adverse-effect-levels (NOAELs) and lowest-observed-adverse-effect-levels (LOAELs), as adopted from the ATSDR (1995) document, are summarized in Table 3 which is separated into three categories based on the route of exposure: oral, inhalation and dermal exposure. Carcinogenic effects in tested animals are summarized in Table 4. However, no acute, intermediate or chronic duration minimal risk levels (MRLs) have been derived by the ATSDR for inhalation or oral or dermal exposure to BaP due to the lack of appropriate data (ATSDR, 1995).

In addition to the key documents from governmental agencies and literature search articles, toxicology information in the TOMES PLUS® database (Hall and Rumack, 1997) also has been used in the following summary of toxic effects of BaP. TOMES (Toxicology and Occupational Medicine System) PLUS® is a computerized database which includes the data systems of HSDB, IRIS, RTECS®, HAZARDTEXT(TM), REPROTEXT®, MEDITEXT®, SERATEXT®, REPROTOX®, CHRIS, OHM/TADS, TERIS, Department of Transportation Emergency Response Guide, New Jersey Hazardous Substance Fact Sheets, Shepard's Catalog of Teratogenic Agents and NIOSH Pocket Guide(TM).

Toxicological Effects in Animals and Plants

Acute Toxicity

Data on the acute toxicity of BaP are inadequate (ATSDR, 1995). The intraperitoneal LD₅₀ in mice for BaP is 232 mg/kg with adverse hematological effects (Salamone, 1981). The subcutaneous LD₅₀ for BaP in rats is 50 mg/kg and it is a mild skin irritant to mice (reported in 1967 and cited in the Registry of Toxic Effects of Chemical Substances (RTECS®) by NIOSH in TOMES PLUS® by Hall and Rumack, 1997).

An NOAEL of 150 mg/kg-day for gastrointestinal, hepatic and renal effects for acute oral exposure in rats is recorded in Table 3. Intra-gastric administration of BaP for four days resulted in suppression of carboxylesterase activity in the intestinal mucosa, and induction of carboxylesterase activity in the liver and the kidney (Nousiainen *et al.*, 1984). Following dermal application of BaP in C57BL/6 male mice for one to two days, an NOAEL of 0.001 mg/cm² and an LOAEL of 0.025 mg/cm² for induction of melanocytes were identified (Iwata *et al.*, 1981). Following dermal application of BaP in C57BL/6 female mice for one to two days and in C34/HeN mice for five days, an LOAEL of 120 µg for contact hypersensitivity was identified (Klemme *et al.*, 1987).

Binding of BaP and metabolites to melanin *in vitro* and in mice and hamsters suggested a role in the induction of melanoma (Roberto *et al.*, 1996). Epidermal cytotoxicity was observed in mice administered 64 µg BaP at the beginning of the first week of the treatment, and cell death was followed by regeneration (Albert *et al.*, 1991).

Subchronic Toxicity

An LOAEL for death after intermediate oral exposure in mice is recorded in Table 3. Oral exposure to 120 mg/kg-day BaP resulted in decreased survival, which appeared to be caused by bone marrow depression and proliferation leading to aplastic anemia, hemorrhage or infection, in two strains of mice whose hepatic aryl hydrocarbon hydroxylase (AHH) activity is not induced by PAHs (non-PAH-responsive or Ah^d/Ah^d) compared to the PAH-responsive or Ah^b/Ah^b mice in a six-month study. The Ah^d/Ah^d mice also exhibited increased relative liver weights (Robinson *et al.*, 1975). Six-week-old female rats administered 2 mg/kg BaP had an adverse endocrine effect of decreased numbers of thymic glucocorticoid receptors (Csaba *et al.*, 1991).

Lack of weight gain in hamsters was induced at 9.8 mg/m³ BaP in the 16-week inhalation bioassay of Thyssen *et al.* (1980) from which an LOAEL of 0.9 mg/kg-day was calculated (OEHHA, 1994). Dermal application of 0.001% and 1.0% BaP on female Guinea pigs twice in two to three weeks induced contact hypersensitivity (Old *et al.*, 1963). Many factors such as oil viscosity and grooming activity affect the bioavailability of BaP from oils in skin (Ingram *et al.*, 1995).

Subchronic intramuscular injections of BaP caused increases in aorta plaque volume in male chickens (Penn and Snyder, 1988) and male (Revis *et al.*, 1984) and female pigeons (Hough *et al.*, 1993). A statistically significant increase in aorta plaque size in white Carneau pigeons injected with 0.1, 10 and 100 mg/kg (ppm) BaP weekly for six months (Revis *et al.*, 1984) led to an LOAEL of 0.014 mg/kg-day for adverse cardiovascular effects (OEHHA, 1994).

Genetic Toxicity

There is relatively uniform evidence that BaP induces genotoxic effects both *in vitro* and in whole animals, including parental and fetal DNA-adducts in monkeys and mice, abnormal sperm levels in mice, inhibition of DNA synthesis in the seminiferous tubules in rats, gene mutations and micronuclei induction which have been reviewed and summarized (OEHHA, 1994; ATSDR, 1995). BaP has been used as a positive control in many *in vivo* and *in vitro* clastogenicity and mutagenicity studies. The development of methods for the detection of genetic damage by PAH exposure in humans used BaP as a positive control (Winker *et al.*, 1995).

Developmental and Reproductive Toxicity

As reported in Table 3, an NOAEL of 40 mg/kg-day for reproductive effects and an NOAEL of 10 mg/kg-day for developmental effects in the progeny were observed in female pregnant CD-1 mice gavaged daily for 10 days during gestation days 7 to 16. An LOAEL of 160 mg/kg-day for reduced percentage of pregnant female mice and an LOAEL of 40 mg/kg-day for reduced pup weight at 20 days were also observed (Mackenzie and Angevine, 1981). An LOAEL of 120 mg/kg-day for fetal resorption, stillbirth, decreased weight gain and birth defects was derived in two strains of non-PAH-responsive (Ah^d/Ah^d) mice administered BaP in the diet for eight days during gestation days 2 to 10 with total sterility in the progeny at higher doses (Legravverend *et al.*, 1984). Oral intubation in female NMR1 mice during days 7 to 16 of pregnancy led to an LOAEL of 10 mg/kg-day for reduced fertility and few ovarian follicles. The possibility of synergism with inorganic lead was also indicated (Kristensen *et al.*, 1995).

For intermediate exposure, white Swiss female mice administered BaP in feed *ad libitum* for 19 to 29 days had an NOAEL of 133.3 mg/kg-day for reproductive toxicity (Rigdon and Neal, 1965). Pregnant rats administered 0.1% BaP in the diet caused fetal resorptions and stillbirth (Rigdon and Rennels, 1964). Intramuscular injections of BaP for three to five months in female pigeons caused infertility with ovarian abnormalities (Hough *et al.*, 1993). Embryotoxicity caused by metabolites of BaP was observed in chickens (Anwer and Mehrotra, 1988). BaP was predominantly activated by cytochrome P₄₅₀ isoenzyme CYP1A1 in a *Xenopus laevis* frog embryo teratogenesis assay and induced malformations and death (Propst *et al.*, 1997).

As summarized in the REPROTOX® database (Hall and Rumack, 1997), BaP is known to cross the placenta in mice and guinea pigs, producing adduct formation in fetal tissues after maternal treatment. BaP inhibited ovulation in C57BL/6N mice and the ovary appeared capable of metabolizing BaP to its toxic metabolites. BaP administered subcutaneously to female mice of A strain on the 18th and 19th days of pregnancy caused an increase in lung adenomas in four subsequent in-bred generations (Turusov *et al.*, 1990). Inhalation by pregnant Wistar rats indicated that BaP accumulated in fetal lungs (Withey *et al.*, 1993).

Immunotoxicity

BaP and mixtures of PAHs have been shown to markedly inhibit the immune system both *in vitro* and *in vivo* and induce autoimmune responses (ATSDR, 1995). Chemical synergism is

Table 3A. Significant Health Effects and Levels of Oral Exposure to BaP (ATSDR, 1990a; 1995)

Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Reference
ACUTE EXPOSURE					
Systemic Toxicity					
Rat (Wistar/Af/Han/Mol/ Kuo)	4 days, once/day (Gavage)	G.I., Hepatic, Renal	150 (M) 150 (M) 150 (M)		Nousiainen <i>et al.</i> (1984)
Reproductive Toxicity					
Mouse (CD-1)	10 days, gestation days 7 to 16 (Gavage)		40 (F)	160 (F) (reduced percentage of pregnant females)	Mackenzie and Angevine (1981)
Developmental Toxicity					
Mouse (B6AKF1, AKR/J)	8 days in gestation days 2 to 10 (Feed)			120 (F) (fetal resorption in Ah ^d /Ah ^d)	Legravverend <i>et al.</i> (1984)
Mouse (CD-1)	10 days in gestation days 7 to 16 (Gavage)		10 (F)	40 (F) (reduced pup weight at 20 days)	Mackenzie and Angevine (1981)
Mouse (NMR1)	7 to 16 days of pregnancy (Oral intubation)			10 (F) (reduced fertility, few ovarian follicles)	Kristensen <i>et al.</i> (1995)
INTERMEDIATE EXPOSURE					
Systemic Toxicity					
Mouse (DBA/2N, AKR/N); (C57B1/b, C3H/HeN, BALB/cAnN)	6 months (Feed)	Hemato- logical, Hepatic		120 (aplastic anemia) 120 (increased liver weight) 120 (reduced survival)	Robinson <i>et al.</i> (1975)
Reproductive Toxicity					
Mouse (White Swiss)	19 to 29 days <i>ad lib</i> (Feed)		133.3 (F)		Rigdon and Neal (1965)

suspected in complex environmental mixtures. The levels of several brain neurotransmitters, which in turn affect the functions of the immune system, were altered in mice brains in which fibrosarcomas had been induced by single subcutaneous injection of BaP (Dasgupta and Lahiri, 1992). Airborne particles from the industrial area of Upper Silesia, Poland containing over 250 PAHs and heavy metals, caused thymus-directed immunotoxicity in female BALB/c mice at single acute intraperitoneal doses ranging from 20 to 330 mg/kg with LD₅₀s ranging from 0.06 to 1 mg/kg (Kozłowska *et al.*, 1996).

Chronic Toxicity

A dose-dependent decrease in survival was noted in hamsters after 60 weeks of inhalation exposure to 46.5 mg/m³ BaP in a 109-week study (Thyssen *et al.*, 1981). Chronic subcutaneous administration of PAH fractions containing BaP induced liver damage in mice (Meiss *et al.*, 1982). Some studies on ecotoxicity and bioavailability of BaP in environmental complex mixtures on various species of fish, shellfish and plants are also available in published literature (U.S. EPA, 1980; Tuvikene, 1995; Hicks, 1996).

Table 3B. Significant Health Effects and Levels of Inhalation Exposure to BaP (ATSDR, 1990a; 1995)

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/m ³)	LOAEL (mg/m ³)	Reference
CHRONIC EXPOSURE					
Systemic Toxicity					
Human	6 months to >6 years	Respiratory		0.0001 (reduced lung function, abnormal chest X-ray, cough, bloody vomit, throat and chest irritation)	Gupta <i>et al.</i> (1993)
Hamster (Syrian golden)	After 60 weeks in a 109-week study, 7 days/week 3 to 4.5 hours/day			9.8 (M) (lack of weight gain and dose- related decrease in survival)	Thyssen <i>et al.</i> (1980)

Table 3C. Significant Health Effects and Levels of Dermal Exposure to BaP (ATSDR, 1990a; 1995)

Species/ (Strain)	Exposure/ Duration/ Frequency (Promoter)	System	NOAEL	LOAEL	Reference
ACUTE EXPOSURE					
Systemic Toxicity					
Mouse (C57BL/6)	1 to 2 days, once/day	Skin	0.001 mg/cm ² (M) (induction of melanocytes)	0.025 mg/cm ² (M) (substantial melanocytes)	Iwata <i>et al.</i> (1981)
Mouse (C57BL/6)	1 to 2 days, once/day	Skin		120 µg (F) (contact hyper- sensitivity)	Klemme <i>et al.</i> (1987)
Immunological/Lymphoreticular Toxicity					
Mouse (C34/HeN)	5 days, twice/5 day	Skin		120 µg (F) (contact hyper- sensitivity)	Klemme <i>et al.</i> (1987)
INTERMEDIATE EXPOSURE					
Immunological/Lymphoreticular Toxicity					
Guinea pig (Hartley)	2 to 3 weeks, twice	Skin	0.001% (F) (slight contact hyper- sensitivity)	1.0% (F) (contact hyper- sensitivity)	Old <i>et al.</i> (1963)

Carcinogenicity

BaP is carcinogenic in laboratory animals by intratracheal instillation, by inhalation and dermal exposure, by intraperitoneal injection and when given in the diet. A very large number of experiments has demonstrated that BaP causes tumors at several sites, by several routes of administration, in both males and females and in several animal species. Many studies, however, are very limited in scope or in data reported and are not suitable for risk assessment (Collins *et al.*, 1991; OEHHA, 1994). The site of tumor induction depends on the route of administration (e.g., stomach tumors are observed following ingestion of BaP). BaP is a complete carcinogen containing both initiator and promoter properties but is more active as a tumor initiator (ATSDR, 1995). BaP has been used as a positive control for many carcinogenicity and mutagenicity bioassays, and also in recent studies on anticancer and antimutagenicity effects of various chemicals and complex mixtures.

Several reports have summarized the many studies of increased incidence of alimentary tract tumors in rodents as a consequence of oral BaP exposure (Collins *et al.*, 1991; U.S. EPA, 1991b;

ATSDR, 1995; WHO, 1996). As early as 1937, Waterman used BaP to induce gastric tumors in laboratory mice (cited by Neal and Rigdon, 1967). In the majority of the studies, there was a single gavage exposure or only one dietary dose was employed, treatment was for a relatively small percentage of the lifespan of the animal and details such as concurrent controls were not reported. U.S. EPA (1991b) evaluated 14 ingestion studies and considered only three of them (Brune *et al.*, 1981; Chouroulinkov *et al.*, 1967; Neal and Rigdon, 1967) as appropriate for calculating a BaP potency slope. This evaluation only reviews the studies which may contribute to the quantitative risk assessment for the oral route.

Administering BaP in the diet to SWR/J Swiss mice induced squamous cell carcinomas of the forestomach in both male and female mice (Rabstein *et al.*, 1973). Horie *et al.* (1965) administered a 0.003% solution of BaP in 95% ethanol by forced drinking to a total of 63 male mice, five days per week for up to 22 months. The mice developed 10 esophageal papillomas, 1 esophageal carcinoma, 13 forestomach papillomas and 2 forestomach carcinomas as compared with no esophageal tumors and 5 forestomach papillomas in the 67 controls. Feeding of palletized chow containing BaP to CFW mice also caused pulmonary tumors and leukemia (Rigdon and Neal, 1966; 1969).

As shown in Table 4, CFW Swiss mice administered feed with BaP *ad libitum* for 30 to 197 days (intermediate exposure) did not have observable cancers at 1.3 mg/kg-day BaP and cancers were observed at levels greater than 2.6 mg/kg-day. In mice administered BaP in the diet for one to seven days (acute exposure), cancers were not observed at 13.3 mg/kg-day and were observed at levels greater than 33.3 mg/kg-day (ATSDR, 1995) based on studies for gastric tumors (Neal and Rigdon, 1967). These levels are reported observations from experiments with limited numbers of animals used.

This Neal and Rigdon (1967) study is the major scientific basis for the quantitative cancer risk assessment for oral exposure to BaP (Collins *et al.*, 1991; U.S. EPA, 1980; 1984; 1991a; 1991b; OEHHA, 1994). BaP at doses of 0.001, 0.01, 0.02, 0.03, 0.04, 0.045, 0.05, 0.1 or 0.25 mg/g of feed (between 1 to 250 ppm) in the diet was administered to 17 to 180 days old CFW Swiss mice, 23 to 73 mice of unspecified gender combinations per dose, for periods of 98 to 197 days. No tumors were found in the control group nor in the groups treated with 1, 10 or 30 ppm BaP. The tumor incidence increased between the 40 and 250 ppm doses at the rate of 2.5, 10, 70, 82 and 90%. Stomach tumors, mostly squamous cell papillomas and some carcinomas, appeared; the incidence was significantly higher than controls ($p < 0.001$) at several doses using the Fisher Exact Test (Table 5). U.S. EPA (1980; 1984; 1985) calculated the q_1^* to be $11.5 \text{ (mg/kg-day)}^{-1}$ using a prototype of the GLOBAL 86 program. Using several models, the upper bounds judged to be the most acceptable q_1^* ranged from $4.5 \text{ (mg/kg-day)}^{-1}$ to $11.5 \text{ (mg/kg-day)}^{-1}$ (U.S. EPA, 1991a; 1991b).

In an additional study reported in the same article (Neal and Rigdon, 1967), groups of 9 to 26 CFW mice were administered diets containing BaP for periods ranging from 1 to 30 days, then observed for up to 105 days. At 0.25 mg/g, the incidence of gastric tumors was 0, 11, 10, 44, 30 and 100% for periods of administration of 1, 2, 4, 5, 7 and 30 days, respectively. Gastric tumors developed in 50% of a group of 33 mice administered BaP 5 mg/g for one day in the diet and kept for observation for 103 to 133 days. The major shortcoming of these Neal and Rigdon (1967) studies from 30 years ago is the lack of lifetime exposure. In addition there are deficiencies in experimental design, good laboratory practice and adequate pathological evaluation compared with more recent studies.

Table 4A. Carcinogenic Effects and Levels of Oral Exposure to BaP (ATSDR, 1990a; 1995)

Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	Dose without observable cancer (mg/kg-day)	Lowest dose with observable cancer (mg/kg-day)	Reference
ACUTE EXPOSURE				
Mouse (CFW Swiss)	1 to 7 days <i>ad lib</i> (Feed)	13.3	33.3 (gastric neoplasms)	Neal and Rigdon (1967)
INTERMEDIATE EXPOSURE				
Mouse (CFW Swiss)	30 to 197 days <i>ad lib</i> (Feed)	1.3	2.6 (gastric tumors)	Neal and Rigdon (1967)
Mouse (CFW Swiss)	23 to 238 days <i>ad lib</i> (Feed)		33.3 (papillomas, squamous cell carcinomas)	Rigdon and Neal (1967)
Mouse (CFW Swiss)	80 to 140 days <i>ad lib</i> (Feed)		33.3 (forestomach tumors in 69/108)	Rigdon and Neal (1967)
CHRONIC EXPOSURE				
Rat (Sprague-Dawley)	2 years (feed or gavage in a 1.5% caffeine solution)		forestomach, esophagus, larynx tumors at all doses	Brune <i>et al.</i> (1981)

The study by Brune *et al.* (1981) is the only reported BaP ingestion experiment of two years duration. BaP in aqueous 1.5% caffeine solution applied orally either in the diet or by gavage to Sprague-Dawley rats, 32 per sex, induced forestomach, esophagus and larynx tumors. It was not possible to determine whether the enhanced tumor response was influenced by the potential irritation effects of gavage, or the potential co-carcinogenic activity of caffeine or some combination of both. U.S. EPA (1991a, b) calculated a range of q_1 's based on male only, male and female, total contact-site tumors or forestomach tumors only, to be between 3.8 and 11.7 (mg/kg-day)⁻¹.

Another relatively long-term study (Chouroulinkov *et al.*, 1967) was used to calculate q_1^* s. In this study, groups of 160 female albino mice of unspecified strain fed a total estimated dose of 8 mg BaP (0.63 mg/kg-day) mixed with olive oil in the diet for 14 months had an incidence of gastric tumors of 5/81 (6.2%). The q_1^* was calculated to be $6.5 \text{ (mg/kg-day)}^{-1}$ (U.S. EPA, 1991a, b).

Swiss mice administered BaP in the feed *ad libitum* for 23 to 239 days or 80 to 140 days had various tumors at 33.3 mg/kg-day (Rigdon and Neal, 1967). Malignant and benign mammary gland tumors were induced by BaP administered by gavage to female CD rats for eight weeks in a one-year study (El-Bayoumy *et al.*, 1995; Hecht *et al.*, 1994). Dietary vitamin A may reduce the forestomach tumorigenesis during the total and postinitiation stages in mice treated with a total of 20 mg or 2 mg BaP (Yamada *et al.*, 1995), and may be protective against BaP-induced respiratory tract cancer in hamsters (Saffiotti *et al.*, 1967).

The numbers of lung adenomas, counted 240 days after treatment with a single intraperitoneal injection of BaP in male A/J mice, correlated with time-integrated DNA adduct levels in a dose-dependent manner (Ross *et al.*, 1995). Lung tumors developed in male A/J mice after a single intraperitoneal injection of BaP (Gunning *et al.*, 1991). Female A/J mice (Weyand *et al.*, 1995; Weyand and Wu, 1995) exhibited forestomach tumors with chronic feeding and lung tumors with a single intraperitoneal injection of BaP as a positive control for manufactured gas plant residues (MGP). Newborn male NMR1 mice developed lung tumors as well as hepatocellular lesions from 100 μg BaP injected intraperitoneally as a positive control for outdoor particulate matter (Heussen *et al.*, 1996). A single intraperitoneal injection of BaP, as a positive control for MGP, induced liver tumors in infant male $B_6C_3F_1$ mice (Rodriguez *et al.*, 1997).

Table 4B. Carcinogenic Effects and Levels of Inhalation Exposure to BaP (ATSDR, 1990a; 1995)

Species/ (Strain)	Exposure/ Duration/ Frequency	System	Dose without observable cancer (mg/m^3)	Lowest dose with observable cancer (mg/m^3)	Reference
CHRONIC EXPOSURE					
Hamster (Syrian golden)	109 weeks 7 days/week 3 to 4.5 hours/day	Respiratory Digestive		9.5 (M) (34.6% increase in respiratory tract tumors, 26.9% in upper digestive tract neoplasms)	Thyssen <i>et al.</i> (1981)

Table 4C. Carcinogenic Effects and Levels of Dermal Exposure to BaP (ATSDR, 1990a; 1995)

Species/ (Strain)	Exposure/ Duration/ Frequency (Promoter)	System	Dose without observable cancer	Lowest dose with observable cancer	Reference
INTERMEDIATE EXPOSURE					
Mouse (SENCAR)	First then 23rd week, twice/week (TPA)	Skin		0.2 mg (F) (6 papillomas per mouse)	Cavalieri <i>et al.</i> (1988)
Mouse (Swiss)	20 weeks, twice/week, once/day	Skin		0.025 mg (F) (tumors in 90%)	Cavalieri <i>et al.</i> (1988)
CHRONIC EXPOSURE					
Mouse (NMR1)	17 to 22 months, 2 days/week, once/day	Skin		1.7 µg (0.016 mg/kg-day) (F) (45% skin tumors)	Habs <i>et al.</i> (1980)
Mouse (C3H/HrJ)	99 weeks, 2 days/week, once/day	Skin		12.5 µg (F) (malignant tumors in 47/50)	Warshawsky and Barkley (1987)

Respiratory tract tumors in hamsters were induced at 9.5 mg/m³ or 46.5 mg/m³ BaP in the 109-week inhalation bioassay of Thyssen *et al.* (1981). Intratracheal instillation of a saline suspension of BaP on ferric oxide particles in hamsters induced respiratory tract tumors (Saffiotti *et al.*, 1972; Feron *et al.*, 1973) with the methodology critically appraised later (Wolterbeek *et al.*, 1995). Data from the Thyssen *et al.* (1981), Saffiotti *et al.* (1972) and Feron *et al.* (1973) studies were used in our previous calculations for inhalation cancer potency (Collins *et al.*, 1991; OEHHA, 1994). Intratracheal instillation of BaP induced pulmonary squamous cell carcinomas and adenocarcinomas in mice (Kim and Lee, 1996).

Repeated intratracheal administration of carbon black particles and diesel soot with and without BaP, and BaP alone as a positive control, induced lung tumors in female Wistar rats (Dasenbrock *et al.*, 1996). Malignant lung tumors increased in a dose-dependent manner in newborn female mice that inhaled PAH-enriched pyrolyzed coal tar pitch exhaust aerosols containing 0.05 or 0.09 mg/m³ BaP in a 10-month study (Schulte *et al.*, 1993). Lung tumors were induced in female Wistar rats inhaling coal tar pitch condensation aerosols containing 0.02 or 0.046 mg/m³ BaP for a lifetime (Heinrich *et al.*, 1994).

Mixtures of PAHs including BaP, such as coal tar, were shown to be dermal carcinogens in animals as early as 1918 by Yamagiwa and Ichikawa. BaP has since been used as a positive

control in dermal studies and usually is administered at a single dose level (ATSDR, 1995). BaP topically applied to the back of female Swiss mice for 20 weeks, twice a week and once a day, resulted in papillomas and squamous cell carcinomas (Cavalieri *et al.*, 1988). In another study reported in the same article, BaP with the promoter 12-O-tetra-decanoylphorbol-13-acetate (TPA) applied on female SENCAR mice at the first week and the 23rd week for two days per week induced skin papillomas. NMR1 female mice, applied with 1.7 µg BaP throughout their lifetime, developed skin papillomas and carcinomas (Habs *et al.*, 1980). C3H female mice administered 12.5 µg BaP on the skin for 99 weeks exhibited 94% malignant skin tumors (Warshawsky and Barkley, 1987). Chronic topical application of 50-nmole BaP, as a positive control for other PAHs, on the skin of Hsd:ICR(Br) mice, confirmed the dermal carcinogenicity of BaP (Warshawsky *et al.*, 1994). Squamous cell carcinomas were induced in 79% and 67% of the male NMR1 mice applied for two years with 0.015% BaP alone and 0.015% BaP with TPA, respectively (Mellert *et al.*, 1994).

Xeroderma pigmentosum (XP) patients are known to have increased incidence of light-induced skin tumors and defects in the XP complementation group A-correcting (XPA) genes are associated with the cancer-prone human disease. Oral treatment of XPA-deficient mice by gavage with 4.3 and 13 mg/kg BaP for 13 weeks, three times per week, induced lymphomas (de Vries *et al.*, 1997).

Toxicological Effects in Humans

No studies were located regarding death, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, neurological, reproductive, developmental, dermal or ocular effects in humans following inhalation, ingestion, dermal or other routes of exposure to BaP. No studies were located regarding acute and subchronic effects in humans (ATSDR, 1995).

Genetic Toxicity

Iron factory workers exposed to 0.5 to 20 ng/m³ BaP had DNA adducts and exhibited increased mutation rates in peripheral lymphocytes (Perera *et al.*, 1988; 1993). DNA adducts and urine metabolites had been detected at higher levels than in controls in Xuan Wei women exposed to 184 to 383 ng/m³ of BaP (Mumford *et al.*, 1993; 1995), and in workers in an electrode paste plant exposed to 900 ng/m³ (Ovrebo *et al.*, 1994). BaP diol epoxide adducts with hemoglobin (Hb) were detected in newspaper vendors exposed to traffic exhaust in the city of Milan, Italy, in the summer of 1993. Adduct concentration was not different for low and high density traffic-exposed smokers. Among the nonsmokers, Hb adducts were detectable in 60% of high exposure subjects and in 28% of those with low exposure (Pastorelli *et al.*, 1996).

Chronic Toxicity

Following chronic inhalation exposure to BaP and particulate matter, respiratory adverse effects were observed in workers at a rubber factory (Gupta *et al.*, 1993; 1994). In Poland, male iron foundry workers chronically exposed to 200 to 500,000 ng/m³ BaP in complex mixtures on top of the coke oven showed depressed serum immunoglobulins (Szczeklik *et al.*, 1994). In Austria, chronic exposure to 651 or 5,396 ng/m³ BaP in PAH mixtures induced immunosuppressive effects in coke oven workers (Winker *et al.*, 1997). Fetal Hb, found in men employed in a cooking plant of the steel mill "Huta Sendzimir" in Krakow, southern Poland and chronically exposed to BaP at concentrations from 900 to 388,900 ng/m³, might be a marker of susceptibility to industrial

pollutants (Stepniewski *et al.*, 1996). Several biomarkers in plasma, blood and urine samples from coke oven workers were evaluated as indicators of exposure to PAHs (Ovrebo *et al.*, 1995).

Carcinogenicity

The first instance of occupational cancer ever to be described (by Sir Percival Pott in 1775) was the scrotal cancer in chimney sweeps who had been exposed since childhood to contact with soot from coal fires containing BaP and other PAHs. Epidemiological evidence suggests that workers intimately exposed to the products of combustion or distillation of bituminous coal containing BaP are at an increased risk for cancers of the skin, respiratory tract, bladder and kidney. Skin cancer in man is well known to have occurred following exposure to poorly refined lubricating and cutting oils with BaP and PAHs (HSDB, 1997). Epidemiological studies have shown that machinists have an increased risk of lung cancer and bladder cancer, and a biomarker study indicates that dermal uptake of PAHs is a major route of exposure (Moen *et al.*, 1996).

Epidemiological studies have shown increased mortality due to lung cancer in humans exposed to coke oven emissions, roofing-tar emissions, fuel pump emissions and cigarette smoke which contain BaP. Excess risks of bladder cancer among aluminum smelter workers exposed to coal tar pitch involving BaP have been reported (ATSDR, 1995). Cancer risk due to occupational exposure to PAHs has been analyzed in Canada to conclude that BaP is associated with lung, bladder, esophagus, stomach, pancreas and prostate cancers in some workers (Nadon *et al.*, 1995).

Long-term iron and steel workers in Anshan, AnHwei Province, China, exhibited a 40% increased risk for lung and stomach cancers with exposure to complex mixtures including BaP from 840 to greater than 3,200 ng/m³ (Xu *et al.*, 1996). A man who had been exposed to BaP for three weeks while he was carrying out an experiment in mice had persistent nodules which were diagnosed as squamous epithelioma (reported in 1938 and reviewed in the IARC Monograph, 1983).

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

The currently available data are insufficient to compare NOAELs and LOAELs to derive the most sensitive noncarcinogenic adverse effects of BaP exposure. The lowest LOAEL appears to be 0.014 mg/kg-day while the lowest NOAEL appears to be 1.3 mg/kg-day.

It was estimated that the daily oral BaP intake from water is 1 ng/day by Santodonato *et al.* (1981). Dividing this value by the default value for male human body weight of 70 kg yields a daily BaP oral dose from drinking water of 1.4×10^{-8} mg/kg-day. Another estimate can be made based on the estimated BaP level in drinking water in the U.S. of approximately 1 ppt (ng/L) (ATSDR, 1995; HSDB, 1997). An "adult man" weighing 70 kg and drinking 2 L/day water would have an intake of 2 ng BaP/day (1 ng/L x 2 L/day = 2 ng/day). Dividing 2 ng/day by 70 kg (body weight) yields a dose of 2.9×10^{-8} mg/kg-day.

At this level, noncarcinogenic health effects are unlikely to occur since this expected dose to humans is on the order of about one-millionth that which causes adverse effects of reduced fertility, oocyte destruction and lack of weight gain in mammals and increased aorta plaque size in pigeons (LOAELs of 10, 10, 0.9 and 0.014 mg/kg-day, respectively) as described previously in this

assessment. However, NOAELs and LOAELs for BaP effects in animals are very scarce and are non-existent for humans. Such scarcity of data constitutes a data gap for BaP. Data for additional toxicologic endpoints are needed.

Carcinogenic Effects

Both the existing OEHHA cancer guidelines (DHS, 1985) and the proposed U.S. EPA cancer guidelines (1996b) prescribe that risk assessments use the most sensitive gender, site and species where a significant increase in cancer incidence is observed. For BaP, this indicates the use of data on gastric tumors including papillomas and squamous cell carcinomas observed in male and female mice due to feeding BaP (Neal and Rigdon, 1967) and shown in Table 5. In addition, large numbers of mice (319 experimental and 289 control) were used to establish the dose-response curve (Collins *et al.*, 1991; OEHHA, 1994).

In its risk assessment, the U.S. EPA (1980; 1984; 1985; 1991a, b) used mainly the data for stomach tumors from oral exposure to BaP in mice by Neal and Rigdon (1967) to estimate cancer potency and unit risks associated with exposure to BaP. Based on the Neal and Rigdon (1967) data, U.S. EPA (1980) first developed an oral q_1^* for human of $11.5 \text{ (mg/kg-day)}^{-1}$. In the final rule of NPDWR, the U.S. EPA (1992b) used an oral q_1^* for human of $5.76 \text{ (mg/kg-day)}^{-1}$. Later, U.S. EPA corrected the q_1^* on IRIS to be $7.3 \text{ (mg/kg-day)}^{-1}$ due to a mistake in one of the calculations. In 1994, U.S. EPA (1997a) included a range of q_1^* s from 4.5 to $11.7 \text{ (mg/kg-day)}^{-1}$ with a geometric mean of $7.3 \text{ (mg/kg-day)}^{-1}$ for humans. Based on the Neal and Rigdon (1967) mouse data, the U.S. EPA (1991a) derived a q_1^* of $11.5 \text{ (mg/kg-day)}^{-1}$ using the LMS model (U.S. EPA, 1980), $9.3 \text{ (mg/kg-day)}^{-1}$ using the Clement two-stage model with the slope from 10% response (U.S. EPA, 1991b), $5.9 \text{ (mg/kg-day)}^{-1}$ using the two-stage model with conditional upper bound (Clement Associates, 1990) and $4.5 \text{ (mg/kg-day)}^{-1}$ using Weibull-type model (U.S. EPA, 1991b). These human q_1^* s were adjusted with the scaling of carcinogen doses by the 2/3 instead of the recently proposed 3/4 power of body weight (U.S. EPA, 1992a), and the life-span of mice was estimated as 630 days (U.S. EPA, 1984) instead of the 730 days (or two years or 12 months or 104 weeks) discussed in OEHHA (1994).

U.S. EPA (1991a) also calculated human q_1^* s based on the Brune *et al.* (1981) two-year rat ingestion study to be 4.7 (male and female, total contact-site larynx, esophagus, forestomach tumors) and 3.8 (male and female, forestomach) (mg/kg-day)^{-1} , respectively. In another evaluation, U.S. EPA (1991b) calculated human q_1^* s based on the same rat data to be 11.7 (male, total contact-site larynx, esophagus, forestomach tumors) and 9.5 (male, forestomach tumors) (mg/kg-day)^{-1} , respectively. These q_1^* s for humans were also adjusted with the scaling factor of 2/3 and the rat lifespan of two years. The average rat body weight was assumed to be 0.4 kg.

The study by Chouroulinkov *et al.* (1967) was selected for slope calculation because it is a long-term study. U.S. EPA (1991a, b) calculated a q_1^* of $6.5 \text{ (mg/kg-day)}^{-1}$ for humans with a scaling factor of 2/3 and a less-than-lifetime adjustment of $(24 \text{ month}/14 \text{ month})^3$. This calculation was based on the result of one dose, and was extrapolated linearly from the observed response of 6.2% at 0.63 mg/kg-day to the background of zero.

U.S. EPA's (1992b) approach to estimating cancer risk for drinking water contaminants (i.e., weight-of-evidence determination and nonthreshold, low-dose extrapolation), is considered to be the most prudent approach that is protective of human health. We also consider BaP-induced carcinogenesis a nonthreshold phenomenon and, as such, applies a nonthreshold, linear

extrapolation model for cancer potency estimation (OEHHA, 1994). Cancer risk associated with exposure to ambient levels of BaP is estimated by extrapolating approximately five orders of magnitude from the experimental data to ambient levels by means of the best fitting LMS model GLOBAL 86 (Howe and van Landingham, 1986), TOX_RISK version 3.5 (Crump *et al.*, 1993) and MSTAGE version 1.1 (Crouch, 1985). Using the computer software programs, the multistage model was fit to the dose-response data from the study of gastric tumors in mice (Neal and Rigdon, 1967) given in Table 5 which is considered as the most relevant data set for estimating the carcinogenic potencies for BaP exposed through ingestion.

For the mouse data, to obtain a statistically acceptable fit of the model to the data, the numbers in the highest three dosage groups (Table 5) were not used (U.S. EPA, 1980; 1984; 1991b; OEHHA, 1994). It is important to note that not all of the data points are used and the data which are not used show a very high tumor incidence (Table 5). The strong carcinogenic response at the high-doses adds to the weight-of-evidence for the carcinogenicity of BaP. However, with this change the p value for goodness of fit for the multistage model is an acceptable 0.37 for GLOBAL 86 and TOX_RISK version 3.5 and 0.51 for MSTAGE version 1.1. Detailed results of the calculations are reported in Table 6. This data set had high variance when it was fitted by an exact two-stage regression model which might be due to the promoter characteristic of BaP (Cox, 1995).

As shown in Table 6, using GLOBAL 86 and MSTAGE version 1.1, the mouse gastric tumor data listed in Table 5 yielded a maximum likelihood estimate (MLE) for q_1 (the linear or slope term, which relates the probability of cancer to the dose of carcinogen administered) of $0.00599 \text{ (mg/kg-day)}^{-1}$ and a q_0 equal to zero. An upper 95% confidence limit on q_1 , q_1^* , equal to $0.02221 \text{ (mg/kg-day)}^{-1}$, also known as the carcinogenic potency, was obtained from the data. The values for q presented here are the same values U.S. EPA (1984) obtained using the same data and methodology.

Two numerical adjustments must be made to convert the q_1^* calculated from the animal data to a q_1^* relevant to humans. First, the experimental less-than-lifetime exposure period (L_e), which was 183 days for the Neal and Rigdon (1967) mouse bioassay, was adjusted to an equivalent lifetime exposure (L), estimated to be 2 years or 730 days for mice, by dividing L_e by L . This term was then raised to the third power, based on the assumption that cancer incidence increases with the third power of age. That is, $(L/L_e)^3$ or $(730 \text{ days}/183 \text{ days})^3$ for mice. Second, cross-species scaling carcinogen doses by the $3/4$ power of body weight proposed by the U.S. EPA (1992a), instead of the previous $2/3$ (OEHHA, 1994), was adopted. A surface area scaling factor, the human to animal body weight ratio raised to the $1/4$ power, was then applied to relate the experimental animal doses to equivalent human doses (U.S. EPA, 1996a, b) instead of the $1/3$ power used in our previous calculations (OEHHA, 1993; 1994). That is, $(\text{human body weight}/\text{animal body weight})^{1/4}$, or $(70 \text{ kg}/0.034 \text{ kg})^{1/4}$ for mice. Therefore:

$$q_1^* \text{ (human)} = q_1^* \text{ (animal)} \times (L/L_e)^3 \times (\text{human bw}/\text{animal bw})^{1/4}$$

$$q_1^* \text{ (human)} = 0.02221 \times (730/183)^3 \times (70/0.034)^{1/4} = 9.5 \text{ (mg/kg-day)}^{-1}$$

If a life-span for mice as estimated by U.S. EPA (1984) to be equal to 630 days was used, q_1^* (human) would be $6.1 \text{ (mg/kg-day)}^{-1}$ as shown in Table 6.

Table 5. Gastric Tumors in Mice from Feeding Benzo(a)pyrene^a

Exposure (ppm or mg/kg food)	Calculated Daily Dose ^b (mg/kg-day) (animal)	Incidence of Gastric Tumors ^{c,d}
0	0	0/289
1	0.078	0/25
10	0.781	0/24
20	1.563	1/23
30	2.344	0/37
40	3.126	1/40
45 ^b	3.516 ^b	4/40
50 ^e	3.908	24/34 ^e
100 ^e	7.815	19/23 ^e
250 ^e	19.538	66/73 ^e

^a Adopted from Collins *et al.* (1991), Cal/EPA (1994), U.S. EPA (1980) and Neal and Rigdon (1967).

^b Calculation is based on a 0.034 kg mouse consuming 13% of its body weight in food daily for 110 days during a 183-day experiment, i.e., 3.516 mg/kg-day = 45 mg/kg food x (0.034 kg x 13% food/day) x (110 days/183 days) x (1/0.034 kg)

^c Number responding with gastric papillomas or carcinomas over number exposed to given food concentration.

^d A Chi-square (χ^2) test yields $p < 0.001$ which indicates a significant association between the incidence of gastric tumors and the dose of BaP.

^e Use of these exposure concentrations does not result in a statistically acceptable fit of the GLOBAL 86, TOX_RISK version 3 and MSTAGE version 1.1 multistage model to the data set.

The estimates of CSF are based on the 95% lower confidence limit on the dose that gives a 10% excess theoretical individual lifetime risk of cancer (LED₁₀) and (body weight)^{3/4} scaling. For determination of the LED₁₀, a goodness of fit criterion of $p > 0.05$ was adopted for the Chi-squared test, whereas $p > 0.01$ is usually considered sufficient for the LMS. Then the CSF was derived by dividing 10% (or 0.1) by the LED₁₀. In TOX_RISK version 3.5, the cross-species scaling factor of 3/4 is built into the program and there is no need for further correction. A q₁* human potency estimate was derived as 9.77 (mg/kg-day)⁻¹ for 730 days and 5.51 (mg/kg-day)⁻¹ for 630 days, and a CSF for human was 12.6 (mg/kg-day)⁻¹ for 730 days and 7.14 (mg/kg-day)⁻¹ for 630 days as shown in Table 6.

The q₁* values of 6.1 (mg/kg-day)⁻¹, 5.51 (mg/kg-day)⁻¹, 9.5 (mg/kg-day)⁻¹ and 9.77 (mg/kg-day)⁻¹ obtained using the Neal and Rigdon (1967) data are consistent with other estimates for BaP carcinogenicity (OEHHA, 1994). In an unpublished study, Zeise and Crouch (1984) examined all existing multiple dose data sets (principally mice) induced by feeding, by gavage and through the drinking water, including the Neal and Rigdon (1967) data. Many data sets of BaP carcinogenicity in rodents were faulty due to lack of controls or lack of explicit information on the conduct of the experiment in the paper. Multistage models were fit to the data sets. Most animal cancer potency value estimates, expressed as coefficients of dose to the first power, were in the range of 0.2 to 1.3

(mg/kg-day)⁻¹. Multiplying these doses by a mouse to man surface area correction factor of (70 kg/0.034 kg)^{1/4} = 6.73604 yielded a range of human potency estimates of 1.3 to 8.8 (mg/kg-day)⁻¹.

Table 6. Cancer Potencies for BaP Based on Mouse Gastric Tumors^a

Program	L (days)	q ₁ * (mg/kg-day) ⁻¹	χ ²	p	k	MLE ₁₀ (mg/kg-day)	LED ₁₀ (mg/kg-day)	CSF (mg/kg-day) ⁻¹
GLOBAL 86		0.02221 mouse	4.2658	0.37	6	3.7200 mouse	4.7431 mouse	0.02108 mouse
	630	6.10 human				0.01354 human	0.01726 human	5.80 human
	730	9.50 human				0.00870 human	0.01108 human	9.03 human
TOX_ RISK v.3	630	5.51 human	4.27	0.37	6	0.01608 human	0.01406 human	7.14 human
	730	9.77 human	4.27	0.37	6	0.00906 human	0.00793 human	12.6 human
MSTAGE v.1.1		0.02221 mouse	4.266	0.51	6	N/A	N/A	N/A
	630	6.10 human						
	730	9.50 human						

^a MLE is the maximum likelihood estimate for q₁ which is the linear or slope term, which relates the probability of cancer to the dose of carcinogen administered. An upper 95% confidence limit on q₁ is q₁*, also known as the carcinogenic potency. Another estimate of the carcinogenic potency is the cancer slope factor (CSF) which is the 95% lower confidence limit on the dose that gives a 10% extra lifetime risk of cancer. The LED₁₀ is the 10% tumor dose. CSF is derived by dividing 10% or 0.1 by LED₁₀.

For exposures to BaP by the ingestion route, the q₁*s and CSFs (Table 6) of 9.5 and 9.03 (mg/kg-day)⁻¹ (GLOBAL 86), 9.77 and 12.6 (mg/kg-day)⁻¹ (TOX_RISK v.3.5) and 9.5 (mg/kg-day)⁻¹ (MSTAGE v.1.1, not applicable for CSF) based on gastric tract tumors in mice (Table 5) can be considered. Provided all three programs do in fact converge successfully there should be no difference in the results obtained. The relatively high chi-square values indicate that none of the three programs has a good fit. In addition, the q₁*s from GLOBAL 86 and MSTAGE v.1.1 are almost identical. Considering all factors, the q₁* of 9.5 (mg/kg-day)⁻¹ and the CSF of 9.03 (mg/kg-day)⁻¹ were selected for the PHG calculations.

U.S. EPA's MCL

As a part of Phase V of primary drinking water regulations mandated by the 1986 Amendment of the Safe Drinking Water Act (SDWA), U.S. EPA (1990) proposed the enforceable MCL and the

non-enforceable Maximum Contaminant Level Goal (MCLG) for 15 PAHs in 1990; several alternative approaches were presented for discussion. These 15 PAHs are part of the priority pollutants listed under the 1986 SDWA Amendment (40 CFR, Part 136, Appendix A, as cited in U.S. EPA, 1992b) based on their occurrence and human exposure. Among them, seven of the PAHs are classified as Group B2, probable human carcinogens, and the other eight are classified as Group D, not classifiable as to human carcinogenicity, by U.S. EPA. Only BaP, one of the seven Group B2 carcinogens of the 15 PAHs, has sufficient data available to make a quantitative estimate of cancer potency. In responding to public comments, U.S. EPA (1992b) later decided to only regulate BaP (due to its strong evidence of carcinogenicity via ingestion) in the final rule of National Primary Drinking Water Regulations (NPDWR) and to promulgate an MCLG of zero and an MCL of 0.2 ppb (200 ppt). The California Department of Health Services (DHS) adopted the same MCL for BaP of 0.2 ppb in 1994. The State of Arizona has established a drinking water guideline for BaP of 3 ppt (HSDB, 1997).

The MCL of 0.2 ppb was the practical quantitation level (PQL) based on U.S. EPA approved analytical chemistry detection methodology and monitoring requirement (U.S. EPA 1992b; 1997). This 0.2 ppb was considered to be associated with a theoretical maximum lifetime excess individual cancer risk of 10^{-4} which was calculated to be 0.5 ppb using an oral q_1^* of $7.3 \text{ (mg/kg-day)}^{-1}$ (U.S. EPA, 1980; 1984; 1985; 1991a). The q_1^* of $7.3 \text{ (mg/kg-day)}^{-1}$ was published on September 1, 1992, on the Integrated Risk Information System (IRIS) database (U.S. EPA, 1997a). IRIS (U.S. EPA, 1997a) made a revision on November 1, 1994, based on further dose-response analysis of ingested BaP (U.S. EPA, 1991b) in several studies to include a range of q_1^* s from 4.5 to $11.7 \text{ (mg/kg-day)}^{-1}$, with a geometric mean of $7.3 \text{ (mg/kg-day)}^{-1}$, corresponding to 10^{-4} cancer risk levels of 0.3 to 0.8 ppb, or 10^{-5} cancer risk levels of 0.03 to 0.08 ppb, or 10^{-6} cancer risk levels of 0.003 to 0.008 ppb (3 to 8 ppt), with a corresponding mean of 10^{-6} cancer risk level of 5 ppt. OEHHA (1993) evaluated U.S. EPA's (1992b) MCL and MCLG, and proposed a health-based standard of $2 \times 10^{-6} \text{ mg/L}$ (or 2 ppt) in drinking water corresponding to a 10^{-6} theoretical excess individual cancer risk with an oral q_1^* of $12 \text{ (mg/kg-day)}^{-1}$ which was rounded from $11.5 \text{ (mg/kg-day)}^{-1}$ (Collins *et al.*, 1991; U.S. EPA, 1980; OEHHA, 1994) based on the Neal and Rigdon (1967) study of gastric tumors in mice.

CALCULATION OF PHG

Calculations of concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or noncarcinogens must take into account the toxicity of the chemical itself, as well as the potential exposure of individuals using the water. Tap water is used directly as drinking water, for preparing foods and beverages. It is also used and for bathing or showering, and in washing, flushing toilets and other household uses resulting in potential dermal and inhalation exposures.

Noncarcinogenic Effects

The data are limited for noncarcinogenic health effects of BaP in animals and there are no data in humans. Such scarcity of data constitutes a data gap for BaP. Data for many toxicologic endpoints are needed. The various health effects in all tested species, duration of exposure, and the highest NOAELs and LOAELs are summarized in Table 3. However, the currently available data are insufficient to evaluate NOAELs and LOAELs to derive the most sensitive acute, intermediate or chronic duration MRLs for noncarcinogenic adverse effects through inhalation or oral or dermal

exposure to BaP (ATSDR, 1995). Therefore, no health-protective concentration was calculated based on noncarcinogenic endpoints for BaP.

Carcinogenic Effects

For carcinogens, the following general equation can be used to calculate the health-protective concentration (C) for BaP in drinking water (in mg/L):

$$C = \frac{BW \times R}{q_1^* \text{ or CSF} \times L/\text{day}} = \text{mg/L}$$

where,

- BW = Adult body weight (a default of 70 kg)
- R = *De minimis* level for lifetime excess individual cancer risk (a default of 10^{-6})
- q_1^* or CSF = Cancer slope factor, q_1^* is the upper 95% confidence limit on the cancer potency slope calculated by the LMS model, and CSF is a potency derived from the lower 95% confidence limit on the 10% tumor dose (LED₁₀). CSF = 10% / LED₁₀. Both potency estimates are converted to human equivalent [in (mg/kg-day)⁻¹] using BW^{3/4} scaling.
- L/day = Daily volume of water consumed by an adult (a default of 2 L/day).

The purpose of calculating two potency estimates for a carcinogen is based on the fact that our current experience-base is almost wholly with the LMS model whereas the new methodology, proposed by U.S. EPA (1996b) in its proposed guidelines for carcinogen risk assessment, is based on the LED₁₀ which has little or no experience-base and may present problems. The LMS model focuses on the linear low dose extrapolation and analysts (e.g., U.S. EPA) have often accepted relatively poor fits to the observed tumor incidence data. The new method places a higher premium on fitting the observed data to estimate the ED₁₀ and the 95% lower bound (LED₁₀), the point from which the low dose extrapolation is made (U.S. EPA, 1996a).

The q_1^* of 9.5 (mg/kg-day)⁻¹ and the CSF of 9.03 (mg/kg-day)⁻¹ are selected for the calculations of public health-protective concentrations. As detailed in the calculations shown below, using the q_1^* for human of 9.5 (mg/kg-day)⁻¹ from GLOBAL 86 or MSTAGE v.1.1, C (in mg/L) would be:

$$C = \frac{70 \text{ kg} \times 10^{-6}}{9.5 \text{ (mg/kg-day)}^{-1} \times 2 \text{ L/day}} = 3.68 \times 10^{-6} \text{ mg/L}$$

$$= 4 \times 10^{-6} \text{ mg/L (rounded)} = 4 \text{ ppt.}$$

Using the CSF of 9.03 (mg/kg-day)⁻¹ from GLOBAL 86, C (in mg/L) would be:

$$C = \frac{70 \text{ kg} \times 10^{-6}}{9.03 \text{ (mg/kg-day)}^{-1} \times 2 \text{ L/day}} = 3.88 \times 10^{-6} \text{ mg/L}$$

$$= 4 \times 10^{-6} \text{ mg/L (rounded)} = 4 \text{ ppt.}$$

Therefore, a rounded value of 4 ppt was selected to be the PHG for BaP in drinking water. The value was selected since it was derived from the majority of the human q_1^* s and CSFs. These q_1^*

and CSF values obtained using the Neal and Rigdon (1967) data are consistent with other estimates for BaP carcinogenicity induced by feeding, by gavage and through the drinking water (Zeise and Crouch, 1984; OEHHA, 1994).

RISK CHARACTERIZATION

For BaP, U.S. EPA (1980; 1984; 1985) first developed an oral q_1^* of $11.5 \text{ (mg/kg-day)}^{-1}$ based on the Neal and Rigdon (1967) study of gastric tumors in mice using the LMS model. After further analysis of data from other studies, a geometric mean oral q_1^* of $7.3 \text{ (mg/kg-day)}^{-1}$ was calculated (U.S. EPA, 1984; 1985; 1991a). In 1992, IRIS adopted this mean q_1^* and 5 ppt was the calculated water concentration associated with a maximum excess individual lifetime cancer risk of 10^{-6} . IRIS (U.S. EPA, 1997a) made a revision in 1994, based on further dose-response analysis of ingested BaP (U.S. EPA, 1991b) to include a range of q_1^* s of 4.5 to $11.7 \text{ (mg/kg-day)}^{-1}$ corresponding to 10^{-6} risk levels of 3 to 8 ppt. These human q_1^* s were adjusted with the scaling factor of $2/3$ instead of the recently proposed $3/4$ power of body weight (U.S. EPA, 1992a), and the life-span of mice was estimated as 630 days (U.S. EPA, 1984) instead of the 730 days discussed in Cal/EPA (1994).

OEHHA (1993) calculates a health-based standard of 2 ppt corresponding to a 10^{-6} risk with an oral q_1^* of $12 \text{ (mg/kg-day)}^{-1}$ which was rounded from $11.5 \text{ (mg/kg-day)}^{-1}$ using the same data set (Neal and Rigdon, 1967) with GLOBAL 86, a scaling factor of $2/3$ and a mouse lifespan of 630 days (Collins *et al.*, 1991; OEHHA, 1994).

Our calculation of a PHG for BaP uses the same data set of gastric tumors in mice (Neal and Rigdon, 1967) and compares the three best available programs for multistage model fitting with a scaling factor of $3/4$ and a mouse lifespan of 730 days to derive oral q_1^* of 9.5 and CSF of 9.03 (mg/kg-day)^{-1} . The corresponding 10^{-6} lifetime risk level is approximately 4 ppt.

For PHGs, our use of the relative source contribution (RSC) has, with a few exceptions, followed U.S. EPA drinking water risk assessment methodology. U.S. EPA has treated carcinogens differently from noncarcinogens with respect to the use of RSCs. For noncarcinogens, RfDs (in mg/kg-day), drinking water equivalent levels (DWELs, in mg/L) and MCLGs (in mg/L) are calculated using UFs, body weights and water consumption rates (L/day) and the RSC, respectively. The RSC range is 20% to 80% (0.2 to 0.8) depending on the availability of scientific data.

U.S. EPA follows a general procedure in promulgating MCLGs:

1. if Group A and B carcinogens (i.e., strong evidence of carcinogenicity) MCLGs are set to zero,
2. if Group C (i.e., limited evidence of carcinogenicity), either an RfD approach is used (as with a noncarcinogen) but an additional UF of 1 to 10 (usually 10) is applied to account for the limited evidence of carcinogenicity, or a quantitative method (potency and low-dose extrapolation) is used and the MCLG is set in the 10^{-5} to 10^{-6} cancer risk range,
3. if Group D (i.e., inadequate or no animal evidence) an RfD approach is used to promulgate the MCLG.

For approaches that use low-dose extrapolation based on quantitative risk assessment, U.S. EPA does not factor in an RSC. The use of low-dose extrapolation is considered by U.S. EPA to be adequately health-protective without the additional source contributions. In developing PHGs, we have adopted the assumption that RSCs should not be factored in for carcinogens grouped in U.S. EPA categories A and B and for C carcinogens for which we have calculated a cancer potency based on low-dose extrapolation. This is an area of uncertainty and scientific debate and it is not clear how this assumption impacts the overall health risk assessment.

The PHG of 4 ppt is consistent with the drinking water concentration associated with a negligible theoretical excess individual cancer risk value of one case per one million exposed persons (10^{-6}). This risk value is assumed to be *de minimis* by federal and state regulatory agencies as acceptable for involuntary exposure to environmental contaminants. The PHG value of 4 ppt is also considered to contain an adequate margin of safety for noncarcinogenic adverse effects including the potential adverse effects on the skin, the hematological, gastrointestinal, immunological and reproductive and developmental systems. The corresponding concentrations at cancer risk levels of 10^{-5} and 10^{-4} would be 40 and 400 ppt, respectively.

OTHER REGULATORY STANDARDS

BaP has been classified as a Group B2 probable human carcinogen by the U.S. EPA. The International Agency for Research on Cancer (IARC) has classified BaP as a Group 2A carcinogen, probably carcinogenic to humans. In toxicology laboratory testing, BaP has been used as a positive control for mutagenicity and carcinogenicity and usually is administered at a single dose level which makes the quantitation of cancer risk difficult. The United States Department of Health and Human Services (DHHS) has also determined that BaP is a known animal carcinogen. Under DHHS, ATSDR has prepared toxicological profiles for BaP (ATSDR, 1990a) and PAHs (ATSDR, 1990b; 1995) under the Comprehensive Environmental Response, Compensation and Liability Act of 1980 (CERCLA) since BaP is one of the 54 PAHs which have been identified in at least 600 of the National Priorities List hazardous waste sites. The World Health Organization (WHO) has published drinking water guidelines for BaP of 7, 0.7 and 0.07 ppb (or 70 ppt) corresponding to theoretical excess lifetime individual cancer risks of 10^{-4} , 10^{-5} and 10^{-6} , respectively, for stomach tumors (WHO, 1996) based on the Neal and Rigdon (1967) feeding study in mice. The risk quantification estimate was prepared by Clement Associates (1990) for the U.S. EPA (1991b).

In addition to the drinking water standards, U.S. EPA has provided estimates of levels of total cancer-causing PAHs including BaP in lakes and streams associated with a risk of human cancer development (U.S. EPA, 1980; ATSDR, 1995). U.S. EPA must be notified within a 24-hour period of time if one pound or more BaP is released to the environment. BaP levels in various kinds of food also have been regulated or monitored worldwide. The Netherlands National Institute of Public Health and the Environment has developed maximum permissible concentrations for BaP of 0.05 ppb (0.05 $\mu\text{g/L}$ or 50 ppt) in water, 0.26 mg/kg in soil and 2.7 mg/kg in sediment as Environmental Quality Objectives (Kalf *et al.*, 1997).

For a work environment involving exposure to BaP, the U.S. National Institute for Occupational Safety and Health (NIOSH) has established a recommended occupational exposure limit of time-weighted average (REL-TWA) for coal tar products of 0.1 mg of PAHs per cubic meter of air (0.1 mg/m^3) for a 10-hour work day within a 40-hour work week due to the risks of lung and skin cancer in workers. The American Conference of Governmental Industrial Hygienists (ACGIH)

has, since 1991, recommended an occupational exposure limit for coal tar products of 0.2 mg/m³ for an eight-hour work day within a 40-hour work week. In 1993, the Occupational Safety and Health Administration (OSHA) established a legally enforceable limit of 0.2 mg/m³ averaged over an eight-hour exposure period. The OSHA Permissible Exposure Limit (PEL) for mineral oil mist, which has an IARC classification of 1 for sufficient evidence of carcinogenicity in human, has been 5 mg/m³ averaged over an eight-hour exposure period. NIOSH has established an REL-TWA for mineral oil mist of 5 mg/m³ for a 10-hour work day, 40-hour work week, with a 10 mg/m³ short-term exposure limit (STEL) (ATSDR, 1995).

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