

US EPA ARCHIVE DOCUMENT

Benzene

TEACH Chemical Summary



U.S. EPA, Toxicity and Exposure Assessments for Children's Health

This TEACH Chemical Summary is a compilation of information derived primarily from U.S. EPA and ATSDR resources, and the TEACH Database. The TEACH Database contains summaries of research studies pertaining to developmental exposure and/or health effects for each chemical or chemical group. TEACH does not perform any evaluation of the validity or quality of these research studies. Research studies that are specific for adults are not included in the TEACH Database, and typically are not described in the TEACH Chemical Summary.

I. INTRODUCTION

Benzene is an organic compound found most often in air as a result of emissions from burning coal and oil, gasoline vapors at gasoline service stations, motor vehicle exhaust, cigarette smoke, wood-burning fires, some adhesives, and other sources (1, 2). Benzene is a clear, colorless, flammable liquid with a gasoline-like odor that can volatilize to vapors in air (2). Currently in the U.S. there are significant concentrations of benzene in ambient air, due in large part to vehicle emissions (1, 2). Benzene concentrations in indoor air are also significant contributors to children's exposures, particularly in homes where people smoke (1-8).

Benzene is classified as a known carcinogen based on occupational studies in adults that demonstrated increased incidence of several types of leukemia in exposed adults (1, 2, 9). Benzene has also been shown to be genotoxic (cause damage to DNA) in experimental animal studies (1, 2, 9). The primary targets of benzene exposure in humans are the hematopoietic (blood cell-forming) system and the immune system (1, 2). Health effects of benzene exposure have been studied less extensively in children than in adults, but evidence suggests benzene may have similar health effects in children (see below).

Some studies of benzene exposure of general human populations have studied exposures to benzene as a component of mixtures of chemicals, for example, gasoline vapors or vehicle exhaust; such exposures have made it difficult to ascribe health effects to benzene exposure alone from those studies. Detailed discussion and analysis of confounding variables in these studies is available in other resources, including the cited research articles themselves and other documents (1, 2).

Pregnant women and children are most likely to be exposed to benzene in indoor air (with higher levels in homes of smokers), in outdoor air, and in drinking water (1-8, 10, 11).

Supporting references and summaries are provided in the TEACH Database at: <http://www.epa.gov/teach/>

Last revised 2/27/2009: includes research articles and other information through 2006.

II. EXPOSURE MEDIA AND POTENTIAL FOR CHILDREN'S EXPOSURE¹

Exposure Media	Relative Potential for Children's Exposure ^{2,3}	Basis ⁴
Indoor Air	Higher	Benzene is a common indoor air pollutant. Sources include cigarette smoke; exhaust from motor vehicles; smoke from wood burning fires; and some household products which contain petroleum-based chemicals such as glues, paints, furniture wax, and lubricants. In homes/dwellings located above contaminated groundwater, benzene vapor is capable of migrating through soil and foundations to enter basements or living spaces and contribute to indoor air concentrations. Benzene could also volatilize to indoor air from contaminated groundwater due to indoor water uses (e.g., showering, dishwashing, laundry).
Ambient Air	Medium	Benzene is a common ambient air pollutant. Outdoor air contamination sources include exhaust from motor vehicles, and emissions from industrial processes and motor vehicle service stations.
Groundwater	Medium	Groundwater contamination can occur from leaking underground storage tanks and from hazardous waste sites where benzene is often present as a component of gasoline and petroleum products.
Drinking Water	Medium	Drinking water contamination with benzene can occur, particularly when groundwater is contaminated with benzene.
Soil	Lower	Benzene is a volatile compound that does not undergo significant partitioning or accumulation in soils. Low concentrations of benzene in surface soils may be detectable at locations where accidental spills of gasoline or petroleum have occurred.
Diet	Lower	Benzene is not typically found in food; FDA restricts use in food packaging.
Sediment	Lower	Benzene is a volatile compound that does not undergo significant partitioning or accumulation in sediments.

¹ For more information about child-specific exposure factors, please refer to the Child-Specific Exposure Factors Handbook (<http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=55145>).

² The Relative Potential for Children's Exposure category reflects a judgment by the TEACH Workgroup, U.S. EPA, that incorporates potential exposure pathways, frequency of exposure, level of exposure, and current state of knowledge. Site-specific conditions may vary and influence the relative potential for exposure. For more information on how these determinations were made, go to http://www.epa.gov/teach/teachprotocols_chemsumm.html.

³ Childhood represents a lifestage rather than a subpopulation, the distinction being that a subpopulation refers to a portion of the population, whereas a lifestage is inclusive of the entire population.

⁴ Information described in this column was derived from several resources (e.g., 1, 2) including studies listed in the TEACH Database (<http://www.epa.gov/teach>).

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III. TOXICITY SUMMARY^{5,6}

Benzene exposure has been shown to affect blood-forming (hematopoietic) cells in adults (1, 2). In developmental experimental animal studies, prenatal exposure to benzene resulted in fetal effects including reduced weight gain, skeletal malformations, and increased incidence of miscarriage (12-17); and persistent decreases in the numbers of blood-forming cells (18, 19). Benzene exposure has also been associated with respiratory difficulties in children including bronchitis, asthma, and wheezing (20-24).

A possible association between developmental exposure to benzene and cancer in children remains equivocal (25-34). Epidemiologic studies of adults show clear evidence of causal association between benzene exposure and certain leukemias (9, 35). The noncancer endpoint (decreased lymphocyte count) used to derive the U.S. EPA RfD and RfC reference values (see below) was based on benzene effects on hematopoietic cells (35). Many factors could increase potential risks of exposure to benzene during childhood. These include activity patterns resulting in greater exposure or delivered dose than adults; key processes such as breathing rates and metabolism that could increase the amount of absorbed benzene; and/or key biochemical processes in the body that increase sensitivity of children (e.g. chemical/target interactions in the immature hematopoietic or blood cell-forming system). However, specific data to make quantitative adjustments for these factors are not currently available (9).

Acute exposure to benzene can result in skin and eye irritation or burning, as well as dizziness, nausea, vomiting, and suffocation (2).

Carcinogenicity weight-of-evidence classification⁷: The U.S. EPA classified benzene as a known human carcinogen: “Epidemiologic studies and case studies provide clear evidence of a causal association between exposure to benzene and acute nonlymphocytic leukemia (ANLL) and also suggest evidence for chronic nonlymphocytic leukemia (CNLL) and chronic lymphocytic leukemia (CLL). Other neoplastic conditions that are associated with an increased risk in humans are hematologic neoplasms, blood disorders such as preleukemia and aplastic anemia, Hodgkin's lymphoma, and myelodysplastic syndrome (MDS). These human data are supported by animal studies. The experimental animal data add to the argument that exposure to benzene increases the risk of cancer in multiple species at multiple organ sites (hematopoietic, oral and nasal, liver, forestomach, preputial gland, lung, ovary, and mammary gland). It is likely that these responses are due to interactions of the metabolites of benzene with DNA” (<http://www.epa.gov/iris/subst/0276.htm>, II.A.1; last Agency Consensus Date, 2000) (35). In 1998, the World Health Organization International Agency for Research on Cancer (IARC) classified benzene as a known (Group 1) human carcinogen based on sufficient evidence that benzene is carcinogenic to humans, and limited evidence that benzene is carcinogenic in experimental animals (<http://monographs.iarc.fr/ENG/Monographs/vol29/volume29.pdf>) (36).

⁵ Please refer to research article summaries listed in the TEACH Database for details about study design considerations (e.g., dose, sample size, exposure measurements).

⁶ This toxicity summary is likely to include information from workplace or other studies of mature (adult) humans or experimental animals if child-specific information is lacking for the chemical of interest. Summaries of articles focusing solely on adults are not listed in the TEACH Database because the TEACH Database contains summaries of articles pertaining to developing organisms.

⁷ For recent information pertaining to carcinogen risk assessment during development, consult Guidelines for Carcinogen Risk Assessment and Supplemental Guidance on Risks from Early Life Exposure at <http://www.epa.gov/cancerguidelines>.

Supporting references and summaries are provided in the TEACH Database at <http://www.epa.gov/teach/>.

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IV. EXPOSURE AND TOXICITY STUDIES FROM THE TEACH DATABASE

This section provides a brief description of human and animal studies listed in the TEACH Database. For more details about study design parameters, e.g., doses and exposure information, please refer to article summaries in the TEACH Database. Any consideration should include an understanding that exposure levels in animal studies, in many cases, are greater than exposure levels normally encountered by humans.

A. HUMAN EXPOSURE AND EFFECTS

- ▶ Two studies are available that measured prenatal or early life exposure to benzene. One study measured concentrations of benzene in cord blood in humans as an estimate of placental transfer of benzene; benzene was detected in fetal cord blood at levels equal to or greater than those levels found in maternal blood (37). Benzene was also detected in breast milk (38).
- ▶ Concentrations of benzene in ambient, indoor, and personal air samples for children have been measured in several studies (4-8). Benzene concentrations were significantly higher in homes with smokers than homes with nonsmokers (4, 6), and higher in homes with attached garages than in homes without attached garages (8). When indoor air concentrations and time spent indoors were considered, indoor air was found to be a significant source of benzene exposure for children (4-6).
- ▶ Concentrations of two chemicals in urine have been explored as biomarkers of children's exposure to benzene. Increased levels of the benzene metabolite trans,trans-muconic acid (t,t-MA) in urine of children 11-14 years of age correlated with proximity of their homes to high traffic areas and not to cigarette smoke exposure (39). However, this metabolite is considered a non-specific biomarker because it can be generated after exposure to other chemicals in addition to benzene, and correlation of this biomarker with benzene exposure remains problematic (40). Urine concentrations of t,t-MA were also measured for children in other studies (41-45). Another biomarker, s-phenylmercapturic acid (PMA) in urine is widely accepted as a biomarker in adults, but this biomarker has not been studied extensively in children. In two studies (46), PMA was measured in urine of infants or children as a control for an occupational exposure study; concentrations of PMA in these infants and children was lower than adults in the same study.
- ▶ Studies on effects of prenatal benzene exposure on pregnancy and birth weight have shown varying results. One study showed no increase in miscarriage for women exposed to benzene (47), while two other studies showed effects including increased rate of miscarriage and decreased birth weight (48, 49). Paternal exposure to benzene did not affect miscarriage incidence (41). Another study suggested an interaction between genetic variations and benzene exposure in causing increased incidence of premature births (42).
- ▶ Parental or prenatal maternal exposure to benzene has been associated with hematologic cancer in their children in some studies and not others. Two studies have shown a significantly increased risk of childhood leukemia associated with paternal exposure to benzene (31, 32), while another showed no such association (33). A case control interview study showed that acute nonlymphocytic leukemia was significantly associated with maternal occupational exposure to benzene during pregnancy (34).

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- ▶ Evidence for an association between childhood exposure to benzene and the incidence of childhood cancer remains equivocal (25-30). A study of over 5,000 Danish children found that the risk of Hodgkin's lymphoma in young children was associated with concentrations of benzene in high traffic areas during pregnancy or early childhood (26). This study found no significant associations between benzene exposure of children and the incidence of leukemia and other types of lymphomas (26). Other studies reported an association between benzene exposure from proximal high traffic density or other sources of benzene and childhood cancer, including leukemia (25, 27, 28, 30). However, another study reported no association between childhood cancer rates and benzene concentrations in high traffic neighborhoods (29).
- ▶ Hematologic changes in children were associated with air concentrations of benzene in one study. Korean children who lived near a petrochemical plant had significant increases and decreases in a number of different types of circulating blood cells as compared to controls, where air benzene levels were 6-15 times higher for the exposed group than the control group (50). However, in another study, measures of immunological parameters in blood of children (total serum IgG and concentrations of antibodies to specific pathogens) were not significantly associated with benzene concentrations in air (51).
- ▶ Benzene exposure has also been associated with respiratory difficulties in children, including increased occurrence of wheezing (20, 21), and increased incidence of obstructive bronchitis (22) and asthma (21, 23, 24, 52).

B. EXPERIMENTAL ANIMAL EXPOSURE AND EFFECTS

- ▶ Benzene was shown to cross the placenta in mice following maternal inhalation exposure, but benzene was not retained in the fetus and placenta (53).
- ▶ Genotoxicity results for prenatal exposure are more equivocal than results for adult exposure. Prenatal exposure of mice to benzene was found to cause genotoxicity (damage to DNA) in some studies but not others. Specifically, benzene exposure via injection of pregnant dams resulted in a significant increase in micronuclei (small nuclei often indicative of chromosomal damage) and sister chromatid exchange in both maternal bone marrow and fetal liver cells at higher doses of benzene (54, 55). However, in another study of prenatal exposure to benzene via maternal gavage, genotoxic activity of benzene or its metabolites was absent in pregnant dam bone marrow cells, but present in fetal liver cells (56). A third study found little or no micronuclei formation in maternal or fetal cells following prenatal benzene exposure by maternal gavage or injection (57).
- ▶ Some studies in rats (12-16), mice (12, 17), and rabbits (12) have found toxic effects in fetuses following maternal inhalation exposure to benzene during pregnancy at doses that also caused reduced maternal weight gain, suggesting maternal toxicity (12-17). Toxic effects in fetuses included increased mortality (12, 13), decreased fetal weight or length (12-17), delayed bone ossification (hardening) (15, 16), and increased incidence of skeletal abnormalities in ribs, feet, or skull (12, 14-16). No fetal abnormalities (other than reduced weight) were observed in two of these studies (13, 17).

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- ▶ Neurological effects in offspring following maternal exposure to benzene during pregnancy were reported in one rat study (58). Significant decreases in exploratory activity and some avoidance behaviors were observed in adult offspring.
- ▶ Adverse effects on erythrocyte (red blood cell) development following prenatal exposure to benzene via maternal inhalation persisted into adulthood in three studies in mice. In one study, prenatal exposure to concentrations of benzene at the current occupational exposure limit resulted in decreased numbers of erythrocyte precursor cells as adults (19). In another study, prenatal exposure to benzene resulted in a reduced number of erythrocyte precursor cells in offspring at two days of age, and this effect persisted into adulthood (18). In a third study, adult male offspring who were exposed to benzene *in utero* had reduced numbers of erythrocyte precursors as compared to unexposed controls, whereas adult female offspring had increased numbers of erythrocyte precursors (59).
- ▶ Following neonatal and early life exposure to benzene via inhalation, significantly increased incidences of multiple types of cancers in liver, lung, skin, and other tissues were observed in mice and rats (60, 61).

V. CONSIDERATIONS FOR DECISION-MAKERS

This section contains information that may be useful to risk assessors, parents, caregivers, physicians, and other decision-makers who are interested in reducing the exposure and adverse health effects in children for this particular chemical. Information in this section focuses on ways to reduce exposure, assess possible exposure, and, for some chemicals, administer treatment.

- ▶ Detailed compilations and analyses of information pertaining to exposure and health effects of benzene are available in the Toxicological Review for Benzene (1) and the Toxicological Profile for Benzene (2). A Hazard Summary for Benzene is also available from the U.S. EPA which summarizes information primarily derived from these two sources (62). Contact information for these agencies is available in these documents. Contact information is also provided on the TEACH Web site.
- ▶ In view of the U.S. EPA Maximum Contaminant Level Goal (MCLG) of 0 for benzene (see Toxicity Summary and Reference Values in this Chemical Summary), caregivers may consider an alternate water supply, e.g. bottled water, where benzene-contaminated ground water may be impacting drinking water.
- ▶ The U.S. Centers for Disease Control provides a document called “Medical Management Guidelines for Benzene” for health care professionals (63).
- ▶ A large-scale, multi-city personal air sampling study of benzene and other chemicals was performed that included children ages 7 and older (10, 64). Environmental tobacco smoke contributed to benzene exposure, with indoor benzene levels 30-50% higher in smoking homes than nonsmoking homes (10).

Supporting references and summaries are provided in the TEACH Database at <http://www.epa.gov/teach/>.

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- ▶ Benzene was included in the chemicals assessed in the National Human Exposure Assessment Survey (NHEXAS) which analyzed samples of indoor air, outdoor air, and drinking water for benzene. Indoor benzene air concentrations exceeded outdoor air concentrations, while most drinking water samples had benzene concentrations below the analytical limit of detection (3, 11).
- ▶ The U.S. EPA used 1999 emissions data for all 50 states to report emissions, modeled ambient air concentration estimates, modeled human exposure, and estimated risk (65). Benzene was the only known carcinogen to meet criterion of a “national cancer risk driver,” meaning upper bound lifetime cancer risk exceeded 10 in a million to more than 10% of the U.S. population (66).
- ▶ Vehicle exhaust is well-established as a major source of benzene exposure in adults (1, 2, 8). Whether vehicle exhaust is a major source of benzene exposure in children is not well studied, though proximity to high traffic areas and the presence of attached garages at home are known to significantly increase exposure of children to benzene (4, 5, 7, 8). Children’s exposure to benzene via vehicle exhaust should therefore be considered when doing an exposure assessment.
- ▶ Benzene in contaminated groundwater can volatilize and contaminate indoor air (67, 68). Such volatilization is called vapor intrusion and should be considered in a benzene exposure assessment (68).
- ▶ Consult “Child-Specific Exposure Factors Handbook”, EPA-600-P-00-002B, for factors to assess children’s drinking water consumption and inhalation rates (69). An updated External Draft of the 2006 version of this handbook is available (70).

VI. TOXICITY REFERENCE VALUES

A. Oral/Ingestion

U.S. EPA Reference Dose (RfD) for Chronic Oral Exposure: 4E-3 (or 0.004) mg/kg/day (1.8E-3 or 0.0018 mg/lb/day), based on decreased lymphocyte count in adult humans (<http://www.epa.gov/iris/subst/0276.htm>, I.A.1) (35). Last agency consensus date 1/23/02.

U.S. EPA Cancer Oral Slope Factor: 1.5E-2 (or 0.015) to 5.5E-2 (or 0.055) per (mg/kg)/day [3.3E-2-12.1E-2 (or 0.033-0.012) per (mg/lb)/day], based on increased risk of leukemia in adults (<http://www.epa.gov/iris/subst/0276.htm>, II.B.1.1) (35). Last agency consensus date 1/3/00.

U.S. EPA Cancer Drinking Water Unit Risk: 4.4E-7 (or 0.00000044) to 1.6E-6 (or 0.0000016) per mg/L, derived by the extrapolation method using linear extrapolation of human adult occupational data (<http://www.epa.gov/iris/subst/0276.htm>, II.B.1.2) (35). Last agency consensus date 1/30/00.

U.S. EPA Drinking Water Concentrations at Specified Risk Levels for Cancer: 1E-4 (or 1 in 10,000), 10²-10³ µg/L; 1E-5 (or 1 in 100,000), 10¹-10² µg/L; 1E-6 (or 1 in 1,000,000), 10⁰-10¹ µg/L (<http://www.epa.gov/iris/subst/0276.htm>, II.B.1) (35). Last agency consensus date 1/3/00.

U.S. EPA Drinking Water Advisories (10 kg or 22 lb. child): 1 day = 0.2 mg/L, 10 day = 0.2 mg/L (<http://www.epa.gov/safewater/contaminants/index.html>) (71). Drinking Water Standards Edition 8/06.

U.S. EPA Maximum Contaminant Level (MCL) for Drinking Water: 0.005 mg/L, with potential health effects of anemia, decrease in blood platelets, and increased risk of cancer (<http://www.epa.gov/safewater/contaminants/index.html>) (71). Drinking Water Standards Edition 8/06.

U.S. EPA Maximum Contaminant Level Goal (MCLG): 0 mg/L (<http://www.epa.gov/safewater/contaminants/index.html>) (71). Drinking Water Standards Edition 8/06.

B. Inhalation

U.S. EPA Reference Concentration (RfC) for Chronic Inhalation Exposure: 3E-2 (or 0.03) mg/m³, based on decreased lymphocyte count in adult humans (<http://www.epa.gov/iris/subst/0276.htm>, I.B.1) (35). Last agency consensus date 1/23/02.

U.S. EPA Carcinogenic Risk from Inhalation Exposure Air Unit Risk: A range of 2.2E-6 (or 0.0000022) to 7.8E-6 (or 0.0000078) is the increase in the lifetime risk of an individual who is exposed for a lifetime to 1 µg/m³ benzene in air; derived using low-dose linearity extrapolation method utilizing maximum likelihood estimates (<http://www.epa.gov/iris/subst/0276.htm>, II.C.1) (35). Last agency consensus date 9/30/98.

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U.S. EPA Air Concentrations at Specified Risk Levels for Cancer: 1E-4 (or 1 in 10,000), 13.0-45.0 $\mu\text{g}/\text{m}^3$; 1E-5 (or 1 in 100,000), 1.3-4.5 $\mu\text{g}/\text{m}^3$; 1E-6 (or 1 in 1,000,000), 0.13-0.45 $\mu\text{g}/\text{m}^3$ (<http://www.epa.gov/iris/subst/0276.htm>, II.C.1) (35). Last agency consensus date 9/30/98.

U.S. ATSDR Minimal Risk Level (MRL): 0.009 ppm (acute inhalation); 0.004 ppm (intermediate inhalation); 0.003 ppm (chronic inhalation); all three values based on immunological effects. (<http://www.atsdr.cdc.gov/mrls/index.html>) (72). Draft values; last revised (agency cover date) 9/05.

VII. U.S. FEDERAL REGULATORY INFORMATION

- ▶ On September 14, 1989, benzene was regulated for certain sources of air pollutant emissions under section 112 of the Clean Air Act (40 CFR Part 61: the "Benzene NESHAP"). Benzene is one of 188 hazardous air pollutants (HAPs) listed under section 112(b) of the 1990 Clean Air Act Amendments and regulated from more than 170 industrial source categories (73).
- ▶ Benzene is listed as number 6 on the 2005 Priority List of Hazardous Substances for the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) section 104 (i), as amended by the Superfund Amendments and Reauthorization Act (SARA). This is a list in the order of priority of concern of substances most commonly found at sites listed on the National Priorities list (NPL); there are currently 275 substances on this list (74).
- ▶ The U.S. EPA requires reporting of quantities of certain chemicals that exceed a defined reportable quantity, and that quantity varies for different chemicals (75). Under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), reporting releases of benzene of any quantity exceeding 10 pounds is required (75).

VIII. BACKGROUND ON CHEMICAL

A. CAS Number: 71-43-2

B. Physical/Chemical Properties: Benzene is a sweet-smelling colorless liquid that volatilizes easily, and dissolves in water. Go to the National Library of Medicine ChemID Web site (<http://chem.sis.nlm.nih.gov/chemidplus>) and search for benzene.

C. Production: Industrial processes and vehicle exhaust are the main sources of benzene in the environment (1, 2, 76). Benzene is commercially recovered from coal and petroleum sources; in 1993, 472 U.S. facilities produced or processed 17.2 billion pounds of benzene. Benzene ranks in top 20 chemicals for U.S. production volume (2).

D. Uses: Benzene is an intermediate used in the production of solvents, plastics, resins, and some types of rubbers, drugs, and pesticides (2, 76). Emissions of benzene can be detected from such products as carpet glue, textured carpet, liquid detergent, and furniture wax. Benzene is also a natural part of crude oil, gasoline (1% to 2% benzene), and cigarette smoke (1, 2). Total reported releases and disposals of benzene in the U.S. was over 6 million pounds in 2005; total releases are likely to be greater than this estimate because not all sources of benzene releases are required to report (77).

E. Environmental Fate: Benzene can volatilize into the air from water and soil (2, 76). Benzene can break down within a few days in air, whereas benzene breaks down more slowly in water and soil. It can also easily leach from the soil into groundwater. Benzene does not bioaccumulate in plants or animals.

F. Synonyms and Trade Names: phenyl hydride; coal naphtha; benzol; cyclohexatriene; benzine; benzolene; phene; 6-annulene; bicarburet of hydrogen; carbon oil; mineral naphtha; motor benzol; nitration benzene; pyrobenzol; for a more complete list, go to <http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp>.

Additional information on benzene is available in the TEACH Database for Benzene, and at the following Web sites:

www.epa.gov/ncea/pdfs/benzenef.pdf

<http://www.cfsan.fda.gov/~dms/benzqa.html>

www.epa.gov/ttn/atw/nata/

<http://www.epa.gov/ttn/atw/hlthef/benzene.html>

<http://www.epa.gov/safewater/dwh/c-voc/benzene.html>

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