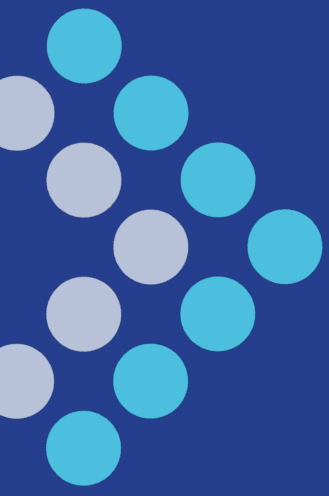
US BioTek LABORATORIES

Environmental Pollutants Reference Guide



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Environmental Pollutants Reference Guide

Benzene Metabolite Trans, trans-muconic acid

Sources of Exposure

Natural component of crude and refined petroleum.

Automotive emissions, poor emission-control devices on older vehicles, poor maintenance practices, automotive-refueling operations and industrial emissions.

Discharge of industrial wastewater from chemical plants, chemical manufacturing sites, and petrochemical and petroleum industries.

Seepage from underground petroleum storage tanks, waste streams.

By-product of various combustion processes - wood burning, organic wastes, tobacco smoke. First and second-hand smoke accounts for the largest source of benzene expsorue of the general public. The amount of benzene in a single cigarette may vary from 5.9-90 micrograms.

Used in the manufacture of Styrofoam, resins, synthetic fibers and rubbers, gums, lubricants, dyes, glues, paints and marking pens.

Used as a solvent in scientific labs, industrial paints, adhesives, paint removers/ strippers, degreasing agents, carburetor cleaner, rubber cements, some arts and crafts supplies, manufacture of faux leather and rubber goods.

Off-gassing from building material, particle board, carpet glue, textured carpet, liquid detergent, furniture wax, structural fires, high-density traffic locales, petrol stations.

Occupational Exposure: industries that produce or use benzene or benzene-containing products - oil refineries, petroleum plants, tire manufacturers, paint and shoe manufacturing plant, petrol stations, active or passive cigarette-smoke inhalation, and areas of heavy vehicular traffic.

Interfering Factors: Sorbic acid and potassium sorbate, common food preservatives, are metabolized to muconic acid, which may therefore cause elevations of this marker. Sources include: processed cheese slices and spreads, salad dressings, mayonnaise, flavored drinks, canned foods, and baked goods. To eliminate this confounding variable, sorbic acid, is assayed and reported on the patient's Environmental Pollutants Profile if detected.

Effects

Lowers blood parameters (hematocrit, haemoglobin level, erythrocyte, leukocyte, platelet counts).

Bone marrow depression with aplastic anemia, leukaemia, thrombocytopaenia.

Human carcinogen, Genotoxic.

Skin and eye irritation.

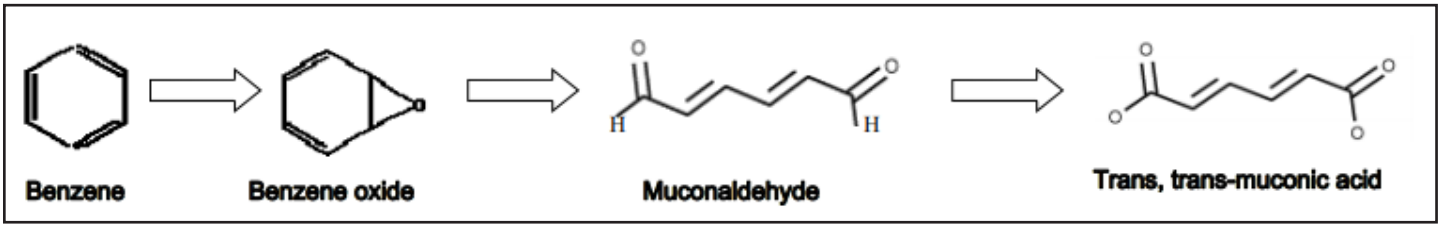
Central Nervous System depression, death.

Metabolism

Following inhalation, most benzene is excreted through exhalation unchanged.

Benzene is metabolized by cytochrome P-450-dependent multifunction oxidase enzymes and excreted as conjugated derivatives (sulfates and glucuronides).

Benzene and its metabolites accumulate in lipid depots.



Paraben Metabolite Para-Hydroxybenzoate

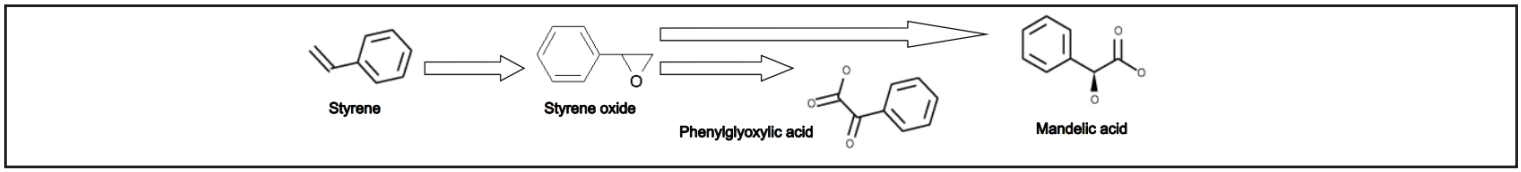
Sources of Exposure	Effects	Metabolism
Used widely as an antimicrobial, a preservative and flavorant in food, as well as cosmetic and pharmaceutical formulations to increase shelf life. Body care products - sprays, fragrances, conditioners, shampoos, hair gels, deodorants, antiperspirants, soaps, hand sanitizers, facial masks and foundations, sunscreens, self-tanners, hair removal creams and shaving gels, nail and skin creams, baby lotion. Pharmaceuticals - injectable drugs, antacids, suppositories, Benadryl™ cream, hydrocortisone creams and ointments, medicated pain-relieving patches, mentholated vapor rubs, chapstick, antifungal and antibacterial preparations. Food products - packaged meats, fish and poultry, mayonnaise, oils, salad dressings, catsup, pickles, relishes, processed fruits and vegetables, frozen dairy products, cakes, pies, pastries, icings, jellies and jams, beers and ciders, soft drinks, fruit juices, syrups, and some candies. May also be derived from bacterial metabolism in the gut. **Occupational Exposure:** industrial oils, fats, glues, shoe polishes, and textiles.	Allergic contact dermatitis. Parabens exhibit estrogenic activity. Animal studies show decreased testosterone levels and sperm count.	Alkyl esters of para-hydroxybenzoic acid, parabens are hydrolyzed to para-hydroxybenzoate, the main metabolite of parabens, via tissue esterases found in skin, subcutaneous fat, liver and kidney. Bioaccumulation of parabens may result from chronic exposure.

Phthalic Acid Ester Metabolite Phthalate

Sources of Exposure	Effects	Metabolism
Used in the manufacture of plastics to soften resins and impart flexibility. Most widely used plasticizers for the manufacture of polybinyl chloride (PVC) plastics utilized in vinyl flooring and tile, wall covering, pool liners, tool handles, insulation of wires and cables, garden hoses, construction materials, weather-stripping, canvas tarps, upholstery, some food wrappers and containers, medical equipment containing flexible plastics such as blood bags and tubing, haemodialysis, children's toys, dishwasher baskets, notebook covers, flea collars, faux leather, shoe soles, traffic cones, latex adhesives, dyes, some pharmaceutical and pesticide formulations. Detergents, lubricating oils, automobile parts, automobile undercoating, carpet backing, solvents, and personal-care products such as soaps, shampoo, hair spray, nail polish, and toothbrushes, baby-care products. Diethyl Phlthalate (parent compound of MEP) reported in over 70% of cosmetic products tested. Make fragrance in cosmetics and household products last longer. **Occupational Exposure:** Plasticizer and PVC processing plants. ***Quinolinate** - Phthalate esters perturb tryptophan metabolism resulting in the accumulation of quinolinic acid, an endogenous excitotoxin implicated in inflammatory neurological disorders. ***Quinolinate** is a metabolite of the essential amino acid tryptophan in the kynurenine pathway. This pathway is chiefly activated by IFN - gamma and IFN - alpha. Quinolinate is markedly elevated in the CNS following trauma or inflammation, and is implicated in neuronal injury through activation of the N-methyl-D-aspartate (NMDA) receptor. Toxicity of phlthalate esters, acting as metabolic disrupters, through accumulation of quinolinic acid, may be of concern with a tryptophan - rich diet and concomitant exposure to phthalate esters.	Endocrine-Disrupting Chemical (EDC). Young infants may be more vulnerable to toxic effects. May alter development of male reproductive system. Developmental and morphological abnormalities including deficits in behavior and cognition. Some reports of decreased sperm production in adult males exposed to environmental levels. Associated with increased waist circumference and insulin resistance in adults.	Phthalates are hydrolyzed in the gut by pancreatic lipase yielding ester derivatives, which are rapidly absorbed. These phthalate esters are metabolized in the liver by cytochrome P-450 dependent multifunction oxidase enzymes, into glucuronide conjugates and excreted in the urine. Monoethylphthalate, MEP, in urine reflects exposure to diethylphthalate (DEP). About 70% is excreted in urine as its free monoester. DEHP and phthalates in general is noted by urinary levels of free phthalic acid, a further breakdown product of phthalates. Phthalates and their metabolites accumulate in lipid depots. Bioaccumulation may result from chronic exposure.

Styrene Metabolites Mandelate, Phenylglyoxylate

Sources of Exposure	Effects	Metabolism
Raw materials (benzene and ethylene) for the manufacture of styrene are supplied primarily from the petroleum industry. Used in the manufacture of synthetic rubbers, synthetic latex, polyesters, and plastic products. Automotive emissions, tobacco smoke, released from building materials, carpet backing. Low-level exposure may occure through ingestion of food products packaged in polystyrene containers. Packaging materials, toys, hobbies, crafts, house wares and appliances, electrical and thermal insulation, fiberglass, pipes, automobile parts, foam cups. Emissions from styrene production and disposal procedures - chemical spills, landfill sites and industrial discharges. **Occupational Exposure:** industries and operations concerned with the fabrication and application of plastics - styrene/polystyrene manufacturing plants, resin manufacturers, synthetic rubber plants, boats and automobile plants, laminators.	Depression of the central nervous system. Dizziness, lightheadedness, headache, drowsiness, nausea, impared balance, manual dexterity and reaction time, difficulty concentrating. Irritation of mucous membranes, dermatitis, nausea, fatigue. Genotoxic.	XStyrene is metabolized in the liver by cytochrome P-450 dependent multifunction oxidase enzymes, into its epoxide derivatives. The major metabolic pathway involves the sequential oxidation to mandelic and phylglyoxylic acids. Styrene oxides are also conjugated with glutathione. Styrene and its metabolites accumulate in lipid depots. Its slow elimination suggests the possibility for bioaccumulation from chronic exposure. The sum of the metabolites, mandelate and phylglyoxylate exhibit a higher correlation ratio than the separate levels of the analytes. A summation value is reported on the patient's Environmental Pollutants Profile.



Toluene Metabolite Hippurate

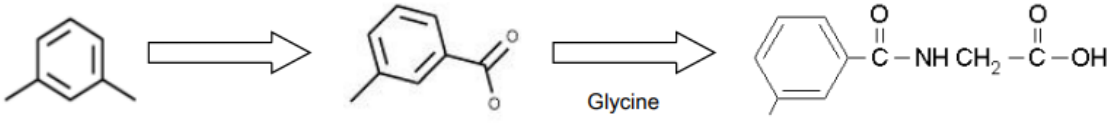
Sources of Exposure	Effects	Metabolism
Mainly by inhalation of vapors. Produced from petroleum refining. Automotive and aircraft emissions, poor emission-control devices on older vehicles, poor maintenance practices, high-density traffic locales, gasoline filling stations, refineries, tobcco smoke. The amount of toluene in a single cigarette may vary from 80 to100 micrograms (µg). Blended into gasoline as a component to increase octane number. Two thirds of its use as as a solvent carrier in paints, inks, thinners, coatings, adhesives, degreasers, pharmaceutical products. Household aerosols, spray paint cans, glues, varnishes, shallac, rust preventatives, solvent-based sanitizing agents and germicides, etc. Additive in cosmetic products. **Occupational Exposure:** paint, printing and leather finsihing-industry, rubber-coating industry, shoemakers. *Hippurate is also the end product of benzoate metabolism. Benzoate may be derived from foods containing sodium benzoate additive.	Depression or excitatory effect on the central nervous system - euphoria followed by disorientation, tremulousness, mood lability, tinnitus, diplopia, hallucinations, dysarthria, ataxia, convulsions, coma. Irritation (eyes, nose, throat), dizziness, taste and olfactory fatigue. Drowsiness, headhache,impaired cognitive and motor function, insomnia, anorexia. Solvent abuse through "sniffing" toluene-containing products may lead to gross disorientation, neurological impairment and death.	Toluene is metabolized in the liver by cytochrome P-450 dependent multifunction oxidase enzymes conjugated principally with glycine, and excreted in the urine as hippuric acid. Smaller amounts may be conjugated with glucuronic acid. Minor amounts undergo hydroxylation to cresols, which are excreted in the urine as sulfate, or glucuronide conjugates. Under conditions of chronic exposure, significant uptake of toluene into lipid-rich tissues (adipose, CNS) may occur. Effects are reversible on cessation of exposure, but are increasingly severe and persistent with increasing concetration and/or duration of exposure. Toluene interferes with the biotransformation of other compounds (benzene, xylene, and styrene) in the liver.

Trimethylbenzene Metabolite 3,4-Dimethylhippurate

Sources of Exposure	Effects	Metabolism
Mainly by inhalation of vapors. Production occurs during petroleum refining. Primary use is as a motor fuel additive. Automotive emissions, poor emission-control devices on older vehicles, poor maintenance practices, diesel engine exhaust. Solvent in coatings, paint thinners, wood preservatives, cleaners, dry cleaners, degreasers, aerosols, pesticides, printing and inks. Component of white spirit, the most widely used solvent in the paint and coating industry. Manufacture of pharmaceuticals, asphalt products, lacquers, varnishes, dyes, perfumes. **Occupational Exposure:** scientific labs, janitor/cleaner, dry cleaning industry, automobile body and related repairers, construction laborers, house painters, screen cleaning processes, ski boots finishing, and telephone cable assembly. People who do considerable home maintenance work or hobby work may be exposed via inhalation or dermal contact with the solvent.	Irritation of mucous membranes, dermatitis, dizziness, "drunkenness", fatigue, headache, anxiety, nervousness. Cyanosis, cognitive and motor impairment, apnea, burst of perspiration, cardiac arrest. Diarrhea, abdominal pains, nausea, blurred vision. Low frustration tolerance, lack of initiative, apathy, depression, irritability (painter's syndrome). Neurotoxic. Carcinogenic. Decreased erythrocyte, leukocyte and platelet counts. Glomerulonephritis, renal dysfunction.	Metabolized in the liver by cytochrome P-450 dependent multifunction oxidase enzymes, conjugated with glucuronic acid, glycine, or sulfates for urinary excretion. Lipophilic and may accumulate in fat and fatty tissues.

Xylene Metabolites 2-Methylhippurate 3-Methylhippurate

Sources of Exposure	Effects	Metabolism
Mainly by inhalation of vapors. Natural component of petroleum and coal tar. Motor and aviation fuel additive. Automotive emissions, poor emission-control devices on older vehicles, poor maintenance practices, aviation fuel, waste and landfill sites, localized industrial discharges and spillage incidents, tobacco smoke. Topical contact or inhalation of: varnish/polishers, paint thinner, paint remover, shellac, rust preventatives, lacquers, inks, dyes, adhesives, cleaning fluids, degreasing agents, household cleaning products. Used as a solvent for rubbers, synthetic resins, gums, inks, paint. Fabric and leather treatments. Used in the synthesis of plasticizers and in the manufacture of polyester fiber, film, insecticide formulations and perfumes. **Occupational Exposure:** paint and printing ink industries, automobile body and related repairer, photographic processing, rubber, leather, plastics, and textile industries, flooring contractor.	Depression of the central nervous system. Neuropsychological and neurophysiological dysfunction. Anemia, thrombocytopaenia, renal damage. Irritation of mucous membranes, dermatitis, nausea, fatigue, heachache, anxiety. Dyspnea, cyanosis.	Xylene is metabolized in the liver by cytochrome P-450-dependent multifunction oxidase enzymes, conjugated principally with glycine and excreted in the urine as methylhippuric acids. Conjugation with sulfate or glucuronic acid represents a minor pathway. Urinary levels of 2, and 3-methylhippurate provide a valid complement to ambient monitoring. Although the 2-isomer exhibits a longer half-life, the 3-isomer is the principle component making up 45-70% of commerical xylene. Xylene does not accumulate significantly in body tissues.



Methyl tert-butyl ether (MTBE) Metabolite Alpha-Hydroxyisobutyrate

Sources of Exposure

Used as a fuel additive in gasoline, MTBE is a compound manufactured by the chemical reaction of methanol and isobutylene. In the U.S., it has not been used in significant quantities in gasoline since 2005.

MTBE is a volatile, flammable and colorless liquid that is extremely water-soluble. Once in the ground, it can travel fast and far through groundwater. MTBE is not easily biodegradable and can remain in underground water for a long time.

Contaminated water is the most likely exposure source for many, via drinking or skin contact. Exposure may also occur thorugh inhaled gas vapors.

Occupational Exposure: gasoline stations, areas of heavy vehicular traffic, exposure to water in areas contaminated with MTBE.

Effects

Acute effects of MTBE inhalation may include drowsiness, dizziness, headache, weakness, and loss of consciousness.

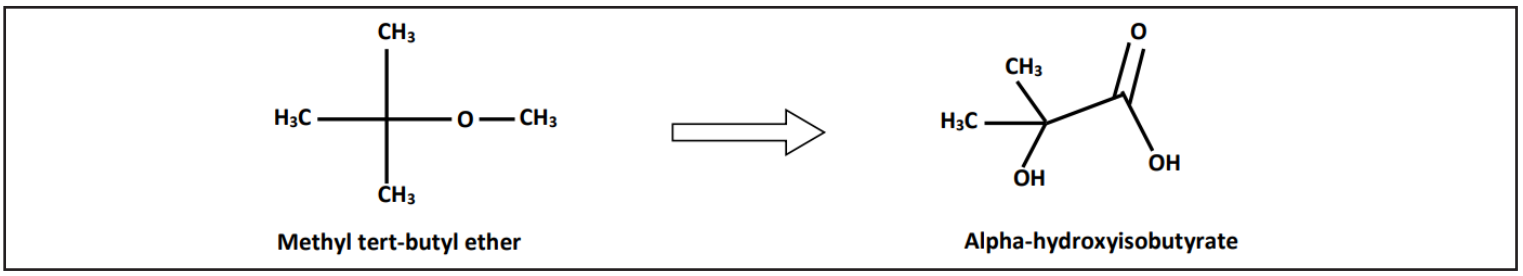
Adverse effects from ingestion may include nausea, vomiting, and abdominal pain. The EPA indicates little likelihood that MTBE in drinking water will cause adverse health effects at concentrations of ≤ 20-40 ppb.

No national standard has been set, but some states have set their own limits for MTBE levels in drinking water. Even at low levels, MTBE can impact drinking water supplies with its offensive taste and odor.

Metabolism

MTBE does not appear to accumulate in the body; it is metabolized and exhaled or excreted in urine rapidly in healthy subjects, usually within a couple of days.

MTBE is metabolized by cytochrome P450 enzymes (CYP2A6).



Detoxification of Environmental Pollutants

The Environmental Pollutants Profile (EPP) screens for chemicals commonly found in the environment due to daily background exposures. The EPP screens for chemicals commonly found in the environment due to daily background exposures. Unlike the OAP, there are no "normal" levels of toxic exposure, so values past the 50% are considered likely to compromise patient health, and to indicate a need for detoxification support.

The Organic Acids profile and the EPP may be collected simultaneously and evaluated together; the nutritional recommendations from the Organic Acids results can guide decisions regarding mitochondrial, liver, and gut support as well as antioxidant status. The basic steps in designing any detoxification program include:

- Elimination of the toxic exposures from the environment
- Adjust diet and lifestyle to support gastrointestinal motility and microbiome diversity and improve hydration to support kidney function
- Exercise or sauna to induce sweating
- Nutritional supports for chemical detoxification:

Chemical	Adipose storage	Phase I enzymes	Phase II pathways	Nutrient supports
Xylene	N/A	CYP2E1	Glycine conjugation	Glycine, antioxidants, iron*, magnesium, manganese*, potassium, rubidium
Styrene	Yes	CYP2E1 and other CYP-450 enzymes	Glutathione conjugation	Glutathione, N-acetylcysteine, vitamin B6
Toluene	Yes	CYP2E1	Glycine conjugation Glucuronidation	Glycine, glycyrrhizin**, calcium-D-glucarate, iron*, magnesium, manganese*, potassium, rubidium
Benzene	Yes	Multiple CYP-450 enzymes	Glucuronidation Sulfonation	Calcium-D-glucarate, glycyrrhizin**, iron*, molybdenum

Trimethylbenzene	Yes	Side-chain oxidation enzymes	Glucuronidation	B3, glycine, glycyrrhizin** glutathione, iron* calcium-D-glucarate,
Phthalates	Yes	Multiple CYP enzymes	Glucuronidation	Calcium-D-glucarate, iron*, glycyrrhizin, antioxidants
Parabens	N/A	Multiple CYP enzymes	Glucuronidation Sulfonation	Calcium-D-glucarate, glycyrrhizin**, iron*, molybdenum
Methyl tert-butyl ether	N/A	CYP2A1, CYP2A6, CYP2B1	Glucuronidation	Calcium-D-glucarate, glycyrrhizin**, iron*

* Supplement only if deficient

**glycyrrhizin is a licorice component, and may be contraindicated if the patient has high blood pressure.

Over 90% of the population, including children, have bioaccumulated environmental toxins in their bodies. Some exposed individuals are able to detoxify these daily background exposures, while others may experience toxic effects at the same levels. The individual differences in detoxification capacity are the result of inheritance, epigenetic programming from the environment, nutritional status, and antioxidant status.

While some toxic chemicals are more likely to deposit in fatty (adipose) tissues, others are processed rapidly and excreted. Chemicals stored in adipose tissues are unlikely to be mobilized and found in the urine unless weight loss is occurring. Chemicals that may be stored long-term in adipose tissues include toluene, styrene, phthalates, etc. While the singular effects of many chemicals have been explored, the additive and cumulative effect of simultaneous exposure to multiple chemicals has not been evaluated, and toxic effects for chemical mixtures is not currently predictable. The available evidence indicates that chemical mixtures often have greater effects at lower doses.

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