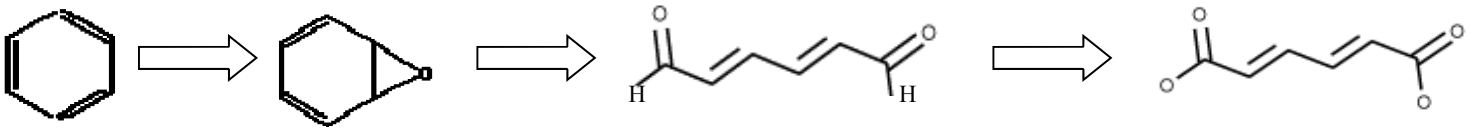
Environmental Pollutants Quick Reference Guide

Benzene Metabolite Trans, trans-muconic acid

Sources of Exposure	Effects	Metabolism
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. Emissions during the production of xylene, toluene, styrene and other compounds. 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 exposure for 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, particleboard, 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.	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.	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.



Benzene → Benzene oxide → Muconaldehyde → Trans, trans-muconic acid

Paraben Metabolite **Para-Hydroxybenzoate**

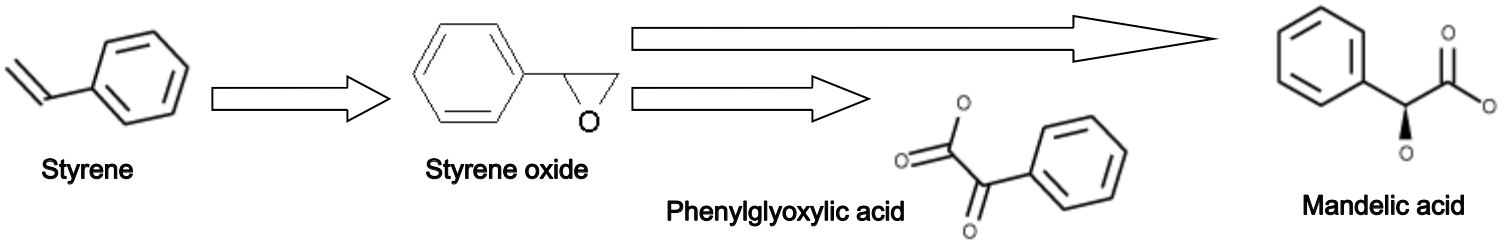
Sources of Exposure	Effects	Metabolism
Used widely as an antimicrobial, a preservative and flavorant in food, as well as cosmetic and pharmaceutical formulations to increase shelf life. Body care products - sprays, fragrances, conditioners, shampoos, hair gels, deodorants, antiperspirants, soaps, hand 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, chap stick, 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, & 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 polyvinyl 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 Phthalate (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 phthalate 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 represents another widely used plasticizer in the manufacture of PVC. Exposure to 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 occur 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, boat and automobile plants, laminators.	Depression of the central nervous system. Dizziness, lightheadedness, headache, drowsiness, nausea, Impaired 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 phenylglyoxylic 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 phenylglyoxylate 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**

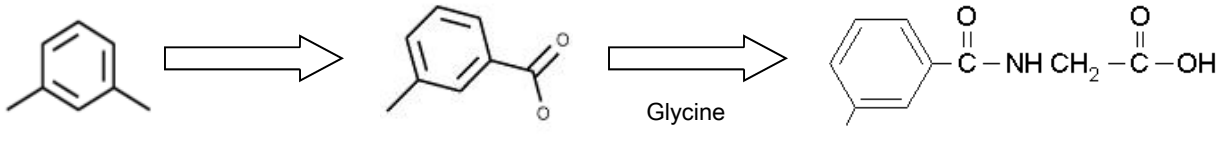
Sources of Exposure	Effects	Metabolism
Mainly by inhalation of vapors. Produced from petroleum refining. Automotive and aircraft emissions, poor emission-control devices on older vehicles, poor maintenance practices, high-density traffic locales, gasoline filling stations, refineries, tobacco smoke. The amount of toluene in a single cigarette may vary from 80 to 100 micrograms (μg). Blended into gasoline as a component to increase octane number. Two thirds of its use as a solvent carrier in paints, inks, thinners, coatings, adhesives, degreasers, pharmaceutical products. Household aerosols, spray paint cans, glues, varnishes, shellac, rust preventatives, solvent-based sanitizing agents and germicides, etc. Additive in cosmetic products. **Occupational Exposure**: paint, printing and leather finishing-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, headache, 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 concentration 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, janitors/cleaners, 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, bursts of perspiration, cardiac arrest. Diarrhea, abdominal pains, nausea, blurred vision. Low frustration tolerance, lack of initiative, apathy, depression, irritability (painter's syndrome). Neurotoxic. Decreased erythrocyte, leukocyte and platelet counts. Carcinogenic 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.

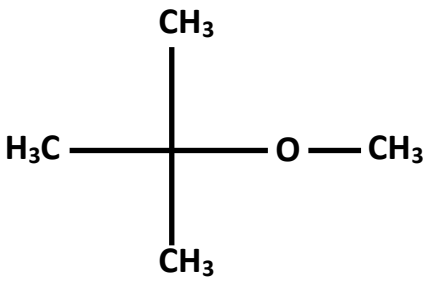
Xylene Metabolites 2-Methylhippurate 3-Methylhippurate

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, 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 repairers, 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, headache, 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 commercial xylene. Xylene does not accumulate significantly in body tissues.

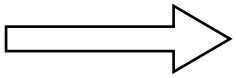


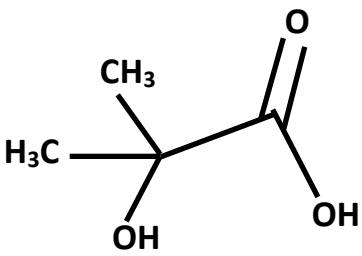
Methyl tert-butyl ether (MTBE) Metabolite **Alpha-Hydroxyisobutyrate**

Sources of Exposure	Effects	Metabolism
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 through inhaled gas vapors. **Occupational Exposure:** gasoline stations, areas of heavy vehicular traffic, exposure to water in areas contaminated with MTBE.	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.	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).



Methyl tert-butyl ether





Alpha-hydroxyisobutyrate