13500 Linden Avenue North Seattle, WA 98133 (206) 365-1256

Xylene Metabolites
2-Methylhippurate, 3-Methylhippurate

Sources of Exposure

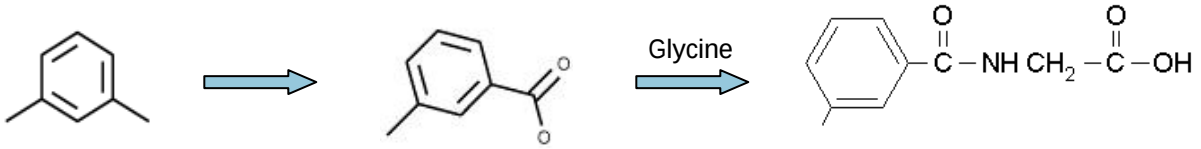
- Mainly by inhalation of vapors.
- Natural component of petroleum and coal tar.
- Motor and aviation fuel additive.
- Automotive emissions, poor emission-control devices on older vehicles, poor maintenance practices, waste and landfill sites, localized industrial discharges and spillage incidents, tobacco 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, paints.
- 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.

Effects

- 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.

Metabolism

- 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, and correlates more strongly to exposure.
- Xylene does not accumulate significantly in body tissues.



m-Xylene **Toluic Acid** **3-Methylhippurate**

Toluene Metabolite
Hippurate

Sources of Exposure

- Mainly by inhalation of vapors.
- Produced from petroleum refining and used as an additive to increase the octane number in gasoline.
- 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).
- 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. Therefore, Hippurate may be elevated for reasons other than toluene exposure.

Effects

- 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.

Metabolism

- Toluene, like its analogue xylene, 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, styrene) in the liver.

Benzene Metabolite
trans, trans-muconic acid

Sources of Exposure

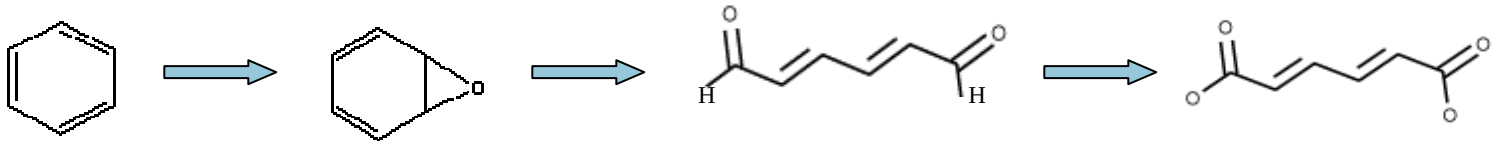
- Natural component of crude and refined petroleum.
- Automotive emissions, poor emission-control devices on older vehicles, poor maintenance practices, automotive-refueling operations and industrial emissions.
- Emissions during the production of xylene, toluene, styrene and other compounds.
- Discharge 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 5.9-90ug.
- 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 plants, 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 Biomonitor 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.
- The majority of Benzene is excreted as conjugated derivatives (sulfates and glucuronides) of phenols. About 20% is metabolized to muconaldehyde, a hematoxic intermediate, before hydroxylation to muconic acid.
- Benzene and its metabolites accumulate in lipid depots.



Benzene **Benzene oxide** **Muconaldehyde** **trans,trans, muconic acid**

Trimethylbenzene Metabolite
3,4-Dimethylhippurate

Sources of Exposure

- Mainly by inhalation of vapors.
- Production occurs during petroleum refining.
- Primary use 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.

Effects

- 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 (‘painters syndrome’).
- Neurotoxic.
- Decreased erythrocyte, leukocyte and platelet counts.
- Carcinogenic.
- Glomerulonephritis, renal dysfunction.

Metabolism

- 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.

Styrene Metabolites
Mandelate, Phenylglyoxylate

Sources of Exposure

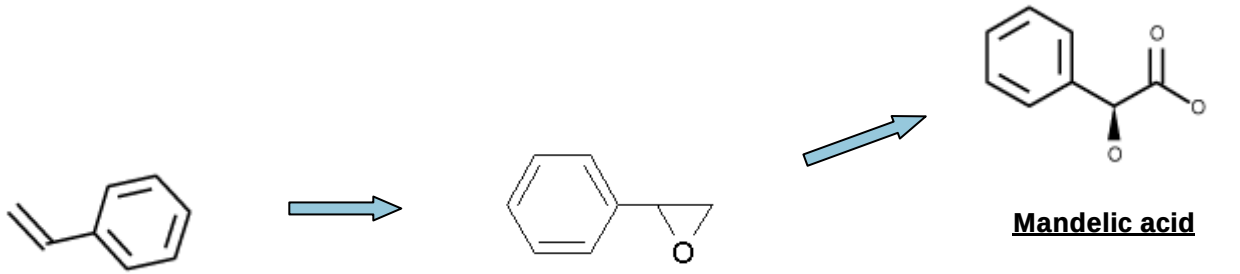
- Raw materials (benzene and ethylene) for the manufacture of styrene are supplied primarily from the petroleum industry.
- Used in the manufacture of synthetic rubbers, synthetic latex, polyesters, and plastic products.
- Automotive emissions, tobacco smoke, released from building materials, carpet backing. Low-level exposure may occur through ingestion of food products packaged in polystyrene containers.
- Packaging materials, toys, hobbies, crafts, housewares 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.

Effects

- Depression of the central nervous system.
- Dizziness, lightheadedness, headache, drowsiness, nausea, impaired balance and manual dexterity and reaction time, difficulty concentrating.
- Irritation of mucous membranes, dermatitis, nausea, fatigue.
- Genotoxic.

Metabolism

- Styrene 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 each analytes. A summation value is reported on the patient's Biomonitor.



Phthalate Metabolite
Phthalic Acid

Sources of Exposure

- 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.
- **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.

Effects

- 'Endocrine-disrupting chemical' (EDC).
- Developmental and morphological abnormalities including deficits in behavior and cognition.

Metabolism

- 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. In addition to glucuronide-bound conjugates of the oxidative metabolites, free phthalic acid, a further breakdown product, also appears in the urine.
- Phthalates and their metabolites accumulate in lipid depots. Bioaccumulation may result from chronic exposure.

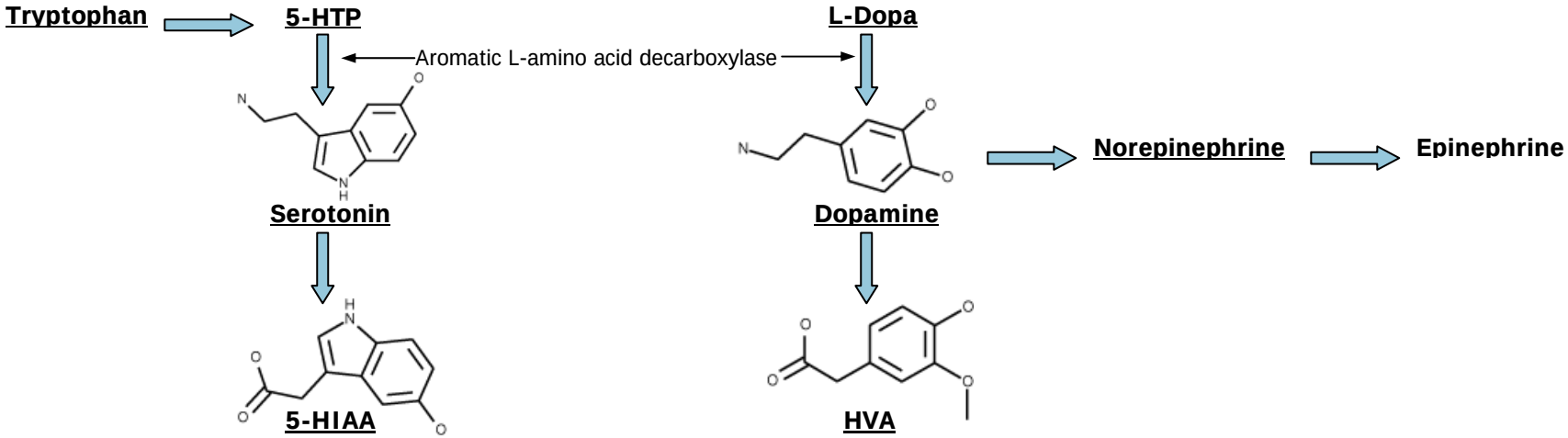
Urinary Markers: Homovanillate (HVA) and 5-Hydroxyindoleacetate (5HIAA)

Exposure to various environmental chemical agents may decrease or increase serotonergic and catecholamine turnover affecting the excretion rates of their respective metabolites, 5HIAA and HVA, in urine. Assessment of these metabolites may serve as a useful indicator of early exposure to urban pollutants. Some chemical agents including; carbon monoxide, toluene and styrene may inhibit principle enzymes involved in the metabolism of serotonin (5-HT) resulting in lower levels of 5HIAA in urine. Conversely, these chemicals, in addition to benzene, have been reported to raise urinary levels of the dopamine (DA) metabolite, HVA. Results of studies from municipal traffic police exposed to higher levels of urban pollutants from exhaust fumes indicate lower and higher urinary levels of 5HIAA and HVA respectively, compared to indoor control workers. [i,ii] In-house analyses of select populations from industrially-dense areas have yielded similar results.

Research supports disturbances in catecholamine and serotonin turnover from various perceived psychosocial stressors in addition to certain psychiatric disorders. Other research has focused on the effects of environmental and occupational chemicals and solvents, used in numerous industries, showing possible interference in catecholamine neurotransmitter metabolism.

It remains to be determined whether certain environmental and occupational chemicals may indeed play a role in the pathogenesis of psychiatric pathologies for which there is a clear alteration in 5HT and DA metabolism.

*Please note that antidepressant medications such as Monoamine Oxidase Inhibitors (MAOIs), Tricyclic Antidepressants (TCAs), and Selective Serotonin Reuptake Inhibitors (SSRIs), including medications used to treat Parkinson's Disease; Catechol-O-Methyltransferase Inhibitors (COMPTs), Levodopa and Dopamine Agonists, may interfere with the ratio of HVA/5HIAA as quantified from the patient's urine sample.



[i] Tomei Francesco, et al. Occupational exposure to urban pollutants and urinary 5-hydroxy-3-indoleacetic acid. *Journal of Environmental Health*, 66(6), 38-42, 2004.
ii Tomei Francesco, et al. Work exposure to urban pollutants and urinary homovanillic acid. *Journal of Environmental Science and Health*, A38 (12), 2909-2918, 2003.