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5th stage

Hydrocarbons Toxicity

A *hydrocarbon* is an organic compound made up primarily of carbon and hydrogen atoms, typically ranging from 1 to 60 carbon atoms in length. This definition includes products derived from plants (pine oil, vegetable oil), animal fats (cod liver oil), natural gas, petroleum, or coal tar. There are two basic types of hydrocarbon molecules, *aliphatic* (straight or branched chains) and *cyclic* (closed ring), each with its own subclasses.

Solvents are a heterogenous class of xenobiotics used to dissolve and to provide a vehicle for delivery of other xenobiotics. The most common industrial solvent is water. The common solvents most familiar to toxicologists are *organic solvents* (containing one or more carbon atom), and most of these are hydrocarbons. Most are liquids in the conditions under which they are used. Specifically named solvents (Stoddard solvent, white naphtha, ligroin) represent mixtures of hydrocarbons emanating from a common petroleum distillation fraction.

Physical properties of hydrocarbons vary by the number of carbon atoms and by molecular structure. Unsubstituted, aliphatic hydrocarbons that contain up to 4 carbons are gaseous at room temperature, 5 to 19 carbon molecules are liquids, and longer-chain molecules tend to be tars or solids. Branching of chains tends to destabilize intermolecular forces, so that less energy is required to separate the molecules. The result is that, for a given molecular size, highly branched molecules have lower boiling points and tend to be more volatile.

TABLE 106–1. Classification and Viscosity of Common Hydrocarbons

Compound	Common Uses	Viscosity (SUS)[a]
Aliphatics		
Gasoline	Motor vehicle fuel	30
Naphtha	Charcoal lighter fluid	29
Kerosene	Heating fuel	35
Turpentine	Paint thinner	33
Mineral spirits	Paint and varnish thinner	30–35
Mineral seal oil	Furniture polish	30–35
Heavy fuel oil	Heating oil	>450
Aromatics		
Benzene	Solvent, reagent, gasoline additive	31
Toluene	Solvent, spray paint solvent	28
Xylene	Solvent, paint thinner, reagent	28
Halogenated		
Methylene chloride	Solvent, paint stripper, propellant	27
Carbon tetrachloride	Solvent, propellant, refrigerant	30
Trichloroethylene	Degreaser, spot remover	27
Tetrachloroethylene	Dry cleaning solvent, chemical intermediate	28

Table 1: *Classification and Viscosity of Common Hydrocarbons*

Gasoline is a mixture of alkanes, alkenes, naphthenes, and aromatic hydrocarbons, predominantly 5 to 10 carbon molecules in size. Gasoline is separated from crude oil in a common distillation fraction. However, most commercially available gasolines are actually blends of up to eight component fractions from refinery processors. More than 1500 individual xenobiotics may be present in commercial grades, but most analytical methods are only able to isolate 150 to 180 compounds from gasolines. Notably, *n*-hexane is present at up to 6%, and benzene is present between 1% and 6%, depending on the grade and the place of origin of the product.

Organic halides contain one or more halogen atoms (fluorine, chlorine, bromine, iodine) usually substituted for a hydrogen atom in the parent structure. Examples include chloroform, trichloroethylene, and the freons.

Oxygenated hydrocarbons demonstrate toxicity specific to the oxidation state of the carbon, as well as to the atoms adjacent to it (the "R" groups). The *alcohols* are widely used as solvents in industry and in household products

PHARMACOLOGY

Inhalation of hydrocarbon vapor depresses consciousness. Acute central nervous (CNS) toxicity from occupational overexposure or recreational abuse parallels the effect of administering an inhaled general anesthetic. The concentration of volatile anesthetic that produces loss of nociception in 50% of patients defines the minimum alveolar concentration (MAC) required to induce anesthesia. Inhaled solvent vapor similarly produces unconsciousness in 50% of subjects when the partial pressure in the lung reaches its median effective dose (ED_{50}). The ED_{50} of occupational parlance is effectively the same as the MAC used in anesthesiology parlance. Virtually all patients will be anesthetized when the partial pressure is raised 30% above the MAC (MAC □□1.3), and death, if ventilation is not supported, typically occurs when the concentration reaches two to four times the MAC.

Occupational exposure to lipid-soluble solvents, such as aromatic, aliphatic, or chlorinated hydrocarbons, are more likely to cause acute and chronic CNS effects than exposure to water-soluble hydrocarbons such as alcohols, ketones, and esters.

Unfortunately, a single mechanism remains elusive. Halothane, isoflurane, sevoflurane, enflurane, and desflurane inhibit fast sodium channels. Toluene, trichloroethylene, perchloroethylene, and others inhibit neuronal calcium currents.

The effect of hydrocarbons on cardiac conduction remains an active arena of toxicologic research. Nearly all classes of hydrocarbons, to varying degrees, augment the dysrhythmogenic potential by "sensitizing" the myocardium.

Cardiac sensitization is incompletely understood. Halothane and isoflurane inactivate sodium channels, whereas chloroform and others attenuate potassium efflux through voltage-gated channels.[133] Sensitization may be mediated by slowed conduction velocity through membrane gap junctions. Halocarbons, in the presence of epinephrine, cause

dephosporylation of this gap junction protein, thereby increasing gap junctional resistance and slowing conduction velocity in myocardial tissue.

TOXICOKINETICS

Human toxicokinetic data are lacking for most hydrocarbons, and much of our understanding of the kinetics comes from animal studies. Hydrocarbons are variably absorbed through ingestion, inhalation, or dermal routes of exposure. Partition coefficients, in particular, are useful predictors of the rate and extent of the absorption and distribution of hydrocarbons into tissues as the higher the value the greater the potential for redistribution. A partition coefficient for a given chemical species is the ratio of concentrations achieved between two different media at equilibrium.

Table 2 lists the partition coefficients for commonly encountered hydrocarbons.

Table 2

TABLE 106–2. Kinetic Parameters of Selected Hydrocarbons

	Partition Coefficients		$t_{1/2}$			
	Blood/Air	Fat/Air	α	β	Elimination	Relevant Metabolites
Aliphatics						
n-Hexane	2.29[a]	159[a]	11 min	99 min	10%–20% exhaled; liver metabolism by CYP 2E1	2-Hexanol, 2,5-hexanedione, γ-valerolactone
Paraffin/tar	Not absorbed or metabolized					
Aromatics						
Benzene	8.19	499[a]	8 h	90 h	12% exhaled; liver metabolism to phenol	Phenol, catechol, hydroquinone, and conjugates
Toluene	18.0[a]	1021[a]	4–5 h	15–72 h	Extensive liver extraction and metabolism	80% metabolized to benzyl alcohol; 70% renally excreted as hippuric acid
o-Xylene	34.9	1877[a]	30–60 min	20–30 h	Liver CYP 2E1 oxidation	Toluic acid, methyl hippuric acid
Halogenated						
Methylene chloride	8.94	120[a]	Apparent $t_{1/2}$ of COHb 13 h	40 min	92% exhaled unchanged. Low doses metabolized; high doses exhaled. Two liver metabolic pathways	(a) CYP 2E1 to CO and CO_2 (b) Glutathione transferase to CO_2, formaldehyde, formic acid
Carbon tetrachloride	2.73	359[a]	84–91 min[a]	91–496 min[a]	Liver CYP 2E1, some lung exhalation (dose-dependent)	Trichloromethyl radical, trichloromethyl peroxy radical, phosgene
Trichloroethylene	8.11	554[a]	3 h	30 h	Liver CYP 2E1—epoxide intermediate; trichloroethanol is glucuronidated and excreted	Chloral hydrate, trichloroethanol, trichloroacetic acid
1,1,1- Trichloroethane	2.53	263[a]	44 min	53 h	91% exhaled; liver CYP 2E1	Trichloroacetic acid, trichloroethanol
Tetrachloroethylene	10.3	1638[a]	160 min	33 h	80% exhaled; liver CYP 2E1	Trichloroacetic acid, trichloroethanol

[a] Fat/blood partition coefficient is obtained by dividing the fat/air coefficient by the blood/air coefficient, as determined in rat models. All coefficients are determined at 98.6°F (37°C).

Inhlation is a major route of exposure for most volatile hydro- carbons. The absorbed dose is determined by the air concentration, duration of exposure, minute ventilation, and the blood-to-air partition coefficient. Most hydrocarbons cross the alveolus through passive diffusion. The driving force for this is the difference in vapor concentration between the alveolus and the blood. Hydrocarbons that are highly soluble in blood and tissues are readily absorbed through inhalation, and blood concentrations rise rapidly following inhalation exposure. Aromatic hydrocarbons are generally well absorbed through inhalation, absorption of aliphatic hydrocarbons varies by molecular weight: aliphatic

hydrocarbons with between 5 and 16 carbons are readily absorbed, through inhalation, whereas those with more than 16 carbons are less readily absorbed.

Absorption of aliphatic hydrocarbons through the digestive tract is inversely related to molecular weight, ranging from complete absorption at lower molecular weights, to approximately 60% for C-14 hydro- carbons, 5% for C-28 hydrocarbons, and essentially no absorption for aliphatic hydrocarbons with more than 32 carbons. Oral absorption of aromatic hydrocarbons with between 5 and 9 carbons ranges from 80% to 97%. Oral absorption data for aromatic hydrocarbons with more than 9 carbons are sparse.

While the skin is a common area of contact with solvents, for most hydrocarbons the dose received from dermal exposure is a small fraction of the dose received through other routes, such as inhalation. When xenobiotics have near equality in the water-to-lipid partition coefficient, their rate of skin absorption is increased. Solvents that contain both hydrophobic and hydrophilic moieties (eg, glycol ethers, dimethylformamide, dimethylsulfoxide) are particularly well absorbed dermally.

The dose received via skin absorption will also depend on the surface area of the skin exposed and the duration of contact. Though highly volatile compounds may have a short duration of skin contact because of evaporation, skin absorption can also occur from contact with hydrocarbon vapor. In studies with human volunteers exposed to varying concentrations of hydrocarbon vapors, the dermal dose accounted for only 0.1%–2% of the inhalation dose.

Once absorbed into the central compartment, hydrocarbons are distributed to target and storage organs based on their tissue-to-blood partition coefficients and on the rate of perfusion of the tissue with blood. During the onset of systemic exposure, hydrocarbons accumulate in tissues that have tissue/blood coefficients greater than 1 (eg, for toluene, the fat-to-blood partition coefficient is 60). Table 2 lists the distribution half-lives of selected hydrocarbons.

Hydrocarbons can be eliminated from the body unchanged, for example, through expired air, or can be metabolized to more polar compounds, which are then excreted in urine or bile.

PATHOPHYSIOLOGY AND CLINICAL FINDINGS

■ RESPIRATORY

Several factors are classically associated with pulmonary toxicity after hydrocarbon ingestion. These include specific physical properties of the xenobiotics ingested, the volume ingested, and the occurrence of vomiting. Physical properties of viscosity, surface tension, and volatility are primary determinants of aspiration potential.

Hydrocarbons with low viscosities (eg, turpentine, gasoline, naphtha) have a higher tendency for aspiration in animal models.

Surface tension is a cohesive force generated by attraction (ie, Van der Waals forces)

between molecules. This influences adherence of a liquid along a surface ("its ability to creep"). The lower the surface tension, the less well the liquid will creep and the higher the aspiration risk.

Volatility is the tendency for a liquid to become a gas. Hydrocarbons with high volatility tend to vaporize, displace oxygen, and potentially lead to transient hypoxia.

It is not clear which physical property is most important in predicting toxicity. Early reports conflicted in attempting to relate risk of pulmonary toxicity to the amount of hydrocarbon ingested, or to the presence or absence of vomiting. One prospective study addressed both of these variables.

It is widely held that aspiration is the main route of injury from ingested simple hydrocarbons. The mechanism of pulmonary injury, however, is not fully understood. Intratracheal instillation of 0.2 mL/kg of kerosene causes physiologic abnormalities in lung mechanics (decreased compliance and total lung capacity) and pathologic changes such as interstitial inflammation, polymorphonuclear exudates, intraalveolar edema and hemorrhage, hyperemia, brochial and bronchiolar necrosis, and vascular thrombosis. These changes most likely reflect both direct toxicity to pulmonary tissue and disruption of the lipid surfactant layer.

Most patients who go on to develop pulmonary toxicity after hydrocarbon ingestion will have an episode of coughing, gagging, or choking. This usually occurs within 30 minutes after ingestion and is presumptive evidence of aspiration. Radiographic evidence of pneumonitis develops in 40%–88% of admitted aspiration patients. Findings can develop as early as 15 minutes or as late as 24 hours after exposure

CARDIAC

The most concerning cardiac effect from hydrocarbon exposure is precipitation of a dysrhythmia by myocardial sensitization (see Pharmacology previously). These events are described with all classes of hydrocarbons, but halogenated compounds are most frequently implicated, followed by aromatic compounds.

CENTRAL NERVOUS SYSTEM

Transient CNS excitation may occur after acute hydrocarbon inhalation or ingestion. More commonly, CNS depression or anesthesia occurs. In cases of aspiration, hypoxemia from pulmonary damage may contribute to the CNS depression. Coma and seizures are reported in 1%–3% of cases. Chronic occupational exposure or volatile substance use may lead to a chronic neurobehavioral syndrome; the painter's syndrome, most notably described after toluene overexposure. The clinical features include ataxia, spasticity, dysarthria, and dementia, consistent with leukoencephalopathy.

Animal models of toluene poisoning reveal norepinephrine and dopamine depletion. The severity and reversibility of this syndrome depends on the intensity and duration of toluene exposure. Infrequent exposure may produce no clinical neurologic signs, whereas heavy (eg, daily) use can lead to significant neurologic impairment after as little as one year, but

more commonly after 2–4 years of ongoing exposure. The specific cognitive and neuropsychological findings in toluene-induced dementia are termed a white matter dementia.

In the occupational setting, exposures are rarely as extensive as those that occur with volatile substance misuse. Given the significantly lesser exposures, the findings among workers overexposed to solvent concentrations above permissible exposure limits are often subclinical, and detected primarily through neurobehavioral testing.

GASTROINTESTINAL

Hydrocarbons irritate gastrointestinal mucous membranes. Nausea and vomiting are common after ingestion.

HEPATIC

The chlorinated hydrocarbons (Table 1) and their metabolites are hepatotoxic. In most cases, activation occurs via a phase I reaction to form a reactive intermediate. In the case of carbon tetrachloride, this intermediate is the trichloromethyl radical. This radical forms covalent bonds with hepatic macromolecules, and may initiate lipid peroxidation. Carbon tetrachloride causes centrilobular necrosis after inhalational, oral ingestion, or dermal exposure.

DERMATOLOGIC

Most hydrocarbon solvents cause nonspecific irritation of skin and mucous membranes. Repeated, prolonged contact can dry and crack the skin. The mechanism of dermal injury appears to be defatting of the lipid layer of the stratum corneum. Up to 9% of workers may develop eczematous lesions from dermal contact.

Contact dermatitis and blistering may progress to partial- and even full-thickness burns. Severity is proportional to duration of exposure. Hydrocarbons are irritating to skin. Acute, prolonged exposure can cause dermatitis and even full-thickness dermal damage. Chronic dermal exposure to kerosene or diesel fuel can cause oil folliculitis. A specific skin lesion called chloracne is associated with exposure to chlorinated aromatic hydrocarbons with highly specific stereochemistry (eg, dioxins, polychlorobiphenyls).

DIAGNOSTIC TESTING

Laboratory and ancillary testing for hydrocarbon toxicity should be guided by available information regarding the specific xenobiotic, the route of exposure, and the best attempt at quantifying the exposure. Inhalation or ingestion of hydrocarbons associated with pulmonary aspiration is most likely to result in pulmonary toxicity. The use of pulse oximetry and arterial blood gas testing in this group of patients is warranted when clinically indicated. Early radiography is indicated in patients who are severely symptomatic; however, radiographs performed immediately after hydrocarbon ingestion demonstrate a low predictive value for the occurrence of aspiration pneumonitis.

Patients observed for 6 hours after an ingestion, who demonstrate no abnormal pulmonary findings, have adequate oxygenation, are not tachypneic, and have a normal chest radiograph after the 6-hour observation period, have a good medical prognosis with very low risk of subsequent deterioration.

The choice of specific diagnostic laboratory tests to assess organ sys- tem toxicity or function following exposure to a hydrocarbon depends on the type, dose, and route of exposure, and on the assessment of the patient's clinical condition. Useful clinical tests may include pulse oximetry and an electrocardiogram (ECG). Laboratory tests include serum or urine electrolytes, arterial blood gas, complete blood counts, and creatine phosphokinase. If a hydrocarbon has specific target organ toxicities (eg, benzene/bone marrow, carbon tetrachloride/liver, or *n*-hexane/peripheral nervous system), evaluating and monitoring target organ system function is indicated.

Specific diagnostic testing for hydrocarbon poisoning can include (1) bioassays for the specific hydrocarbon or its metabolites in blood, breath, or urine, or (2) assessment of toxicity. Bioassays for a hydrocarbon are seldom necessary for diagnosis or management of hydrocarbon poisoning in the emergency setting and rarely clinically available.

When deciding whether to obtain a bioassay for a hydrocarbon, the clinician should determine the following: (1) What is the most informative biologic sample (blood, urine, breath) and how should it be collected, handled, and stored? (2) What are the kinetics of the hydrocarbon and the timing of exposure, and how should the results be interpreted in light of these kinetics? (3) What ranges of concentrations are associated with toxicity? Most hydrocarbon bioassays are performed by only a few, specialized clinical laboratories.

Chronic overexposures to hydrocarbons, as occur with volatile substance use, can result in persistent damage to the central nervous system. Damage can be detected and quantified using neuroimaging methods such as magnetic resonance imaging (MRI) or positron emission tomography (PET).

MANAGEMENT

Identification of the specific type, route, and amount of hydrocarbon exposure is rarely essential to achieve effective management.

Decontamination is one of the cardinal principles of toxicology, with priority that is second only to stabilization of the cardiopulmonary status. Safe decontamination can avoid further absorption and avoids secondary casualties in those attempting to provide care.

Exposed clothing should be removed and safely discarded as further absorption or inhalation of hydrocarbons from grossly contaminated clothing can worsen systemic toxicity. Decontamination of the skin should have a high priority in massive hydrocarbon exposures, particularly those exposures involving highly toxic hydrocarbons (Table 3). Water alone may be ineffective in decontaminating most hydrocarbons, but early decontamination with soap and water may be adequate. The caregiver should remain aware that certain hydrocarbons are highly flammable and pose a fire risk to hospital staff. Several studies have attempted to evaluate the role of gastric decontamination after hydrocarbon

ingestion. Results were largely inconclusive and the level of evidence, poor.

In the absence of a contraindication, gastric emptying is potentially useful only when the hydrocarbon has inherent severe toxicity or is co-ingested with a more potent xenobiotic (Table 3). Patients who have no symptoms at home or upon initial medical evaluation are unlikely to need gastric emptying. For patients who do undergo gastric emptying, gastric lavage is likely the superior method. If lavage is performed, a small nasogastric tube (18-French, not a large-bore tube) should be employed. If no gag reflex is present, an endotracheal tube should be placed prior to lavage.

Activated charcoal (AC) has limited ability to decrease gastrointestinal absorption of hydrocarbons and may distend the stomach and predispose patients to vomiting and aspiration. The use of AC may be justified in patients with mixed overdoses, but its role in isolated hydrocarbon ingestions appears very limited. The use of cathartics and promotility agents for hydrocarbon ingestions is also of limited importance in current management.

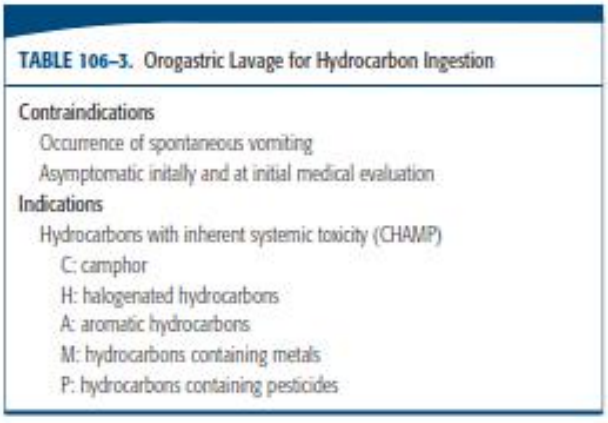

TABLE 106–3. Orogastric Lavage for Hydrocarbon Ingestion

Contraindications
Occurrence of spontaneous vomiting
Asymptomatic initally and at initial medical evaluation
Indications
Hydrocarbons with inherent systemic toxicity (CHAMP)
C: camphor
H: halogenated hydrocarbons
A: aromatic hydrocarbons
M: hydrocarbons containing metals
P: hydrocarbons containing pesticides

Table 3: *Orogastric Lavage for Hydrocarbon Ingestion.*

Antibiotics are frequently administered in the setting of hydrocarbon pneumonitis to treat possible bacterial superinfection. Despite this, animal models, including guinea pigs, dogs, and baboons, did not demonstrate any efficacy of prophylactic antibiotics.

Antibiotic administration may be justified in severely poisoned patients. Ideally, sputum cultures should direct antibiotic use. These, however, are often delayed and are not useful in critically ill patients. Most authorities do not recommend prophylactic antibiotics. Most recommend close observation of temperature and blood leukocyte count, as delayed elevation (24 hours after presentation) of temperature and/or leukocytes may signal bacterial superinfection

Corticosteroids, like antibiotics, have been prophylactically administered in the setting of hydrocarbon pulmonary toxicity. The rationale for their use is prevention and limitation of the inflammatory response in the lungs after hydrocarbon injury. Animal models do not show any benefit of corticosteroid administration. In one study, corticosteroids increased the risk for bacterial superinfection with or without concomitant antibiotics. Furthermore, two controlled human trials failed to show a benefit from corticosteroid administration.

Respiratory distress requiring mechanical ventilation in this setting may be associated with large ventilation–perfusion mismatch.

Management of dysrhythmias associated with hydrocarbon toxicity should include consideration of electrolyte and acid–base abnormalities such as hypokalemia and acidosis result from toluene, hypoxemia, hypotension, and hypothermia.

A number of investigators have suggested protocols for determining which patients can be safely discharged. None of these protocols has been prospectively validated. However, rational guidelines for hospitalization can be recommended. Those patients, who have clinical evidence of toxicity, and most individuals with intentional ingestions, should be hospitalized. Patients, who do not have any initial symptoms, have normal chest radiographs obtained at least 6 hours after ingestion, and who do not develop symptoms during the 6-hour observation period can be safely discharged. Care should be individualized for patients who are asymptomatic but who have radiographic evidence of hydrocarbon pneumonitis, and for patients who have initial respiratory symptoms but quickly become asymptomatic during medical evaluation. Reliable patients may be considered for possible discharge with next-day follow up.