CHAPTER 106
HYDROCARBONS

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Our present world could not exist without hydrocarbons. Nearly everything we touch today is either comprised of or coated with hydrocarbon products. In the practice of clinical toxicology, initial efforts usually entail precisely determining the specific xenobiotics that might be involved in a specific exposure, followed by defining the type and extent of the exposure. In this regard, hydrocarbon exposures are always clinically challenging. Despite significant chemical diversity, most classification schemes group hydrocarbons by specific uses or applications, rather than by chemical structure or physiologic properties. Most hydrocarbons in everyday use, such as gasoline, charcoal starter, and lamp oil, are actually mixtures of chemicals obtained from a common distillation fraction. The chemical diversity within a mixture makes it challenging to try to assess individual contribution to toxicity. As a result, generalities are often needed to describe the behavior of these complex mixtures. This chapter focuses primarily on toxicity of hydrocarbons present in such mixtures. Individual hydrocarbons are addressed only when they are commonly available in purified form, or when individual xenobiotics present unique toxicologic concerns.

HISTORY AND EPIDEMIOLOGY

Organic chemistry originated in the industrial revolution and evolved largely because of advances in coal tar technology. Coal liberates hydrocarbons in the coking process, when bituminous (soft) coal is heated to remove coal gas. The gas is then separated into a variety of natural gases. The viscous residue from the heating process forms coal tar, which can be further distilled into kerosene and other hydrocarbon mixtures.

Over the years, crude oil has replaced coal tar as the most common source for distillation of organic compounds. Crude oil distillation involves heating the oil to fixed temperatures in large-scale processors that separate hydrocarbons into fractions by vapor (boiling) point. Because of the relationship between boiling point and molecular weight, distillation roughly divides hydrocarbons into like-sized molecules. The most volatile fractions come off early, as gases. These are used primarily as heating fuels. The least volatile fractions (larger than about 10 carbons) are used chiefly for lubricants or as paraffins, petroleum jelly, or asphalt. The remaining volatile distillation fractions (C_5 to C_{10}) are the ones most commonly used in combustion fuels and as solvents. Petroleum distillates are also used as chemical feedstocks and as precursors or intermediates for production. The many contemporary applications of petroleum distillates in consumer and household products include paints and thinners, furniture polish, lamp oils, and lubricants (Table 106–1).

Mineral oil, castor oil, and glycerine are commonly used as laxatives. Hydrocarbon-based ointments, petroleum jelly, and camphor are used topically on skin and mucous membranes. Volatile oils (or essential oils) are fragrant hydrocarbon plant extracts. Examples include menthol, eucalyptus oil, clove oil, sassafras oil, and pennyroyal, among others. These oils have had a variety of medicinal uses over many centuries and are enjoying a resurgence with recent popularity of herbal products (Chap. 43). Phenol and substituted phenols are common medical disinfectants (Chap. 102). Diethyl ether and halogenated hydrocarbon compounds, like chloroform, were among the first general anesthetics used more than 150 years ago. Cyclopropane and trichloroethylene (TCE) were also widely used anesthetics.[135]

Three populations appear to be at particular risk for hydrocarbon-related illness, children who have unintentional exposures, often dermal or ingestions, workers with occupational exposures, often dermal and inhalational, and adolescents or young adults who intentionally abuse solvents through inhalation. Specific occupations at risk for exposure include petrochemical workers, plastics and rubber workers, painters, laboratory workers, painters, and hazardous waste workers. The Occupational Safety and Health Administration (OSHA) estimates that nearly 238,000 American workers are exposed annually to significant concentrations of benzene alone.[22] But the epidemiology of hydrocarbon exposure and hydrocarbon-related illness is difficult to assess. Most exposures do not involve ingestion, and most do not result in illness. Because a common property of hydrocarbons is volatility, inhalation is extremely common. Lipid solubility facilitates dermal absorption when skin is exposed.[63] Exposures may range from self-pumping gasoline, to painting a spare bedroom, to applying or removing fingernail polish. Table 106-1 lists frequently encountered hydrocarbon compounds and properties.

During the years 2003 to 2007, American poison centers reported 52,398 average yearly human hydrocarbons exposures to the American Association of Poison Control Centers (AAPCC). These exposures accounted for 2.2% of total human exposures reported. The incidence of exposures has not changed appreciably in the AAPCC database since the first report in 1983. Over the most recent 5-year period, 3% of reported human exposures to hydrocarbons involved minor exposures in children younger than 6 years of age. Exposures in young children appear to be declining over the past decade of AAPCC reports, but this may be an artifact of the way in which cases are reported to the database. Within the AAPCC database, many thousands of hydrocarbon exposures are not listed as such, but are ascribed to chemicals, pesticides, personal care products, cleaning substances, paints, automotive products (see Chap. 135). The alarming rate of intentional misuse of volatile solvents by young people and the concomitant risk of death from volatile substance abuse is discussed in Chap. 81.

CHEMISTRY

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 (gasoline, vegetable oil), animal fats (cod liver oil), natural gas, petroleum, and coal tar. There are two basic types of hydrocarbon molecules, *aliphatic* (straight or branched chains) and *cyclic* (closed ring), each with its own subclasses. The aliphatic compounds include the *paraffins* (*alkanes*, with a generic formula C_nH_{2n+2}); the *olefins* (*alkenes* have one double bond and *alkadienes* have two double bonds); *acetylenes* (*alkynes*, with at least one triple bond; and the *acyclic terpenes* (polymers of isoprene, C_5H_8). Some aliphatic compounds have branches in which a subchain also contains carbon atoms; both the chain and branches are essentially straight.

The cyclic hydrocarbons include *alicyclic* (three or more carbon atoms in a ring structure, with properties similar to the aliphatics) and *aromatic* compounds, as well as the *cyclic terpenes*. The alicyclics are further divided into *cycloparaffins* (*naphthenes*) such as cyclohexane and the *cycloolefins* (two or more double bonds) such as cyclopentadiene.

Saturated hydrocarbons contain carbon atoms that exist only in their most reduced state. This means that each carbon is bonded to either hydrogen or to another carbon, with no double or triple bonds

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

[a] Direct values for kinematic viscosity in Saybolt universal seconds (SUS) were not available for the following compounds: naphtha, xylene, methylene chloride, carbon tetrachloride, trichloroethylene, perchloroethylene, and toluene. SUS was calculated by converting from available measurements in centipoise viscosity and/or centistokes viscosity using the following conversions: the value in centistokes is estimated by dividing centipoise by density at 68°F (20°C); SUS is approximated from centistokes using $y = 3.2533x + 26.08$ ($R^2 = 0.9998$). Centipoise viscosity for naphtha was estimated from the value for butylbenzene. Centipoise viscosity for xylene is the average of *o*-, *m*-, and *p*-xlylene.

present. Conversely, *unsaturated* compounds are those with hydrogens removed, in which double or triple bonds exist.

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.

Aromatic hydrocarbons are divided into the *benzene* group (one ring), *naphthalene* group (two rings), and the *anthracene* group (three rings). *Polycyclic aromatic hydrocarbons* (polynuclear aromatic hydrocarbons) have multiple, fused benzene-like rings. Aromatic organic compounds may also be *heterocyclic* (where oxygen or nitrogen substitutes for carbon in the ring). Structurally, all of these molecules are flat, with reactive electron clouds above and below the ring.

The *cyclic terpenes* are the principal components of the variety of plant-derived essential oils, often providing color, odor, and flavor. *Limonene* in lemon oil, *menthol* in mint oil, *pinene* in turpentine, and *camphor* are all terpenes (Chap. 42).[108]

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.[104]

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. A number of additives may go into the final formulation: alkyl leads, ethylene dichloride, and ethylene dibromide in leaded gasoline, and oxygenates such as methyl *t*-butyl ether (MTBE), as well as methanol and ethanol.[170]

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. Their toxicity is discussed in Chaps. 77 and 107. *Ethers* contain an oxygen bound on either side by a carbon atom. Acute toxicity from ethers tends to mirror that of the corresponding alcohols. *Aldehydes* and *ketones* contain a single carbon-oxygen double bond (C=O), the former at a terminal carbon, the latter somewhere in the middle. Organic *acids, esters, amides,* and *acyl halides* represent more oxidized states of carbon; human toxicity is agent-specific.

Phenols consist of benzene rings with an attached hydroxyl (alcohol) group. The parent compound, phenol, has only one hydroxyl group attached to benzene. The toxicity of phenol can be dramatically altered by addition of other functional groups to the benzene ring (Chap. 102). Cresols, catechols, and salicylate are examples of substituted phenols.

A variety of amines, amides, nitroso and nitro compounds, as well as phosphates, sulfites, and sulfates are used commercially and industrially. The addition of these functional groups to hydrocarbons dramatically alters the toxicity of the compound.

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.[140] 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 (see Chap. 67). 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.[87] Dose–response curves suggest that essentially no individual

will be rendered unconscious by an inhaled dose 30% below the MAC. However, impairment of cognitive and motor function may occur with much lower exposures.[18]

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.[94] The property of an inhaled anesthetic that correlates most closely with its ability to extinguish nociception is its lipid solubility. The Meyer-Overton hypothesis, proposed more than 100 years ago, implies that an anesthetic dissolves into some critical lipid compartment of the CNS, causing inhibition of neuronal transmission. In this construct, the target structure for general anesthetics is the neuronal lipid membrane itself.[64]

Inhaled hydrocarbons and other volatile anesthetic xenobiotics (Chap. 67) exhibit pharmacodynamic properties suggestive of a receptor-ligand interaction. The sigmoidal dose-response curves exhibit a near-linear midrange with a plateau effect at higher inhaled concentrations. Different xenobiotics produce curves whose linear segments parallel one another, implying that each xenobiotic produces the same physiologic effect at a particular concentration related to that xenobiotic's potency.[121] Thus, it has long been tempting to find the single, intangible "receptor" responsible for general anesthesia, and in doing so, to improve upon the Meyer-Overton hypothesis.

Unfortunately, a single mechanism remains elusive. Halothane, isoflurane, sevoflurane, enflurane, and desflurane inhibit fast sodium channels.[117] Toluene, trichloroethylene, perchloroethylene, and others inhibit neuronal calcium currents.[113,136] The halogenated hydrocarbons increase the outward potassium rectifying current.[137] Specific ligand-receptor interactions occur,[43] such as the inhibition of receptor function at nicotinic,[165] and at the glutamate receptors,[42] as well as enhancement of type-A γ-aminobutyric acid ($GABA_A$) and glycine receptor currents.[16] Independent of other mechanisms, halogenated hydrocarbons appear to decrease exocytosis of neuronal synaptic vesicles.[68] This growing body of research suggests that the Meyer-Overton hypothesis is too simplistic to explain the differences in pharmacologic profiles observed with this wide class of xenobiotics.

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. Sensitization occurs with both xenobiotic and class specificity. Ethylene and aliphatic ethers are very poor sensitizers. Aromatic, and even more so the halogenated hydrocarbons, are often potent sensitizers.[23]

Cardiac sensitization is incompletely understood.[43] Halothane and isoflurane inactivate sodium channels,[141] whereas chloroform and others attenuate potassium efflux through voltage-gated channels.[133] Sensitization may be mediated by slowed conduction velocity through membrane gap junctions. Dephosphorylation of connexin-43 results in a configurational change that increases gap junctional resistance. 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.[77]

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. The blood-to-air and tissue-to-air tissue-to-blood coefficients directly relate to the pulmonary uptake and distribution of hydrocarbons. The tissue-to-blood partition coefficient is commonly determined by dividing the tissue-to-air coefficient by the blood-to-air coefficient.[53,120] Table 106–2 lists the partition coefficients for commonly encountered hydrocarbons. Where human data is limited, rat data is presented in the table, because human and rat data often correlate.[120]

Inhalation is a major route of exposure for most volatile hydrocarbons. 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.[3]

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 hydrocarbons, 5% for C-28 hydrocarbons, and essentially no absorption for aliphatic hydrocarbons with more than 32 carbons.[3] 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 many hydrocarbons the dose received from dermal exposure is a small fraction of the dose received through other routes, such as inhalation. The skin is comprised of both hydrophilic (proteinaceous portion of cells) and lipophilic (cell membranes) regions. While many hydrocarbons can remove lipids from the stratum corneum, permeability is not simply the result of lipid removal; permeability also increases with hydration of the skin. 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.[94] Other factors, in addition to the partition coefficient and permeability constant, that determine penetration across the skin, include the thickness of the skin layer, the difference in concentration of the solvent on either side of the epithelium, the diffusion constant, and skin integrity (ie, normal versus cut or abraded).

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. With massive exposure (eg, whole-body immersion), dermal absorption may contribute significantly to toxicity. Significant dermal absorption with resultant toxicity is described with carbon tetrachloride,[76] tetrachloroethylene,[63] and phenol.[93]

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

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	459[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).

in tissues that have tissue/blood coefficients greater than 1 (eg, for toluene, the fat-to-blood partition coefficient is 60). Table 106-2 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. Table 106-2 lists the blood elimination half-lives (for first-order elimination processes) and metabolites of selected hydrocarbons. Some hydrocarbons are metabolized to toxic compounds (eg, methylene chloride, carbon tetrachloride, *n*-hexane, methyl-*n*-butyl ketone). The specific toxicities of these metabolites are discussed under Special Cases later in the chapter.

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.

Dynamic (or absolute) viscosity is the measurement of the ability of a fluid to resist flow. This property is measured with a rheometer and is typically given in units of pascal-seconds. More frequently, engineers work with *kinematic viscosity*, measured in square millimeters per second, or centistokes. Dynamic viscosity is converted to kinematic viscosity by dividing the dynamic viscosity by the fluid's density. An older system for measuring viscosity was initially popularized by the petroleum industry and expresses kinematic viscosity in units of Saybolt Universal seconds (SUS). Unfortunately, many policy statements were developed in an era when SUS units were popular, so many still describe viscosity in SUS units. Various look-up tables and calculators are available to convert kinematic viscosity to SUS units. Table 106-1 shows kinematic viscosity of common hydrocarbons, measured in SUS. A unit conversion approximation is given in the table's footnote.

Hydrocarbons with low viscosities (less than 60 SUS; eg, turpentine, gasoline, naphtha) have a higher tendency for aspiration in animal models. The US Consumer Products Safety Commission issued a rule requiring child-resistant packaging for products that contain 10% or more hydrocarbon by weight and that have a viscosity less than 100 SUS.[160]

Surface tension is a cohesive force generated by attraction (ie, Van der Waals forces) between molecules.[118] 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.[55]

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. The cooperative kerosene poisoning (COKP) study was a multicenter study that enrolled 760 cases of hydrocarbon ingestion. Of these, 409 could provide an estimate of the amount ingested. Patients who reportedly ingested more than 30 mL had a 52% chance of developing pulmonary complications, compared with 39% of those who ingested less than 10 mL. Risk of central nervous complications was 41%, compared with 24% using the same criterion. There was a 53% incidence of pulmonary toxicity when vomiting occurred, compared with 37% when there was no history of vomiting.[122] While this knowledge may help modify the index of suspicion regarding possible pulmonary toxicity, none of these parameters is completely predictive. Severe hydrocarbon pneumonitis may occur after ingestion of "low-risk" hydrocarbons.[131] Patients may develop severe lung injury after low-volume (less than 5 mL) ingestions, as well as after ingestions with no history of coughing, gagging, or vomiting.[9]

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, bronchial and bronchiolar necrosis, and vascular thrombosis.[11,61,156] These changes most likely reflect both direct toxicity to pulmonary tissue and disruption of the lipid surfactant layer.[173]

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. The majority of patients who have respiratory signs and symptoms beyond the initial history of gagging, choking, and coughing develop radiographic pneumonitis.[9] Absence of tachypnea on initial evaluation has 80% negative predictive value for pneumonitis.[168] Pulmonary toxicity may manifest as crackles, rhonchi, bronchospasm, tachypnea, hypoxemia, hemoptysis, acute lung injury (hemorrhagic or non-hemorrhagic), or respiratory distress.[156] Cyanosis develops in approximately 2% to 3% of patients.[99] This may result from simple asphyxiant effects from volatilized hydrocarbons, from ventilation–perfusion mismatch, or, rarely, from methemoglobinemia (aniline, nitrobenzene, or nitrite-containing hydrocarbons). Clinical findings often worsen over the first several days but typically resolve within a week. Death is rare (less than 2%), and typically occurs after a severe, progressive respiratory insult marked by hypoxia, ventilation–perfusion mismatch, and barotrauma.[14,180]

Intravenous (IV) and subcutaneous injection of hydrocarbons have been reported.[129,162] Severe hydrocarbon pneumonitis may occur following intravenous exposure. Animal experiments show that intravascular hydrocarbons injure the first capillary bed encountered. Intravenous injection thus causes pulmonary toxicity, and portal vein injection leads to direct hepatic injury.[127,175] The clinical course after IV hydrocarbon injection mirrors that of aspiration injury.

Radiographic evidence of pneumonitis develops in 40%–88% of admitted aspiration patients.[15,44,114,125] Findings can develop as early as 15 minutes or as late as 24 hours after exposure (Fig. 106–1).[36,51,122,163] Chest radiographs performed immediately on initial presentation are not useful in predicting infiltrates in either symptomatic or asymptomatic patients.[168] Ninety percent of patients who develop radiographic abnormalities do so by 4 hours postingestion.[36] Clinical signs of pneumonia (eg, crackles, rhonchi) are evident in 40%–50% of patients.[44] A small percentage (less than 5%) are completely asymptomatic after a period of observation, but still have radiographic findings.[9]

Specific radiologic findings include perihilar densities, bronchovascular markings, bibasilar infiltrates, and pneumonic consolidation. Right-sided involvement occurs in 75% of cases and bilateral involvement in approximately 50%. Upper-lobe involvement is uncommon. Pleural effusions develop in 3% of cases, with one-third appearing within 24 hours.[98] Pneumothorax, pneumomediastinum, and pneumatoceles occur uncommonly.[11,17,79] Initial radiographs after ingestion may reveal two liquid densities in the stomach, known as the "double bubble" sign. This represents an air–fluid (hydrocarbon or water) and a hydrocarbon–water interface, as the hydrocarbon is not miscible with gastric fluids (primarily water) and may have a specific gravity less than that of water.[37]

Radiographic resolution does not correlate with clinical improvement, but rather lags behind by several days to weeks. There are few reports of long-term follow up on patients with hydrocarbon pneumonitis.[25,51,62,125,152] Frequent respiratory tract infections are described in individuals after hydrocarbon pneumonitis, but studies addressing this are poorly controlled.[51,156] Delayed formation of pneumatoceles may occur.[17,79] Bronchiectasis and pulmonary fibrosis are reported but appear to be uncommon.[59,125] In one study, 80% of patients examined 8–14 years after hydrocarbon-induced pneumonitis had asymptomatic minor pulmonary function abnormalities. The abnormalities were consistent with small-airway obstruction and loss of elastic recoil. The authors hypothesized that this group may be predisposed to chronic obstructive pulmonary disease.[62]

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.[13,126] Malignant dysrhythmias occur after exposure to high concentrations of volatile inhalants or inhaled anesthetics. Atrial fibrillation, ventricular tachycardia, junctional rhythm, ventricular fibrillation, and cardiac arrest are reported.[103,111,126] This is termed the "sudden sniffing death syndrome." Myocardial depression occurs by an unclear mechanism. Prolongation of the QT interval raises concern for torsades de pointes.[14,88,133]

Any route of exposure to hydrocarbons may result in cardiotoxicity. Classically, sudden death follows an episode of sudden exertion.[74] Tachydysrhythmias, cardiomegaly, and myocardial infarction are rarely reported after ingestion of hydrocarbons.[74,143] A retrospective followup cohort of exposed methylene chloride workers did not find evidence of excess long-term cardiac disease.[115]

CENTRAL NERVOUS SYSTEM

Transient CNS excitation may occur after acute hydrocarbon inhalation or ingestion.[88] More commonly, CNS depression or anesthesia occurs.[44] In cases of aspiration, hypoxemia from pulmonary damage may contribute to the CNS depression.[96,176] Coma and seizures are reported in 1%–3% of cases.[114,125,179] Chronic occupational exposure to 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.[49] Autopsy studies of the brains of chronic toluene abusers show atrophy and mottling of the white matter, as though the lipid-based myelin were dissolved away. Microscopic examination shows a consistent pattern of myelin and oligodendrocyte loss with relative preservation of axons.[86] Animal models of toluene poisoning reveal norepinephrine and dopamine depletion. The severity and reversibility of this syndrome depends on the intensity

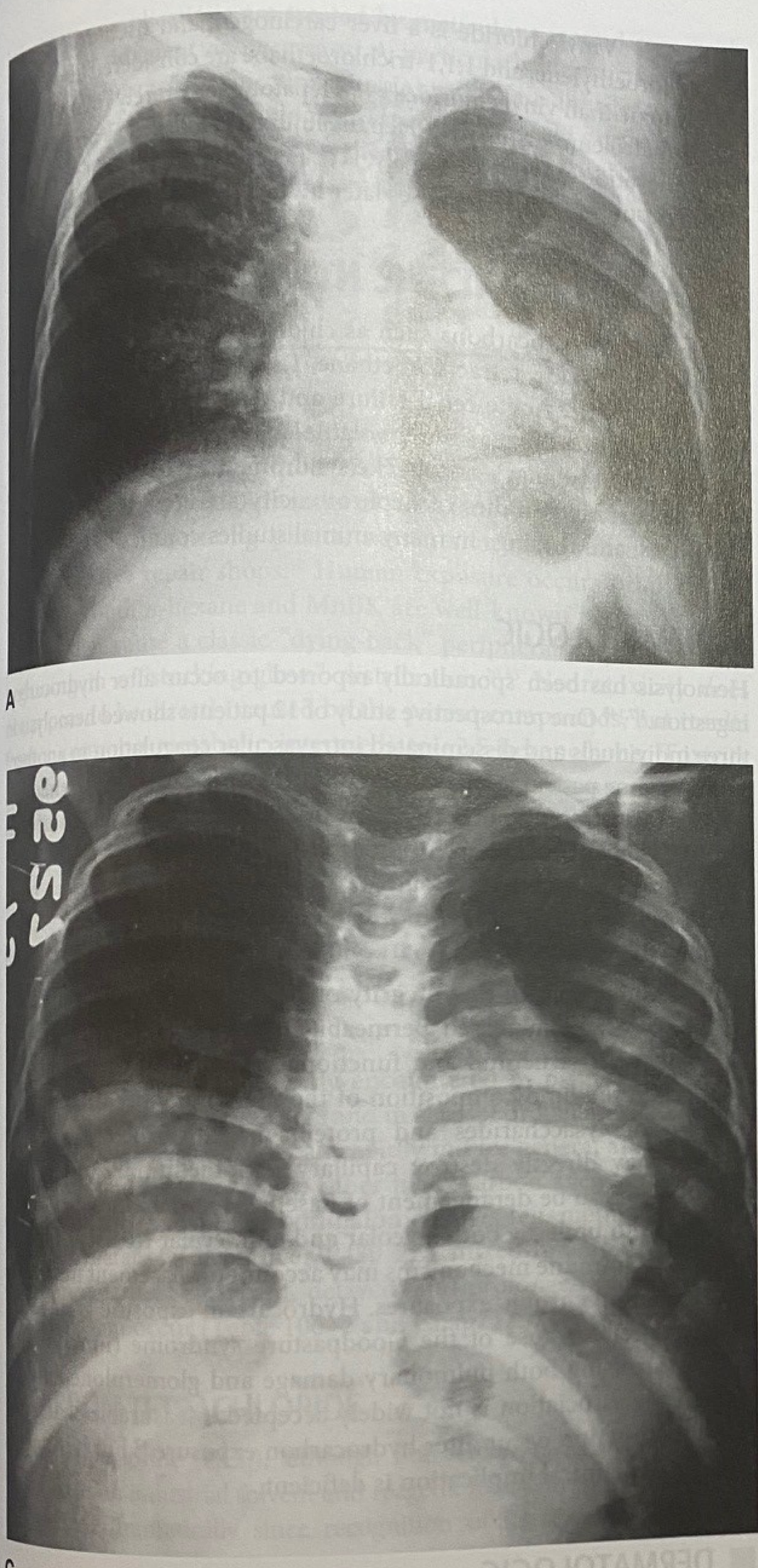

FIGURE 106–1. Three sequential radiographs of a young girl with severe hydrocarbon aspiration pneumonitis. (**A**) Initial: Patchy densities appear in basilar areas of both lung fields with increased interstitial markings and peribronchial thickening. (**B**) Day 2: More extensive diffuse alveolar infiltrates are apparent. (**C**) Day 6: Dense consolidation and atelectasis are evident in the right lower lobe. (*Images contributed by Nancy Genieser, MD, Professor of Radiology, New York University.*)

and duration of toluene exposure.[132] 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.[46,52]

Initial findings of white matter dementia include behavioral changes, impaired sense of smell, impaired concentration, and mild unsteadiness of hand movements and gait. Further exposure leads to slurred speech, head tremor, poor vision, deafness, stiff-legged and staggering gait, and subsequent dementia. Physical findings may include nystagmus, ataxia, tremor, spasticity with hyperreflexia, abnormal Babinski reflexes, deafness, impaired vision, and a broad-based, staggering gait. An abnormal brainstem auditory-evoked response appears to be a sensitive indicator of toluene-induced CNS damage. The electroencephalogram can show mild, diffuse slowing. Computed tomography in severe cases shows mild-to-moderate cerebellar and cortical atrophy. MRI findings are consistent with white matter disease. Most cases show significant clinical improvement after 6 months of abstinence, although with moderate to severe abuse, improvement may be incomplete. Chronic toluene misuse is addicting and can produce withdrawal.[132]

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. In rare cases, however, a worker may be acutely overexposed to solvent concentrations that can produce acute CNS depression. Repeated, symptomatic overexposures over long periods of time have the potential to lead to a chronic encephalopathy, as evident from the experience with solvent abusers.[46]

PERIPHERAL NERVOUS SYSTEM

Peripheral neuropathy is well described following occupational exposure to *n*-hexane or methyl-*n*-butyl ketone (MnBK).[20] This axonopathy results from a common metabolic intermediate; 2,5-hexanedione. The mechanism by which this intermediate causes peripheral neuropathy probably relates to decreased phosphorylation of neurofilament proteins, with disruption of the axonal cytoskeleton (see Special Cases below). Methyl ethyl ketone (MEK) may exacerbate this neurotoxicity, probably by interfering with metabolic pathways of *n*-hexane and MnBK.[8,130] Other organic solvents, such as carbon disulfide, acrylamide, and ethylene oxide, may cause a similar peripheral axonopathy.[58] Cranial and peripheral neuropathies are reported after acute and chronic exposure to trichloroethylene (TCE).[78,92,149] Pathologically, TCE appears to induce a myelinopathy.[47,58]

Trichloroethylene is also associated with trigeminal neuralgia.[31,45,92] Trigeminal nerve damage was documented by evoked potentials following 15 minutes of TCE inhalation.[92] Some evidence suggests that decomposition products or impurities in TCE may be responsible for cranial neuropathy.[31,45]

Axonopathy from MnBK or *n*-hexane exposure typically begins in the distal extremities and progresses proximally (a classic, "dying-back" neuropathy) (see Chap. 18). Exposure to one of these hydrocarbons should be considered in the differential diagnosis of the patient with Guillain-Barré syndrome (GBS) although sensory findings are present with MnBK and absent in GBS.[139] The longest axons appear to be affected initially, so that the patient manifests a "length-dependent polyneuropathy." With discontinuation of exposure many of the effects reverse over weeks to months.[69,82,123,178] Alternatively, the phenomenon of "coasting" may occur, in which neuropathy progresses for a time (weeks to months) after discontinuation of the toxic insult.[139] A reversible peripheral neuropathy occurred in 40% of chronic toluene abusers and was characterized by severe motor weakness without sensory deficits or areflexia.[148] It is unclear whether the toluene in this series may have been contaminated by *n*-hexane or MnBK.[8,140]

GASTROINTESTINAL

Hydrocarbons irritate gastrointestinal mucous membranes. Nausea and vomiting are common after ingestion. As discussed earlier, vomiting may increase risk of pulmonary toxicity.[112,114,131] Hematemesis was reported in 5% of cases in one study.[112] Gastrointestinal ulcerations are seen in animal studies.[83]

HEPATIC

The chlorinated hydrocarbons (Table 106–1) and their metabolites are hepatotoxic. In most cases, activation occurs via a phase I reaction to form a reactive intermediate (Chap. 12). 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.[22] Carbon tetrachloride causes centrilobular necrosis after inhalational, oral ingestion, or dermal exposure.[101] Hepatotoxicity in animals has been ranked for common hydrocarbons as follows: carbon tetrachloride is greater than benzene, trichloroethylene is greater than pentane.[174] Vinyl chloride is a liver carcinogen, and trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane are considered less hepatotoxic than vinyl chloride.[101,154] Hepatotoxicity rarely follows tion of petroleum distillates.[75] Hepatic injury, manifested as amino ferase elevation and hepatomegaly, is usually reversible except in overexposures (see Special Cases later in the chapter).

RENAL

Halogenated hydrocarbons such as chloroform, carbon tetrachlo ethylene dichloride, tetrachloroethane, 1,1,1-trichloroethane, and are nephrotoxic. Acute renal failure and distal renal tubular occur in some painters and volatile-substance abusers.[81] causes a renal tubular acidosis like syndrome (see Toluene later chapter). Human studies of nephrotoxicity are confounded by exposures, and findings in many animal studies conflict.[2]

HEMATOLOGIC

Hemolysis has been sporadically reported to occur after hydrocar ingestion.[1,7,146] One retrospective study of 12 patients showed hemoly three individuals and disseminated intravascular coagulation in anoth Although one patient required transfusion, hemolysis is usually mild does not require red blood cell transfusion (also see discussion of ben zene's effects on bone marrow, under Benzene later in the chapter).

IMMUNOLOGIC

Hydrocarbons disturb the integrity of membrane lipid bilayers, caus ing swelling and increased permeability to protons and other ions. This alters the structural and functional integrity of the membran Changes in the lipid composition of the membrane occur, and mem brane lipopolysaccharides and proteins are disturbed.[138] Resulting toxicity may directly destroy capillary endothelium.[21] Additionally there appears to be derangement of basement membranes, and this postulated to underlie both alveolar and glomerular toxicity of hydro carbons.[144] Immune mechanisms may account for basement membrane dysfunction in chronic exposures. Hydrocarbon exposure is suggested as one possible cause of the Goodpasture syndrome (immune dis function causing both pulmonary damage and glomerulonephritis), though the association is not widely accepted. Measurable changes in immune function occur after hydrocarbon exposure,[12] but our knowledge of any clinical implication is deficient.

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.[177] Limonene and turpentine contain sensitizers that can rarely result in contact allergy (Chap. 20).

Contact dermatitis and blistering may progress to partial- and full-thickness burns.[65] Severity is proportional to duration of exposure. Hydrocarbons are irritating to skin. Acute, prolonged exposure can cause dermatitis and even full-thickness dermal damage.[65] 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).

Soft-tissue injection of hydrocarbon is locally toxic, leading to necrosis. Secondary cellulitis, abscess formation, and fasciitis can occur

Infectious complications are treated by meticulous wound care, with surgical debridement as necessary. A particularly destructive injury involves high-pressure injection-gun injury. These injuries typically involve the extremities, with high-pressure injection of grease or paint into the fascial planes and tendon sheaths. Emergent surgical debridement is necessary in most of these cases.[48,106]

HYDROCARBONS WITH SPECIFIC AND UNIQUE TOXICITY

n-HEXANE

Hexane is a six-carbon simple aliphatic hydrocarbon. It is a constituent of some brake-cleaning fluids, rubber cement, glues, spray paints, coatings, and silicones. Outbreaks of *n*-hexane–related neurotoxicity have occurred in printing plants, sandal shops, furniture factories, and automotive repair shops.[32] Human exposure occurs primarily by inhalation. Both *n*-hexane and MnBK are well-known peripheral neurotoxins that cause a classic "dying-back" peripheral polyneuropathy, beginning in a "stocking-glove" distribution.[20,33] Neurotoxicity does not appear to be directly caused by the parent compounds, but results from a common metabolic intermediate—2,5-hexanedione. Toxicity appears related to the ability of this intermediate to form a ringed pyrrole structure, which causes decreased phosphorylation of neurofilament proteins, disrupting the axonal cytoskeleton.[58] Similar five- and seven-carbon species do not induce similar neurotoxicity, except those that are direct precursor intermediates in the metabolic pathway producing 2,5-hexanedione[58,150] (see Fig. 106–2).

METHYLENE CHLORIDE

Methylene chloride is commonly encountered in paint removers, as well as in cleaners and degreasers and in aerosol propellants. Like other halogenated hydrocarbons, it can rapidly induce general anesthesia by inhalation or ingestion. Unlike other hydrocarbon agents, methylene chloride and similar one carbon halomethanes (eg, methylene dibromide) are metabolized by liver P450 2E1 mixed-function oxidase to carbon monoxide. Significant, delayed, and prolonged carboxyhemoglobinemia can occur (Table 106–2 and Chap. 125).[4,124]

CARBON TETRACHLORIDE

Carbon tetrachloride (CCl_4), although not actually a hydrocarbon, has been used as an industrial solvent and reagent. Its use in the United States has declined dramatically since recognition of its toxicity caused the Environmental Protection Agency (EPA) to restrict its commercial use.[3] Absorption occurs by all routes, including dermal. CCl_4 is an irritant to skin and mucous membranes and is a potent gastric irritant when ingested. As with other halogenated hydrocarbons, aspiration can result in pneumonitis, and systemic absorption may result in ventricular dysrhythmias.

More unique to CCl_4 exposures are hepatotoxicity and nephrotoxicity. Both occur more commonly with repetitive exposure (eg, occupational exposures).[34,76,153] Toxicity follows phase-I dehalogenation of the parent compound, which produces free radicals, causes lipid peroxidation and the production of protein adducts.[22] Localization of specific phase-I hepatic enzymes in the centrilobular area of the liver results in regionalized (zone 3) centrilobular injury after CCl_4 exposure (Chap. 26). Hepatotoxicity is typically manifested as reversible aminotransferase concentration elevations with or without hepatomegaly. Cirrhosis is reported in both animal models and in humans with prolonged overexposures. Nephrotoxicity is less-well studied but may result from a similar mechanism. The proximal convoluted tubule and the loop of Henle appear to be specifically targeted.[50] Carbon tetrachloride is a suspected human carcinogen.[3]

TRICHLOROETHYLENE

Trichloroethylene is a commonly used industrial solvent, cleanser, and degreaser. TCE was used for years as a general anesthetic agent, and hundreds of disposal sites in the United States. remain sources of ongoing human exposure. Its use as a general anesthetic was abandoned because of acute cardiotoxicity. TCE is also hepatotoxic, neurotoxic, and nephrotoxic in humans and animals. A recent report links TCE exposure to the development of neurodegenerative diseases, such as Parkinsonism.[54] This study has not been repeated or further validated.

An interagency group convened by the National Research Council recently assessed health risks associated with TCE. This group noted that compelling recent information implicates TCE as a human carcinogen. The final report calls upon federal agencies to finalize risk assessments so that informed risk management decisions about TCE can be made expeditiously.[107]

BENZENE

Benzene is hematotoxic and associated with acute hemolysis, or the delayed development of aplastic anemia and acute myelogenous leukemia.[5,57,89,100,119] Other aromatic hydrocarbons that are reported to cause similar hematologic effects most likely are contaminated with benzene. An excess risk of hematologic toxicity has not been demonstrated in groups with long-term exposure to toluene, xylene, or other aromatic hydrocarbons.[10,40,128,164,172] Other hematologic malignancies also may be linked to benzene, including chronic myelocytic leukemia, myelodysplastic syndromes, and lymphoma.[155] Chromosomal changes are believed to provide a marker for carcinogenicity.[159] Because of the carcinogenic risk, most benzene-based solvents have been unilaterally removed from the US market, and OSHA has limited the permissible worker exposure level to 1 ppm.[72]

TOLUENE

Toluene has essentially replaced benzene as the primary organic solvent in many commercial products. Many oil paints and stains contain primarily toluene as solvent. As such, it is readily available and readily abused as an inhalant. The CNS sequelae of chronic solvent inhalation are most frequently related to chronic toluene exposure.

Chronic toluene abuse can also cause a syndrome that resembles transient distal renal tubular acidosis (RTA).[151,166] Although the mechanism is incompletely understood, the acidosis results in great part from

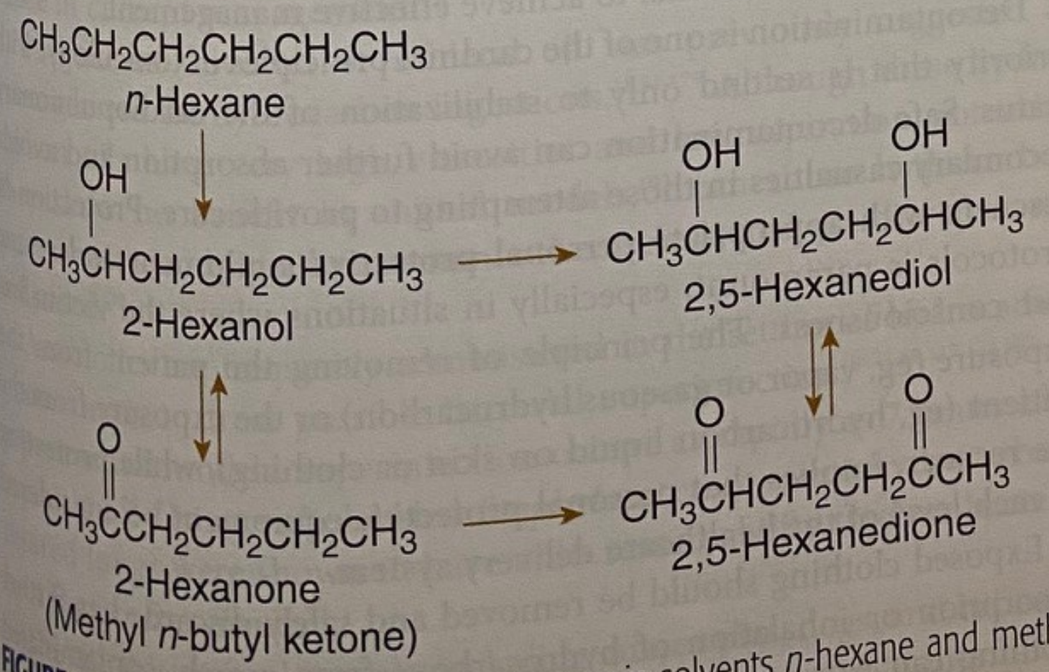

FIGURE 106–2. The metabolism of both organic solvents *n*-hexane and methyl *n*-butyl ketone produce the same common metabolite, 2,5-hexanedione.

the urinary excretion of hippuric acid (Table 106-2).[30,80] Renal potassium loss may be severe and can result in symptomatic hypokalemia.[80] Clinical findings are a hyperchloremic metabolic acidosis, hypokalemia, and aciduria. Typically an associated transient azotemia occurs, as well as proteinuria and an active urine sediment.[148,166] Some have reported a proximal RTA, or the Fanconi syndrome.[105,166] A metabolic acidosis resulting from the metabolism of toluene to benzyl alcohol through alcohol dehydrogenase to benzoic acid may be an adequate explanation for the serum and urine acid–base disturbances.

PINE OIL AND TERPENES

Pine oil is an active ingredient in many household cleaning products. It is a mixture of unsaturated hydrocarbons comprised of terpenes, camphenes, and pinenes. The major components are terpenes, which are found in plants and flowers. Wood distillates are products derived from pine trees and include pine oil and turpentine. Patients who ingest pine oil often emit a strong pine odor. Wood distillates are readily absorbed from the gastrointestinal tract and ingestion may cause CNS and pulmonary toxicity without aspiration.

The clinical features of pine oil ingestion can include CNS depression, respiratory failure, and gastrointestinal dysfunction and are rarely fatal.[85,171] Aspiration pneumonitis remains the primary clinical concern. Acute toxicity is similar to that of petroleum distillate ingestion, and management is similar. Rare reported complications of wood distillate ingestion include turpentine-associated thrombocytopenic purpura, acute renal failure, and hemorrhagic cystitis.[90,167]

TAR AND ASPHALT INJURY

Tar and asphalt injuries are common occupational hazards among construction workers. Asphalt workers are at risk for toxic gas exposure of hydrogen sulfide, carbon monoxide, propane, methane, and volatilized hydrocarbons.[70] In addition, cutaneous exposure to these hot hydrocarbon mixtures can cause severe burns. The material quickly hardens and is very difficult to remove. However immediate cooling with cold water is important to limit further thermal injury. Complete removal is essential to ensure proper burn management and to limit infectious complications. Attempts to mechanically remove hardened tar or asphalt often cause further damage. Dissolving the material with mineral oil, petroleum jelly, or antibacterial ointments are met with variable success. Surface-active agents combined with an ointment (De-Solv-it, Tween-80, Polysorbate 80) are more effective.[41,147,158]

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. In the asymptomatic patient, early radiography is not cost-effective. 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.[9,168]

The choice of specific diagnostic laboratory tests to assess organ system 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).[116] Laboratory tests include serum or urine electrolytes, arterial blood gas, complete blood count, and creatine phosphokinase. If a hydrocarbon has specific target organ toxicities (eg, benzene/bone marrow, carbon tetrachloride/liver, *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. Exceptions might include testing to assist in differential diagnosis (eg, testing for carbon tetrachloride in a comatose patient with unexplained hepatic and renal toxicity or a carboxyhemoglobin determination in a paint stripper with chest pain), testing for worker compensation purposes (eg, testing for urinary trichloroethanol and trichloroacetic acid in a worker exposed to trichloroethylene with unexplained headache, dizziness), or for forensic purposes (eg, sudden death in a huffer).

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 with 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. The analytic toxicologist can often assist the clinician in determining the appropriate choice and timing of a bioassay. Table 106-2 provides useful information on the elimination kinetics of selected hydrocarbons and on their common metabolites.

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). Major MRI findings in patients with chronic toluene abuse include atrophy, white matter T2 hyperintensity, and T2 hypointensity involving the basal ganglia and thalamus. Neurobehavioral testing can be used to detect subtle central nervous system effects following chronic occupational overexposures.

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 avoid secondary casualties in those attempting to provide care. Protection of rescuers with appropriate personal protective equipment and rescue protocols is paramount, especially in situations where the victim has lost consciousness. The principle of removing the patient from the exposure (eg, vapor or gaseous hydrocarbon) or the exposure from the patient (eg, hydrocarbon liquid on skin or clothing), while protecting the rescuer, implies that personal protective equipment be considered at each level of the healthcare delivery system.

Exposed clothing should be removed and safely discarded as hazardous. Dermal absorption or inhalation of hydrocarbons from grossly contaminated clothing can worsen systemic toxicity.[145] Decontamination of the skin

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

should have a high priority in massive hydrocarbon exposures, particularly those exposures involving highly toxic hydrocarbons (Table 106–3). 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 (see Chap. 130).

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 subset of patients who were randomized to receive gastric lavage, 44% had pulmonary complications, compared with 47% of those who were not lavaged. Available studies do not offer a conclusive answer to the question of gastric emptying after hydrocarbon ingestion.[122]

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 106-3). Patients who have no symptoms at home or upon initial medical evaluation are unlikely to need gastric emptying.[9,95] For patients who do undergo gastric emptying, gastric lavage is likely the superior method.[109,110,122] 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 (Chap. 7).

Activated charcoal (AC) has limited ability to decrease gastrointestinal absorption of hydrocarbons and may distend the stomach and predispose patients to vomiting and aspiration.[90,102,169] 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.

The use of olive oil or mineral oil was previously suggested as management for hydrocarbon ingestions.[15,51,179] Although these hydrocarbon oils have very high viscosities and low aspiration potential, they show no benefit in animal models,[102] can cause hydrocarbon pneumonitis and lipoid pneumonia themselves, and are therefore not indicated.[39]

Antibiotics are frequently administered in the setting of hydrocarbon pneumonitis to treat possible bacterial superinfection.[36,71,88,112,122,163] In experimental models, superinfection occurs as rapidly as 7 hours after aspiration.[71] Using radiolabeled *Staphylococcus aureus*, hydrocarbon-injured lungs were shown to have a decreased ability to clear bacteria by 4 hours after insult.[27]

Despite this, animal models, including guinea pigs, dogs, and baboons, did not demonstrate any efficacy of prophylactic antibiotics.[24,142,175] One study showed that administered antibiotic altered bacterial lung flora to predominantly Gram-negative organisms, compared to Gram-positive lung cultures in the controls.[24] These studies led to decreased use of prophylactic antibiotics, so that clinical evidence of infection dictated therapy for most clinicians.[44] This approach, however, is not without limitations. Abnormal lung auscultation, fever, leukocytosis, and abnormal radiographic findings are the initial manifestations of both bacterial pneumonia and hydrocarbon pneumonitis. Abnormal temperatures are reported to occur in 50%–90% of patients with hydrocarbon toxicity.[15,36,112,114] An elevated temperature is often initially noted, with the temperature reaching maximum at 8–12 hours, then declining over several days.[36,114] Leukocytosis is frequently reported, present in up to 60% of patients who aspirate hydrocarbons.[112,114,125]

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. No human studies are available to support either approach, and this issue remains controversial.

Corticosteroids, like antibiotics, have been prophylactically administered in the setting of hydrocarbon pulmonary toxicity.[59,122] 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.[6,24,142] In one study, corticosteroids increased the risk for bacterial superinfection with or without concomitant antibiotics.[24] Furthermore, two controlled human trials failed to show a benefit from corticosteroid administration.[66,97] It is clear that corticosteroid use does not improve the acute course of hydrocarbon pulmonary toxicity, although some authors suggest improved outcome with delayed corticosteroid therapy there is little supporting evidence.[79,84] Coupled with the possible increased risk of bacterial superinfection, corticosteroid administration in this setting is not recommended.

Patients with severe hydrocarbon toxicity pose unique problems for management. Respiratory distress requiring mechanical ventilation in this setting may be associated with a large ventilation–perfusion mismatch. The use of positive end-expiratory pressure (PEEP) in this setting is often beneficial. However, very high levels of PEEP may be required with subsequent increased risk of barotrauma.[131,180] High-frequency jet ventilation (HFJV), using very high respiratory rates (220–260) with small tidal volumes, has helped to decrease the need for PEEP.[28] Patients who continue to have severe ventilation–perfusion mismatch despite PEEP and HFJV have benefitted from extracorporeal membrane oxygenation (ECMO).[67,73,180] ECMO appears to be a useful option in severe pulmonary toxicity after other treatments have failed.

Cyanosis is uncommon after hydrocarbon toxicity. Although this is most often caused by severe hypoxia, methemoglobinemia associated with hydrocarbon exposure is reported.[35,91] The potential for methemoglobinemia should be investigated in patients who remain cyanotic following normalization of arterial oxygen tension.

Hypotension in severe hydrocarbon toxicity raises additional concerns. The etiology of hypotension in this setting is often compromise of cardiac output because of high levels of PEEP. Hydrocarbons do not have significant direct cardiovascular effects, and decreasing the PEEP may improve hemodynamics. The use of β-adrenergic agonists such as dopamine, epinephrine, isoproterenol, and norepinephrine should be avoided if possible, as certain hydrocarbons predispose to dysrhythmias.[14,126]

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. Ventricular fibrillation poses a specific concern, as common resuscitation algorithms recommend epinephrine administration to treat this rhythm. If it is ascertained that the dysrhythmia emanates from myocardial sensitization by a hydrocarbon solvent, catecholamines should be avoided. In this setting, lidocaine has been used successfully, as have β-adrenergic antagonists.[103]

Hyperbaric oxygen (HBO) was studied in a rat model of severe kerosene-induced pneumonitis.[134] HBO at 4 ATA showed some benefit in 24-hour survival rates. No followup studies have been performed. Patients with carbon tetrachloride poisoning, however, may benefit from hyperbaric oxygen (see Antidotes in Depth A37: Hyperbaric Oxygen).[26,157]

In the past, hospital admission was routinely recommended for patients who had ingested hydrocarbons, because of concern over possible delayed symptom onset and progression of toxicity.[36,60] Several reports documented patients with relatively asymptomatic presentations who rapidly decompensated with respiratory compromise. However, progressive symptoms after hydrocarbon ingestion are rare.[9,95] In a retrospective study of 950 patients, only 14 (1.5%) had progression of pulmonary toxicity.[9] Of these 14, seven had persistence of symptoms for less than 24 hours. Eight hundred patients were asymptomatic on initial evaluation with normal chest radiographs, remained asymptomatic after 6–8 hours of observation, and had a normal repeat radiograph. No patient in this group of 800 had progressive symptoms, and all were discharged without clinical deterioration. Seventy-one of the 950 patients had initial respiratory symptoms but were asymptomatic at initial medical evaluation. Of the 71 patients, 36 had radiographic evidence of pneumonitis. Among these 36 patients, 2 (6%) developed progression of pulmonary symptoms during their 6-hour observation period. Of the 35 who had a normal radiograph, 2 (6%) developed pulmonary symptoms and radiographic pneumonitis during the 6-hour observation period. The four patients who were hospitalized for progression of symptoms became asymptomatic over the next 24 hours and had no complications.

A separate poison center-based study evaluated 120 asymptomatic patients for an 18-hour telephone followup period.[95] Sixty-two patients had initial pulmonary symptoms that quickly resolved. One of the 62 patients (1.6%) developed progressive pulmonary toxicity. This patient was hospitalized and had resolution of symptoms within 24 hours without complications.

A number of investigators have suggested protocols for determining which patients can be safely discharged.[9,83,95] 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 followup.

SUMMARY

Hydrocarbons are a diverse group of xenobiotics that can cause toxicity by inhalation, ingestion, or dermal absorption. Most hydrocarbons occur as mixtures of several to many chemicals. Ubiquitous use of hydrocarbons in our society means that exposures are extremely common. Populations at particular risk for toxicity include children who ingest hydrocarbon compounds, workers who are occupationally exposed by inhalation or dermal absorption, and youths who intentionally inhale volatile hydrocarbons.

Toxicity is largely determined by the route of exposure, and is xenobiotic-specific. Aspiration pneumonitis is the primary concern after hydrocarbon ingestion. Many hydrocarbons are poorly absorbed from the gastrointestinal tract and unlikely to produce systemic poisoning. Acute systemic toxicity is unlikely to occur in the absence of CNS effects such as excitation or sedation. Most hydrocarbons are capable of producing profound CNS depression, even general anesthesia if absorbed systemically.

Specific hydrocarbons may demonstrate specific organ toxicity. Halogenated hydrocarbons are cardiotoxic, hepatotoxic, and nephrotoxic. Most are also acutely toxic to the CNS and some are peripheral neurotoxins. Diagnosis is predominantly clinical. Diagnostic studies are rarely specific, and hydrocarbon-specific studies are seldom helpful in the acute setting. Skin decontamination is important in massive dermal exposure. Gastrointestinal decontamination, as well as the use of prophylactic antibiotics or corticosteroids are rarely if ever indicated initially. Management is largely supportive, and no specific antidotes are available.

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