CHAPTER 13

Pharmaceuticals

Contents

1. Introduction 467
2. History 468
3. Hydrocarbon pharmaceuticals 471
   3.1. Mineral oil 471
   3.2. Paraffin oil 472
   3.3. Steroids 474
   3.4. Carotenoids and vitamins 483
      3.4.1. Hydrocarbon carotenoids 484
      3.4.2. Non-hydrocarbon carotenoids 485
4. Misuse and toxicity of hydrocarbons 487
   4.1. Lower-molecular-weight hydrocarbons 488
   4.2. Polynuclear aromatic hydrocarbons 492
References 496

1. INTRODUCTION

Hydrocarbons are a heterogeneous group of naturally occurring and manifested organic chemicals that are primarily composed of carbon and hydrogen molecules (Forbes, 1958a, 1958b, 1959; Guthrie, 1960; Warren, 2006; Speight, 2007). They are quite abundant in modern society – their use includes fuels, paints, paint and spot removers, dry-cleaning solutions, lamp oil, lubricants, rubber cement, and solvents. In addition, many volatile substances that contain hydrocarbons (e.g., glue, propellants) are commonly abused for their euphoric effects.

Hydrocarbons can be classified as being aliphatic, in which the carbon moieties are arranged in a linear or branched chain, or aromatic, in which the carbon moieties are arranged in a ring (Chapter 1) (Clayden et al., 2001). Halogenated hydrocarbons are a subgroup of aromatic hydrocarbons, in which one of the hydrogen molecules is substituted by a halogen group. The most important halogenated hydrocarbons include carbon tetrachloride, trichloroethylene, tetrachloroethylene, trichloroethane, chloroform, and methylene chloride.

The hydrocarbons can be derived from either petroleum or wood. Petroleum distillates include kerosene, gasoline, and naphtha, while

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wood-derived hydrocarbons include turpentine and pine oil. The length of the chains as well as the degree of branching determine the phase of the hydrocarbon at room temperature; most are liquid, but some short-chain hydrocarbons (e.g., butane) are gas at room temperature, while other long-chain hydrocarbons (e.g., waxes) are solid at room temperature.

A *pharmaceutical drug* (*medicine*, *medication*) is any chemical substance intended for use in the medical diagnosis, treatment, cure, or prevention of disease.

On the other hand, a drug (a chemical which is a sub-category of *pharmaceuticals*) is (1) a chemical substance that affects the processes of the mind or body or (2) a substance used recreationally for its effects on the central nervous system, such as a narcotic. In this respect, a *designer drug* is a new drug of abuse similar in action to an older abused drug and usually created by making a small chemical modification in the older one while a *mind-altering drug* is a drug that produces an altered state of consciousness. These are *not* the subject of this text.

Medications can be classified in various ways, such as, for example, by (1) chemical properties, (2) mode of administration, (3) biological system affected, or (4) therapeutic effects.

Since hydrocarbons are the simplest organic compounds containing only carbon and hydrogen, they can be straight-chain, branched-chain, or cyclic molecules (Chapter 1) but generally offer little in the way of pharmaceutical properties. Nevertheless there are those hydrocarbons that do have pharmaceutical properties. Thus, for the purposes of this chapter and in the context of this book, medications are classified as (1) hydrocarbons and (2) non-hydrocarbons, with the focus of this chapter being on the hydrocarbon medications. The definition and interpretation of hydrocarbons and non-hydrocarbons as used here in this chapter is the same as the definition and interpretation given elsewhere in this text (Chapter 1).

2. HISTORY

The earliest written documents indicate that the use of drugs such as herbs, powders, and poultices had a place in religion and mysticism as well as medicine (Forbes, 1958a, 1958b, 1959; Guthrie, 1960; Bough and Trammel, 2006). In the period 3000–4000 BC, the Chinese documented the use of herbal medicine to cure illness in humans and valuable animals and made early discoveries about the medicinal values of herbs – many of which are still recognized in modern pharmacy (Table 13.1).

Table 13.1 Brief timeline of the use of drugs

4000 BC
The Sumerians use opium, suggested by the fact that they have an ideogram for it with the meaning *joy* or *rejoicing*
3500 BC
Earliest historical record of the production of alcohol — the description of a brewery in an Egyptian papyrus
3000 BC
Approximate date of the supposed origin of the use of tea in China
2500 BC
Earliest historical evidence of the eating of poppy seeds among the Lake Dwellers in Switzerland
2000 BC
Earliest record of prohibitionist teaching, by an Egyptian priest, who forbids a pupil to enter a tavern where beer is sold
300 BC
Theophrastus (371—287 BC), Greek naturalist and philosopher, records what has remained as the earliest reference to the use of poppy juice
350 AD
Earliest mention of tea in a Chinese dictionary
1000 AD
Opium is widely used in China and the Far East

Sumerian clay tablets from 2100 BC (recovered for the level Ur III) contain pharmacologic descriptions involving ingredients such as salt, saltpeter, thyme, seeds, roots, and bark. Early Hindus used snake root to treat mental disorders, and Egyptians used opium to treat gastrointestinal disorders.

Hippocrates (460–375 BC), a Greek physician (after whom the Hippocratic Oath is named), believed that there was limited use for drugs. He noted that sick people generally got well even if drugs were not used. However, the scientific basis for medicine was formed shortly after his time by the Greek philosopher Aristotle (384–322 BC), who based his ideas on biology-related observations and systematic classifications and recorded much of what was known about natural science at the time, including similarities and differences between the biology of humans and animals. His student Theophrastus, known as the father of botany, systematically classified medicinal plants. Dioscorides (40–90 AD), from Asia Minor, worked with medicinal plants as well as drugs from mineral and animal sources, and recorded drug names, sources, identification, preparation, dosage, and usage. His work established a structure used and developed for future pharmacopeias. Also from Asia Minor, Galen (130–200 AD) practiced and taught pharmacy and medicine. His contributions focused on correct compounding and are still useful today.

During the Middle Ages, much emphasis was placed on combining multiple ingredients in medicines so that they could be used for any ailment. However, the Middle Ages produced little advancement in the area of pharmacy in Europe. However, during this time, the Arab scientists and medical doctors contributed to drug knowledge by recording new information about crude preparations.

In 1498, the first official *pharmacopeia* was published in Florence, Italy. The goal was to provide a source for uniform pharmaceutical standards. In 1606, the Society of Apothecaries of London was formed. At that time, an apothecary was similar to a modern pharmacist, preparing and selling medicinal substances. When King James I granted a charter to the society in 1617, he created the first official organization of pharmacists in the Anglo-Saxon world.

During the eighteenth century, pharmaceutical and medical services were provided in the Americas (which would become the United States) by governors, religious leaders, and educators. These men used imported drugs as well as drugs derived from local plants. In 1821, the Philadelphia College of Pharmacy was founded; it was the first association of pharmacists in America. As the development of drugs continued, pharmaceutical education developed with a stronger focus on chemistry and standardization.

Scientists began developing biological compounds in the late 1700s and throughout the 1800s. The first diseases these drugs affected were smallpox, diphtheria, and tetanus. Louis Pasteur (1822–1895), who is responsible for numerous scientific achievements, discovered that weakened forms of microbes could be used as immunizations for more virulent forms of microbes. His work led to the development of vaccines for chicken cholera, anthrax, and swine erysipelas as well as modern rabies vaccines for humans and dogs.

In 1903, the first US government inspection and licensure policies were implemented for those manufacturing viruses, serums, toxins, and analogous products. The Pure Food and Drug Act, passed in 1906, gave the US government the ability to enforce United States Pharmacopeia (USP) standards and to bring action against those who adulterated or misbranded drugs. This act was prompted by the exposure of popular patent medicines for humans and animals as largely ineffective – and sometimes harmful — concoctions.

Until the 1920s in some medical schools, *materia medica* (diluted pharmacy courses) was taught and the term *materia medica* has since been replaced by the term *pharmacology*, which was the early study of compounding and preparing drugs, usually from natural sources.

The introduction of chemotherapy in 1936 and overall drug industry growth after World War II kept the momentum going. As these changes occurred, a greater emphasis was placed on pharmacology in the medical curriculum. Unfortunately, the veterinary field lagged behind in drug development because of economic factors as well as the fact that the profession was much smaller. After 1950, scientific exploration in the veterinary drug industry began to increase, and although economic and societal factors still contribute to slower progress in this area, significant growth has occurred. During the twentieth century and into the twenty-first century, remarkable changes have occurred in the production and use of drugs.

3. HYDROCARBON PHARMACEUTICALS

3.1. Mineral oil

The term *mineral oil* is used in two different senses: (1) for petroleum (crude oil) (petroleum) as naturally occurring in geological formations, and (2) for a refined by-product of the distillation of petroleum (Speight, 2007). It is the second meaning that is implied here by the use of the term; mineral oils should not be confused with essential oils – which are concentrated, hydrophobic liquids containing volatile aroma compounds and are isolated from (biological) plants.

Mineral oil is used to designate liquid by-products in the distillation of petroleum to produce naphtha and other products (Speight and Ozum, 2002; Speight, 2007, 2008). Mineral oil in this sense is transparent, colorless, and composed mainly of alkanes (typically 15–40 carbons) and cyclic paraffins. It has a density of approximately 0.8 g/cm and is currently considered to be of relatively low value. It is, however, still available in some drug stores and can be purchased as light and heavy grades.

There are three basic classes of refined mineral oils: (1) paraffin oils, based on n-alkanes; (2) naphthenic oils, based on cycloalkanes; (3) aromatic oils, based on aromatic hydrocarbons.

Mineral oil with added fragrance is marketed as *baby oil* in the United States, Canada, and Great Britain. While baby oil is primarily marketed as a general skin ointment, other applications exist in common use. It is often used to alleviate mild eczema (and diaper rash), particularly when the use of corticosteroid cream is not desirable. Mineral or baby oil can also be employed in small quantities (2–3 drops daily) to clean inside ears. Over a period of a few weeks, the mineral oil softens dried or hardened earwax so that a gentle flush of water can remove the debris. In the case of a damaged or perforated eardrum, however, mineral oil should not be used, as oil in the middle ear can promote ear infections.

During the mid-decades of the twentieth century, mineral oil was taken orally as a lubricative for the alimentary tract and was particularly in common use by coal miners who ingested a large amount of coal dust during their work. In most countries, the use of mineral oil as a laxative is considered obsolete mainly due to its potentially harmful effects on the lungs if accidentally aspirated. Furthermore, the oil may be absorbed to a small percentage into internal tissue and cause adverse reactions to the body. In addition, mineral oil temporarily coats the intestines and prevents the uptake of certain essential vitamins and nutrients.

3.2. Paraffin oil

Paraffin oil or liquid paraffin oil is obtained in the process of petroleum distillation (Speight and Ozum, 2002; Speight 2007, 2008). It is a colorless and odorless oil that is used for varied purposes. In some cases *paraffin oil* and *mineral oil* are synonymous terms. In other cases there are subtle, often undetectable differences in composition and properties that can only be determined by careful and detailed analysis of the two.

Liquid paraffin oil is a mineral oil, and is a by-product of petroleum distillation. It is transparent, colorless, odorless and tasteless oil, which is mainly composed of heavier alkanes. It is not soluble in water and is known to have low reactivity. Paraffin oil and paraffin wax have found a wide range of industrial, medical, as well as cosmetic uses in modern times. Liquid paraffin oil usually comes in two forms, heavy liquid paraffin oil and light liquid paraffin oil.

Remembering that there is high-boiling paraffin oil and lower boiling paraffin oil (kerosene range), liquid paraffin oil has found numerous applications – from manufacturing candles to the production of cosmetics or beauty products. Several of the most noteworthy uses of liquid paraffin oil are:

- As a fuel in burning lamps and used as a fuel in many parts of the world; in this case the oil is usually a high-boiling kerosene fraction and should not be used for medicinal purposes.
- As a laxative – this oil is not absorbed by the intestinal tract.

- In the manufacture of penicillin, and is an important ingredient in many medicated creams, ointments, and balms.
- In the production of paints, dyes, pigments, wax, polythene, and insecticides.
- As a solvent and lubricant in the industrial sector.
- In the textile industry – mainly for spinning, weaving, and lubricating the sewing machines.
- In the cosmetic industry as well for the preparation of a number of solid and liquid brilliantine, moisturizers, cold cream, and lotions as well as in make-up products such as lipstick, lip balm, and foundation cream.
- In skin treatment, especially in treating diaper rash and eczema, and to preserve unstable or reactive substances.

Liquid paraffin (high boiling mineral oil) is a mixture of higher-molecular-weight alkanes, and has a number of names, including nujol, adepsine oil, alboline, glymol, medicinal paraffin, or saxol. It has a density of approximately 0.8 g/cm^3.

Liquid paraffin (medicinal) is used to aid problems of the gastrointestinal tract and it passes through the tract without itself being taken into the body. In the food industry, where paraffin oil may be called *wax*, it can be used as a lubricant in mechanical mixing, applied to baking tins to ensure that loaves are easily released when cooked and as a coating for fruit or other items requiring a "shiny" appearance for sale.

Paraffin oil (boiling in the kerosene boiling range) can pose certain health hazards, especially if it is inhaled or ingested, and also due to repeated or prolonged skin exposure. Inhalation of paraffin oil can irritate the respiratory tract, and cause cough, shortness of breath and, occasionally, lead to hydrocarbon pneumonitis. On the other hand, prolonged skin exposure to this oil can cause skin irritation, which can lead to contact dermatitis, especially in individuals who already have skin disorders or diseases. Ingestion of paraffin oil can cause upset of the intestinal tract.

Paraffin oil which has not been highly refined is often considered as a carcinogen or cancer-causing agent. Therefore, adequate precaution is required while using paraffin oil. Ideally, liquid paraffin oil should be stored in a cool and well-ventilated place, in a tightly closed container. As some paraffin oil is highly inflammable, be sure to keep it away from any source of heat or ignition, and also out of direct sunlight. Lastly, while using this oil for various purposes, be sure to follow the instructions mentioned on the label of the product, regarding the handling and storage of liquid paraffin oil.

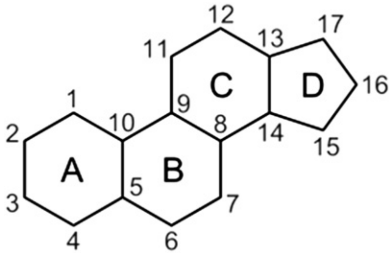


Figure 13.1 Numbering of the sterane ring system and carbon system when the typical alkyl side chain is included

3.3. Steroids

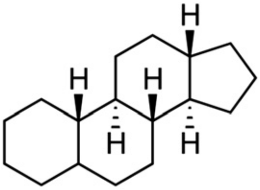
The term *steroid* is applied to a group of naturally occurring or synthetic fat-soluble organic compounds (lipids), whose structure is chemically based on the hydrocarbon sterane nucleus.

Sterane, the patent compound of steroids, is a hydrocarbon based on the 17 carbon atom four-ring perhydrocyclopentanophenanthrene ring system (fully hydrogenated cyclopentanoperhydrophenanthrene ring) (Figure 13.1). The sterane structure constitutes the core of all non-hydrocarbon sterols and steroids.

The characteristic base structure of a sterane (the degraded and saturated version of a steroid) (Figure 13.1) has three cyclohexane rings and one cyclopentane ring, and a side chain emerging from C_{17}.

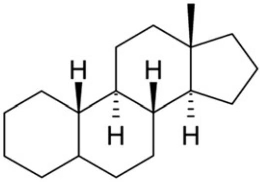
Sterane is the hypothetical parent molecule for any steroid hormone. The name was originally conceived to achieve forms of systemic nomenclature, but is now supplanted by the fundamental structural variants such as: gonane, estrane, cholestane, and pregnane.

Gonane is the fundamental tetracyclic unit (Figure 13.1) with no methyl groups at C-10 and C-13 and with no side chain at the C-17 steroid nucleus. *Gonane* exists as either of two isomers, known as 5α-gonane and 5β-gonane.

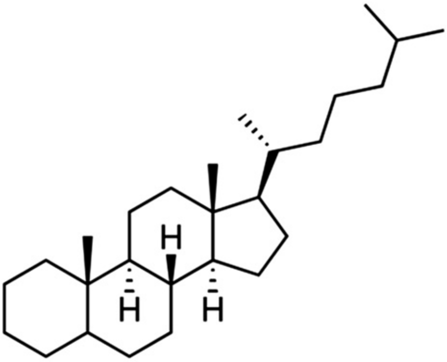


Gonane

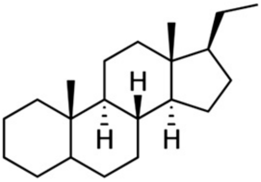
Estrane is a sterane derivative – estrenes are estrane derivatives containing a double bond.


Estrane

Cholestane is a saturated hydrocarbon 27-carbon sterane which serves as the basis for many organic molecules. Derivatives are classified into two families: (1) sterols (with an alcohol group) and (2) cholestenes (with a double bond). Some steroids, such as cholesterol, are both a sterol and a cholestene.


Cholestane

Pregnane is the parent hydrocarbon for two series of steroids stemming from 5α-pregnane (originally allopregnane) and 5β-pregnane (17β-ethyletiocholane):


Pregnane

5β-Pregnane is the parent of the progesterones, pregnane alcohols, ketones, and several adrenocortical hormones, and is found largely in urine as a metabolic product of 5β-pregnane compounds.

During diagenesis and catagenesis, the biological stereospecificity of sterols, particularly at C-5, C-14, C-17 and C-20, is usually lost, and a large range of isomers is generated (Figure 13.2). The term *alpha-beta-beta sterane*

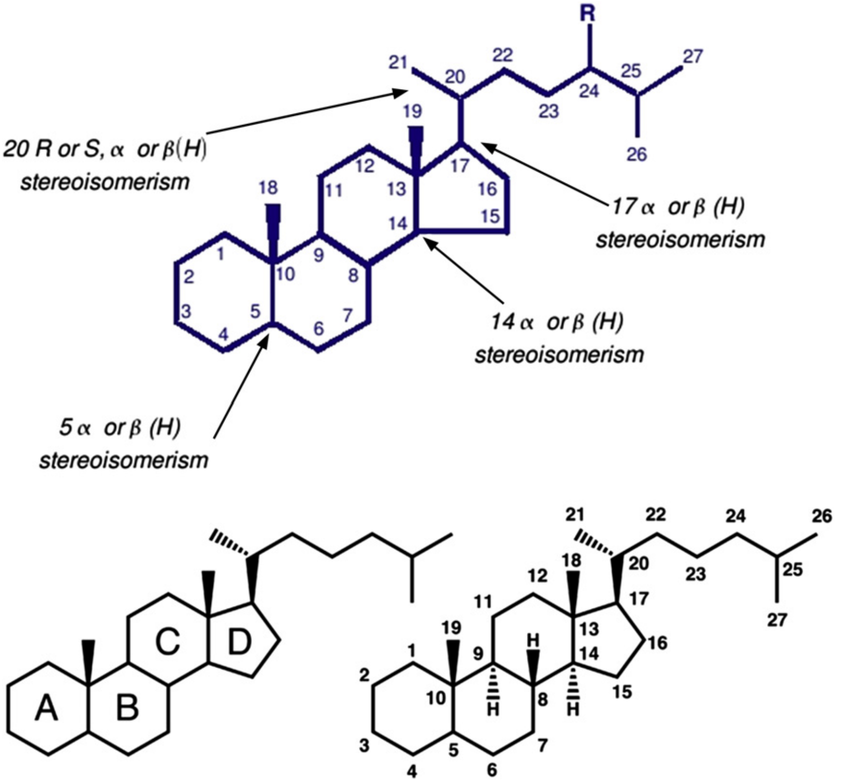


Figure 13.2 Sterane nomenclature and stereoisomerism

(sometimes just alpha-beta) is commonly used as short-hand to denote steranes with the 5-alpha(H), 14-beta(H), 17-beta(H) configuration, while *alpha-alpha-alpha* sterane would denote 5-alpha(H), 14-alpha(H), 17-alpha (H) stereochemistry. The notation 14-alpha(H) indicates that the hydrogen is located below the plane of the paper, whereas in 14-beta(H) it is above the plane.

In steranes, if no other carbon number is cited, *S* and *R* always refer to the stereochemistry at C-20. The prefix *nor*, as for example in 24-norcholestane, indicates that the molecule is formally derived for the parent structure by loss of the indicated carbon atom, i.e., C-24 is removed from cholestane.

The term *desmethylsteranes* is sometimes used to distinguish steranes that do not possess an additional alkyl group at ring A, i.e., at carbon atoms C-1 to C-4. *Diasteranes* (Figure 13.3) are rearranged steranes that have no biological precursors, and are most likely formed during diagenesis and catagenesis.

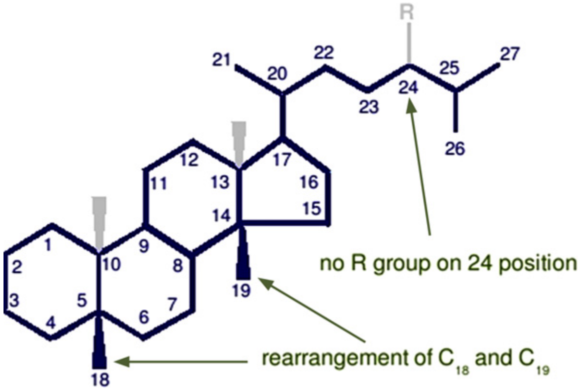


Figure 13.3 Diasterane

Steranes may be rearranged into diasteranes during diagenesis. Thus the diasterane/sterane ratio may be a signal of the maturity of the source rock. Norcholestane, shown above, a cholestane with one carbon missing, has some interesting uses as a biomarker. Only three series of these C_{26} steranes are known: 21-, 24- and 27-norcholestane. 24-Norcholestane has a particular source or depositional environment meaning, whereas 21- and 27-norcholestane are markers for maturity (Figure 13.4).

Sterane finds some use as a drug (the general equivalent is the non-hydrocarbon prednisolone) but offers more information when considered as a biomarker in determining the origin of petroleum.

Biomarkers (*molecular fossils*) from ancient sediments, petroleum source rocks, and petroleum are of uppermost importance for organic geochemists in order to characterize and identify oils, establish correlations, and develop paleo-environmental interpretations (Fleck et al., 2000).

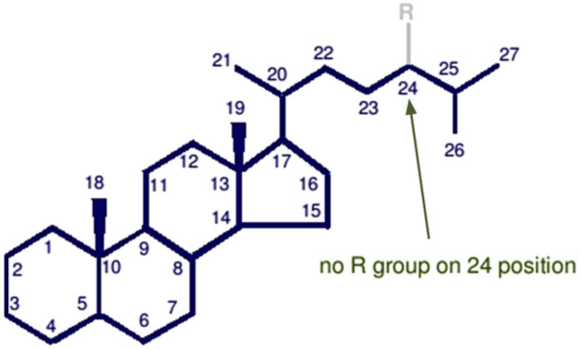


Figure 13.4 Norcholestane, a C_{27} to C_{30} sterane without the R group on its chain

For the most common sterane markers used in studies dealing with ancient sediments, four major classes of sterols are considered as precursors and derive from eukaryotic organisms. They contain 27 carbon atoms (e.g., cholesterol found in animals, algae or plankton), 28 carbon atoms (e.g., ergosterol found in fungi), 29 carbon atoms (sitosterol, stigmasterol found in vascular plants and some algae) and 30 carbon atoms (sterols from marine-derived biomass). In addition to the variability in the organic sources, transformation of the biomass in the water column and the sediments as well as early diagenetic processes modify the initial structure of the precursor molecules, leading to the formation of steranes.

Among them, the regular steranes are the most widely used in organic geochemistry. Especially the relative proportions on the C$_{27}$, C2$_8$, C$_{29}$ steranes are used for the assessment of organic input to the sediments and of paleoenvironmental conditions of deposition.

One of the environments in which petroleum is believed to be formed is a lacustrine environment (in addition to the marine environment). The lacustrine environment is usually characterized by a higher relative concentration in C$_{28}$ steranes (Huang and Meinschein, 1979). A low concentration of these steranes in an environment sample suggests the absence of typically fresh aquatic organisms (the absence of a true lacustrine environment is also supported by geological evidence); this is probably because of shallow fresh water conditions (in opposition to deep lacustrine), related to swamp type environments. Foliage fall and turnover of plants are the dominant source of plant debris. These are utilized in the food web by heterotrophs. C$_{27}$ sterols can thus originate from organisms living on the plant debris, i.e., variable invertebrates (Huang and Meinschein, 1979), and/or from the microbial degradation of C$_{28}$ and C$_{29}$ sterol side chains (Murohisa and Iida, 1993). In order to unravel all these possibilities and improve the paleoenvironmental assessment, correlation of organic information with the geological and biological context is necessary (Volkman, 2008); it is necessary to adjust the paleoenvironmental interpretation of steranes by considering geological and biological information.

In fact, biomarkers add complementary information to the fossil palynomorph record (Schwark and Empt, 2006). Steranes are important constituents of eukaryotic cell membranes and are preserved in sediments as steranes. C$_{28}$ and C$_{29}$ steranes are indicators for the presence of green and C$_{27}$ steranes for the presence of red algae, respectively. The relative abundance of steranes allows the investigation of the fossil record for Paleozoic algal diversification and evolution.

For example, a sharp increase of the C_{28}/C_{29}-sterane ratio from <0.55 to >0.70 at the Devonian/Carboniferous boundary implies a fundamental change in the green algae assemblage from more primitive, mainly C_{29}-sterane-producing algae, to modern C_{28}-sterane-producing algae. A pronounced but short-lived rise in the C_{28}-sterane content occurs that is attributed to an episodic increase in prasinophytes. The gradual radiation of algae may have been triggered by frequent mass extinctions in the Upper Devonian culminating with the massive decline of acritarchs at the D/C-boundary. The coeval rise in the C_{28}/C_{29}-sterane ratio indicates the presence of a non-encysting algal group and coincides with the global augmentation of numerous filamentous Codiacea (Siphonales) and the rise of euspondyle and metaspondyle Dasycladales.

A *steroid* is characterized by its sterane core to which non-hydrocarbon functional groups may be incorporated or attached. The core is a carbon structure of four fused rings: three cyclohexane rings and one cyclopentane ring (Figure 13.1). The steroids vary by the functional groups attached to these rings and the oxidation state of the rings.

The sterane core of steroids is composed of 17 carbon atoms bonded together to form four fused rings: three cyclohexane rings (designated as rings A, B, and C) and one cyclopentane ring (the D ring) (Figure 13.1). The steroids vary by the functional groups attached to these rings and by the oxidation state of the rings. Sterols are forms of steroids, with a hydroxyl group at position-3 and a skeleton derived from cholestane (Figure 13.2).

Many hormones, body constituents, and drugs are steroids – not necessarily hydrocarbons but based on the sterane core.

All the corticosteroid hormones of the adrenal cortex (glucocorticoids or mineralocorticoids), all the sex hormones (sex hormones are found in higher quantities in one sex than in the other; male sex hormones are androgens, which include testosterone; female sex hormones are estrogens and progesterone), all vitamins of the vitamin D group (calciferol), the bile acids (ursodeoxycholic acid and analogs), cardiac aglycones, sterols like cholesterol, toad poison, saponins, some carcinogenic hydrocarbons, and some corticosteroid drugs like prednisone are all steroids. Synthetic chemical analogs of many of the naturally occurring steroids are vital in medicine. Both natural and synthetic steroids are used to treat many disorders and play a vital role in the normal functioning of the body.

Steroidal drugs may be of three types – anabolic, androgenic, and cortico-steroids. *Anabolic steroids* are chemically derived from testosterone. Many attempts were made to separate the anabolic effects of the hormones from their androgenic effects, but with little success. Thus anabolic compounds may cause androgenic side effects, especially when used for extended periods.

Anabolic effects are seen as the growth or thickening of the body's non-reproductive tract tissues including the skeletal muscles, bones, the larynx, and vocal chords, and a decrease in body fat. *Androgenic steroid* effects are seen in the growth of the male reproductive tract and the development of male secondary sexual characteristics. Medically, anabolic steroids were given for osteoporosis in women but it not recommended nowadays.

Corticosteroid is a general name for the group of hormones that have a cortisone-like action. They are man-made steroids that mimic the activity of cortisone. Cortisone is produced naturally in the body and is involved in regulating inflammation, thus dealing with injury. Thus corticosteroids are not the same as anabolic steroids. Corticosteroids are used in the treatment of many diseases like asthma, eczema, allergies, arthritis, colitis, and kidney disease.

Anabolic steroids control or contribute to the large muscle mass of males because of the nitrogen-retaining effects of androgen. They may have a property of protein building and when taken lead to an increase in muscle bulk and strength.

Anabolic steroids were developed in the late 1930s to treat hypogonadism – a condition in which the testes do not produce sufficient testosterone for normal growth, development, and sexual functioning. The primary medical uses of anabolic steroids are to treat delayed puberty, some types of impotence, and wasting of the body caused by HIV infection or other diseases. Around the same time, scientists discovered that these compounds could facilitate the growth of skeletal muscles in laboratory animals, which led to their use first by bodybuilders and weightlifters, then by athletes in a variety of other sports.

Anabolic steroids are illegal without a prescription but steroidal supplements can be bought over-the-counter legally. Such supplements are more commonly called dietary supplements, though they are not food products. Steroidal supplements contain dehydroepiandrosterone (DHEA) and/or androstenedione. If large quantities of steroidal supplements substantially increase testosterone levels in the body, they might most likely produce the same side effects as anabolic steroids.

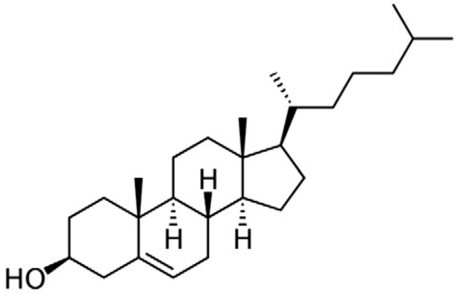
Medically, anabolic steroids may be used for many purposes, including: (1) stimulating protein anabolism in debilitating illness and in acute renal failure; (2) promoting growth in children with pituitary dwarfism and other growth disorders; (3) retention of nitrogen and calcium may benefit patients with osteoporosis and patients receiving corticosteroid therapy; and (4) stimulation of bone marrow function in hypoplastic anaemia.

However, when abused, anabolic steroids can have serious side effects. Athletes and bodybuilders aiming to improve their strength, stamina, speed, or body size have always abused them. Steroids appear to work by decreasing the amount of time necessary for recovering between bouts of exercise. Because of this, trainees can exercise more often, or more intensely, without overwhelming the body's ability to adapt, or over-training.

It is important to understand that using steroids does not increase skill, agility, or performance. These are determined by many factors, including genetics, body size, age, sex, diet, and how hard the athlete trains.

Anabolic steroids are not legal in organized sports. Most professional and amateur sports organizations and medical associations ban *anabolic steroids*. Athletes who test positive for steroids will be suspended or disqualified and may lose their chance to compete in their sport.

Cholesterol contains a hydroxyl group that also provides slightly hydrophilic features to a substance which otherwise is structured like a hydrocarbon and hence a lipo-soluble substance:



Cholesterol

This specific feature increases the water-retaining capacity of wool fat (*adeps lanae*) in which it is contained. Lanolin is the term for a mixture of wool fat (65 grams), paraffin oil (15 grams) and water (20 grams), and is a frequent component of W/O emulsions in pharmaceutical skin ointments. In the cosmetic field, *wool fat* and *lanolin* are synonyms. Cholesterol has excellent skin-protecting effects and is a component of the natural skin barrier.

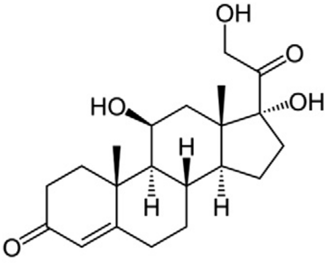
Cholesterol is a main component for the human metabolism. It is transported in the blood stream with the help of lipoproteins whose main components are proteins and phosphatidylcholine. Chylomicrons which can be imagined as minuscule emulsion-like droplets help to transport the cholesterol assimilated with the daily nutrition from the small intestines via the lymphatic system into the blood vessels. A significant product of the cholesterol metabolism is *pregnenolone*, a gestagen which is the base substance for bile acids and steroid hormones.

Plant sterols (*phytosterols*) are structurally related to cholesterol and can therefore replace the animal cholesterol in skin care creams. This explains the excellent skin care characteristics of avocado oil, which is rich in phytosterols. The biosynthesis of cholesterol in the human body starts with activated acetic acid (acetyl-CoA) via the terpenes geraniol (monoterpene), farnesol (sesquiterpene), and squalene (triterpene). Squalene is a significant re-fattening ingredient of the human sebum and is metabolized into lanosterine, which is a precursor of cholesterol also contained in wool fat and has similar emulsifying properties in creams.

Progesterone, which forms from pregnenolone, is the base substance for *androgens* (such as testosterone) but also for the *estrogens* (such as estrone and estradiol). In contrast to androgens, estrogens have an aromatic ring. This leads to the fact that the hydroxyl group located right at the ring has phenolic characteristics. This specific feature is the reason for its structural resemblance to plant isoflavones (polyphenols), which are also called *phytohormones*.

Soybean and red-clover-based phytohormones are mainly used in anti-aging products and skin care products for blemished skin. Contrary to phytohormones, steroid hormones and extracts containing steroid hormones are banned in many European countries.

The *glucocorticoids* include *cortisol* (hydrocortisone). The biosynthesis of cortisol and cortisone from progesterone occurs in the adrenal cortex. Cortisone as such is inactive; cortisol, however, has manifold physiological effects. Taken orally, inactive cortisone is transformed in the liver into active cortisol.



Cortisol

Cortisol is characterized by its anti-inflammatory and immune-suppressive effects and is applied in ointments against all kinds of allergies and skin reactions. The skin condition frequently improves within a few days already. A disadvantage though is the atrophic skin condition developing after long-term use. The skin becomes thinner and more permeable for externally affecting irritants and allergens. All in all, the skin becomes more sensitive to relapses. In order to reduce these and other side effects, a whole series of artificial corticoids has been developed in addition to hydrocortisone.

Another source for the technical manufacturing of cortisol besides the phytosterol *sitosterol* is the herbal *diosgenin*. Diosgenin belongs to the group of herbal *saponins* with a steroidal ring system. It is also base substance for the industrially produced progesterone.

Like bile acids, saponins also are surface active and have formerly been used for cleansing purposes. In India and other Asian regions the fruits of the wash nut tree (soap nut) with their specifically high saponin content are used still today. Unlike the anionic emulsifying bile acids, the cleansing effect of saponins results from the (glycosidic) linkage of water-soluble sugar residues with the steroidal ring system. That is why saponins can be compared with non-ionic emulsifiers like modern-day sugar tensides, which are used for facial cleansing.

Cardiac glycosides have a similar glycosidic steroidal structure as saponins. The main active agent digitoxin is extracted from the leaves of the purple foxglove (*Digitalis purpurea*).

Also related to saponins are the *steroidal alkaloids* of the solanum family. The most famous representative here is solanine, which occurs in potatoes and has a low toxic effect.

In connection with steroids, vitamin D3 is worth mentioning as it is formed from 7-dehydrocholesterol, which is a prestage of cholesterol. 7-Dehydrocholesterol occurs in the stratum spinosum and stratum basale of the skin and is transformed into vitamin D3 by influence of UVB light. During this process one of the four steroidal rings is opened. The vitamin is also assimilated with the daily nutrition. This is all the more important the less the skin is exposed to sunlight and the more sun screens are used. A major source for the vitamin is the consumption of fish, especially those with high fat content like herring, salmon, and mackerel.

3.4. Carotenoids and vitamins

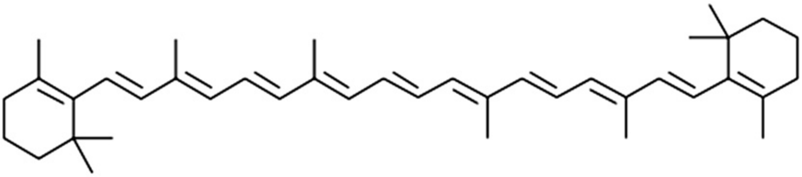
Carotenoids are organic pigments that are naturally occurring in the chloroplasts and chromoplasts of plants and some other photosynthetic organisms such as algae, various types of fungi, and various types of bacteria.

There are several hundred known carotenoids; they are split into two classes: (1) carotenes – pure hydrocarbons, and (2) xanthophylls, which contain oxygen. However, in contrast to the steroids where the true hydrocarbons play a limited pharmaceutical role, the carotenoid hydrocarbons have a much greater role as pharmaceuticals.

3.4.1. Hydrocarbon carotenoids

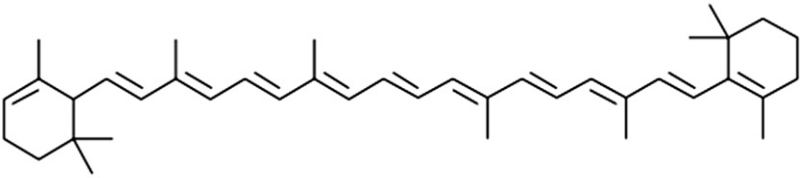
Hydrocarbon carotenoids (carotenes) fall into a group of hydrocarbon compounds having the formula $C_{40}H_x$, which are synthesized by plants but cannot be made by animals. Carotene is an orange photosynthetic pigment important for photosynthesis. Carotenes are all colored to the human eye. They are responsible for the orange color of the carrot, after which this class of chemicals is named, and for the colors of many other fruits and vegetables. Carotenes are also responsible for the orange (but not all of the yellow) colors in dry foliage. They also (in lower concentrations) impart the yellow coloration to milk-fat and butter.

β-Carotene is composed of two retinyl groups, and can be stored in the liver and body fat and converted to retinal as needed, thus making it a form of vitamin A for humans and some other mammals:



β-Carotene

α-Carotene and γ-carotene, due to their single retinyl group (beta-ionone ring), also have some vitamin A activity (though less than β-carotene), as does the xanthophyll carotenoid β-cryptoxanthin. All other carotenoids, including lycopene, have no beta-ring and thus no vitamin A activity (although they may have antioxidant activity and thus biological activity in other ways).

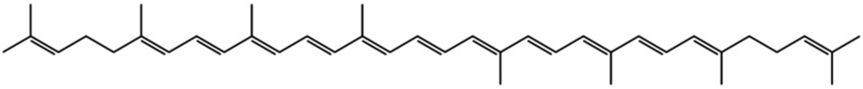


α-Carotene

The two ends of the β-carotene molecule are structurally identical (β-rings). Specifically, the group of nine carbon atoms at each end form a β-ring. The α-carotene molecule has a β-ring at one end; the other end is called an *ε-ring* (there is no such designation as an *α-ring*). These and similar names for the ends of the carotenoid molecules form the basis of a systematic naming scheme, according to which:

- α-carotene is β,ε-carotene;
- β-carotene is β,β-carotene;
- γ-carotene (with one β ring and one uncyclized end that is labeled *psi*) is β,Ψ-carotene;
- δ-carotene (with one ε-ring and one uncyclized end) is ε,Ψ-carotene;
- ε-carotene is ε,ε-carotene
- lycopene is Ψ,Ψ-carotene

Probably the most well-known carotenoid is the compound that gives this group its name: *carotene*, which is found in carrots and also apricots. Crude palm oil, however, is the richest source of carotenoids in nature in terms of retinol (provitamin A) equivalent. The Vietnamese *Gac fruit* contains the highest known concentration of the carotenoid lycopene.



Lycopene

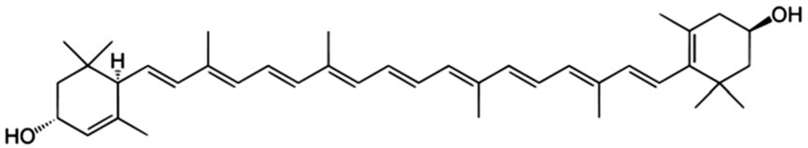
Lycopene is a bright red carotene and carotenoid pigment and phytochemical found in tomatoes and other red fruits and vegetables, such as carrots, watermelons, and papayas (but not strawberries or cherries). Although lycopene is chemically a carotene, it has no vitamin A activity.

In plants, algae, and other photosynthetic organisms, lycopene is an important intermediate in the biosynthesis of many carotenoids, including β-carotene, responsible for yellow, orange, or red pigmentation, photosynthesis, and photo-protection. Like all carotenoids, lycopene is a polyunsaturated hydrocarbon (an unsubstituted alkene). Structurally, lycopene is a tetraterpene assembled from eight isoprene units, composed entirely of carbon and hydrogen, and is insoluble in water.

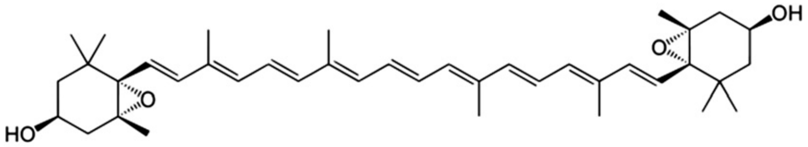
The 11 conjugated double bonds in lycopene give it its deep red color and are responsible for its antioxidant activity.

3.4.2. Non-hydrocarbon carotenoids

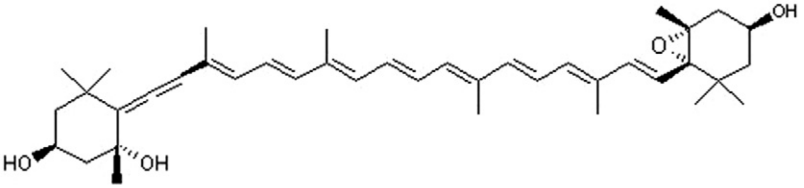
The non-hydrocarbon carotenoids are important components of light harvesting in plants, expanding the absorption spectra of photosynthesis. The major carotenoids in this context are lutein, violaxanthin, and neoxanthin.



Lutein



Violaxanthin



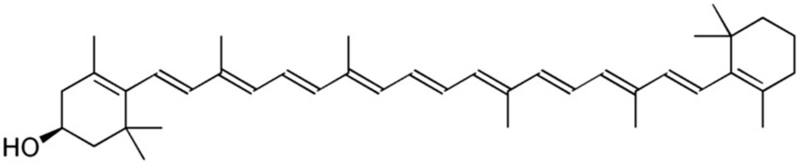
Neoxanthin

Additionally, there is considerable evidence which indicates a photo-protective role of xanthophylls, preventing damage by dissipating excess light. In mammals, carotenoids exhibit immunomodulatory actions, likely related to their anticarcinogenic effects.

Carotenoids generally absorb blue light and they serve two key roles in plants and algae: they absorb light energy for use in photosynthesis, and they protect chlorophyll from photo-damage. In humans, four carotenoids (β-carotene, α-carotene, γ-carotene, and β-cryptoxanthin) have vitamin activity and can also act as antioxidants.

Carotenoids belong to the category of tetraterpenoids (i.e., they contain 40 carbon atoms) – structurally they are in the form of a polyene chain which is sometimes terminated by rings.

Xanthophylls are not pure hydrocarbons and often yellow, hence their class name.



Cryptoxanthin

The carbon–carbon double bonds (C=C)interact with each other through conjugation, which allows electrons in the molecule to move freely across these areas of the molecule. As the number of double bonds increases, electrons associated with conjugated systems have more room to move, and require less energy to change states. This causes the range of energies of light absorbed by the molecule to decrease. As more frequencies of light are absorbed from the short end of the visible spectrum, the compounds acquire an increasingly red appearance.

In photosynthetic organisms, specifically flora, carotenoids play a vital role in the photosynthetic reaction center. They either participate in the energy-transfer process, or protect the reaction center from auto-oxidation. In humans, carotenoids have been linked to oxidation-preventing mechanisms.

Carotenoids have many physiological functions. Given their structure, carotenoids are efficient free-radical scavengers, and they enhance the vertebrate immune system. There are several dozen carotenoids in foods people consume, and most carotenoids have antioxidant activity.

Humans and animals are incapable of synthesizing carotenoids, and must obtain them through their diet, yet they are common and often in ornamental features. For example, the pink color of flamingos and salmon, and the red coloring of lobsters are due to carotenoids.

The most common carotenoids include lycopene and the vitamin A precursor β-carotene. In plants, the xanthophyll *lutein* is the most abundant carotenoid and its role in preventing age-related eye disease is currently under investigation. Lutein and the other carotenoid pigments found in mature leaves are often not obvious because of the presence of chlorophyll. However, when chlorophyll is not present, as in young foliage and also dying deciduous foliage (such as autumn leaves), the yellows, reds, and oranges of the carotenoids are predominant. For the same reason, carotenoid colors often predominate in ripe fruit (e.g., oranges, tomatoes, bananas), after being unmasked by the disappearance of chlorophyll.

4. MISUSE AND TOXICITY OF HYDROCARBONS

Toxicity from hydrocarbon ingestion can affect many different organs, but the lungs are the most commonly affected organ. The chemical properties of the individual hydrocarbon determine the specific toxicity, while the dose and route of ingestion affect which organs are exposed to the toxicity.

The recreational use of inhaling hydrocarbons and other volatile solvents for the purposes of creating a euphoric state is becoming increasingly common. There are several methods for this misuse, including (1) *sniffing* (directly inhaling vapors); (2) *huffing* (placing a hydrocarbon-saturated cloth over the mouth and nose and then inhaling); or (3) *bagging* (inhaling through an opening in a plastic bag filled with hydrocarbon vapors).

4.1. Lower-molecular-weight hydrocarbons

Exposure to hydrocarbons is common in modern society and there are consequential effects (FR, 2001).

There is often a misconception of the effects and toxicity of hydrocarbons because of the perceived low chemical reactivity.

For example, methane is not classed as a toxic chemical; however, it is an asphyxiant because it will displace oxygen in an enclosed space. While the gas is not in itself dangerous to humans, it causes a slow asphyxiation by displacing the oxygen normally present in the air in a closed environment. Asphyxia will result if the oxygen concentration is reduced to below 19.5% by displacement. Persons exposed over an extended period of time will suffer from lack of oxygen, leading to brain damage or brain death, damage to other organs, and death. Symptoms of the low oxygen levels would be trouble focusing and sleepiness.

Methane is also highly flammable and will form explosive mixtures with air. Methane is violently reactive with oxidizers, halogens, and some halogen-containing compounds. The concentrations at which flammable or explosive mixtures form are much lower than the concentration at which asphyxiation risk is significant. When structures are built on or near landfills, methane off-gas can penetrate the buildings' interiors and expose occupants to significant levels of methane. Some buildings have specially engineered recovery systems below their basements to actively capture such fugitive off-gas and vent it away from the building.

Similar, but often less drastic, effects are evident when the lower-molecular-weight hydrocarbon gases are considered.

Hydrocarbons are easily accessible in products such as gasoline, turpentine, furniture polish, household cleansers, propellants, kerosene, and other fuels. Although hydrocarbons include all compounds composed predominantly of carbon and hydrogen, the compounds of interest are derived from petroleum and wood. Most of the dangerous hydrocarbons are derived from petroleum distillates and include aliphatic (straight-chain) hydrocarbons and aromatic (benzene-containing) hydrocarbons. Other hydrocarbons such as pine oil and turpentine are derived from wood.

Types of exposure include unintentional ingestion, intentional recreational abuse, unintentional inhalation, and dermal exposure or oral ingestion in a suicide attempt. The highest rates of morbidity and mortality result from accidental ingestion by children younger than 5 years. Aspiration pneumonitis is the most common complication of hydrocarbon ingestion, followed by central nervous system (CNS) and cardiovascular complications.

The toxicity of hydrocarbons is directly related to their physical properties, specifically the viscosity, volatility, surface tension, and chemical activity of the side chains. The viscosity is a measure of resistance to flow and is measured in Saybolt Seconds Universal (SSU). Substances with a lower viscosity (SSU <60, e.g., turpentine, gasoline, naphtha) are associated with a higher chance of aspiration. The surface tension is a cohesive force created by van der Waals forces between molecules and is a measure of a liquid's ability to *creep*. Like the viscosity, the surface tension is also inversely related to aspiration risk; the lower the viscosity, the higher the risk of aspiration.

Volatility is the tendency for a liquid to change phases and become a gas. Hydrocarbons with a high volatility can vaporize and displace oxygen, which can lead to a transient state of hypoxia. Not surprisingly, the degree of volatility is directly related to the risk of aspiration. The amount of hydrocarbon ingested has not consistently been linked to the degree of aspiration, and hence pulmonary toxicity.

Toxicity from hydrocarbon exposure can be thought of as different syndromes, depending on which organ system is predominantly involved. Organ systems that can be affected by hydrocarbons include the pulmonary, neurologic, cardiac, gastrointestinal, hepatic, renal, dermatologic, and hematologic systems.

Pulmonary complications, especially aspiration, are the most frequently reported adverse effect of hydrocarbon exposure. The lower the viscosity and higher the volatility, the greater the risk of pulmonary aspiration. The hydrophobic nature of hydrocarbons allows them to penetrate deep into the tracheobronchial tree, producing inflammation and bronchospasm. The volatile chemical may displace alveolar oxygen, leading to hypoxia. Direct contact with alveolar membranes can lead to hemorrhage, hyperemia, edema, surfactant inactivation, leukocyte infiltration, and vascular thrombosis. The result is poor oxygen exchange, atelectasis, and pneumonitis.

While the aliphatic hydrocarbons have little gastrointestinal absorption, aspiration frequently occurs, either initially, or in a semi-delayed fashion as the patient coughs or vomits, thereby resulting in pulmonary effects. Once aspirated, the hydrocarbons can create a severe pneumonitis.

Hydrocarbon pneumonitis results from a direct toxic effect by the hydrocarbon on the lung parenchyma. The type II pneumocytes are most affected, and as such, surfactant production and function are altered. The end result of hydrocarbon aspiration is interstitial inflammation, intra-alveolar hemorrhage and edema, hyperemia, bronchial necrosis, and vascular necrosis.

Pulmonary toxicity is the result of hydrocarbon aspiration. Respiratory symptoms generally begin in the first few hours after exposure and usually resolve in 2–8 days. Complications include hypoxia, barotrauma due to mechanical ventilation, and acute respiratory distress syndrome (ARDS). Prolonged hypoxia may result in encephalopathy, seizures, and death.

Hydrocarbon toxicity produces various effects on the central nervous system. Initial effects are similar to the disinhibition observed in patients with alcohol intoxication. Narcotic-like depression may also be observed. Euphoria may develop, as in alcohol or narcotic toxicity. Eventually, lethargy, headache, drowsiness, and coma may follow. Seizures are uncommon and are believed to be due to hypoxia.

Toxicity to the central nervous system can result from several mechanisms, including direct injury to the brain, or indirectly as a result of severe hypoxia or simple asphyxiation.

Many of the hydrocarbons that affect the central nervous system directly are able to make their way across the blood–brain barrier because certain hydrocarbons are highly lipophilic. In addition, for individuals who are *huffing* or *bagging*, the act of re-breathing can result in hypercarbia, which can contribute to decreased levels of arousal.

Prolonged abuse of hydrocarbons can result in white matter degeneration (leukoencephalopathy). In addition, prolonged exposure to certain hydrocarbons (e.g., n-hexane or methyl-n-butyl ketone (MnBK)) can result in peripheral neuropathy.

Cardiac effects are a major concern and include myocardial sensitization to catecholamines as well as direct myocardial damage. Sudden death has been reported as a result of coronary vasospasm due to hydrocarbon inhalation. Pulmonary toxicity is the major cause of morbidity and mortality from hydrocarbon poisoning and long-term exposure may result in significant morbidity.

Chronic exposure to toluene, an aromatic hydrocarbon, can result in a distal renal tubular acidosis and present with an anion gap acidosis.

A patient may have chronic exposure either via an occupational environment or by repeated recreational inhalation.

Prolonged exposure to certain aromatic hydrocarbons (especially benzene) can lead to an increased risk of aplastic anemia, multiple myeloma, and acute myelogenous leukemia. In addition, hemolysis has been reported following the acute ingestion of various types of hydrocarbons.

Hydrocarbons are also reported to cause bone marrow toxicity and hemolysis. Chlorinated hydrocarbon toxicity may cause hepatic and renal failure, and toluene toxicity may lead to renal tubular acidosis. Direct contact with the skin and mucous membranes may cause effects ranging from local irritation to extensive skin discoloration and dermatitis.

Inhalation injury due to hydrocarbons can occur as a result of either accidental or intentional exposure. Inhalant abuse, the deliberate inhalation of hydrocarbons as a form of recreational drug use, has become a significant health issue and data indicate that, among adolescents, inhalants are the second most widely used class of illicit drugs. Death from intentional inhalation of hydrocarbon fumes is not uncommon and is usually due to sudden cardiac events or depression.

Deliberate inhalation of volatile hydrocarbons for their mood-altering effects is popular among adolescents. Their low cost, ready availability, and ease of use contribute to this problem. Volatile hydrocarbons are contained in glues, solvents, lighter fluid, gasoline, and paints. Most inhalants are composed of several compounds, and almost all pressurized aerosol products can be abused because the propellants are volatile hydrocarbons.

Recreational abuse of hydrocarbons by inhalation is accomplished in three ways: (1) sniffing, (2) huffing, and (3) bagging. *Sniffing*, the least potent delivery method, is the inhalation of the volatile substance through the nostrils. *Huffing* involves placing of a rag soaked with an inhalant such as gasoline or lighter fluid over the nose and mouth. *Bagging* involves repeated deep inhalations from a plastic or paper bag filled with a particular hydrocarbon such as spray paint or another propellant.

Two primary organ systems are affected by inhalation hydrocarbon toxicity: (1) the central nervous system and (2) the cardiopulmonary system. Volatile hydrocarbons are highly lipid soluble and readily cross the blood–brain barrier. Rapid absorption occurs across the large surface area of the pulmonary vascular bed, and peak blood levels are noted approximately 15–30 minutes after inhalation. Confusion, disorientation, disinhibition, and euphoria are exhibited early. Speech becomes slurred, and motor function becomes impaired, with gait becoming staggered. Hallucinations are frequently described, followed by central nervous system depression, drowsiness, and sleep. Coma can occur with prolonged or repeated exposures – this is less likely to happen because intentional exposure ceases as the user becomes drowsy.

With acute intoxication, death due to asphyxiation from a plastic bag over the head or from aspiration of stomach contents is not unusual. Also, trauma-related injury and motor vehicle accidents have been reported, resulting from disinhibition and disorientation following inhalation.

With long-term hydrocarbon inhalation, damage to the central nervous system occurs, including loss of cognitive functions, gait disturbances, and loss of coordination. Other, less common complications of long-term hydrocarbon inhalation include restrictive pulmonary disease, pulmonary hypertension, and reduced diffusion capacity. Pulmonary toxicity can occur as a result of hydrocarbon aspiration.

The common idea that solvent inhalation is innocuous undoubtedly contributes to solvent-inhalant abuse. The wide availability of organic solvents in commonly used household products makes them readily accessible. Commonly abused hydrocarbon products include the following: (1) liquids – model glue, gasoline, contact cement (rubber cement), lacquers, nail-polish remover, dry-cleaning fluids; (2) aerosols – spray paints, butane fuel, lighter fluid, cooking sprays, cosmetics, hairspray, toiletries, deodorants. The hydrocarbon chemicals found in abused inhalants include: (1) propane; (2) butane; (3) n-hexane; (4) benzene; (5) toluene; and (6) xylene.

4.2. Polynuclear aromatic hydrocarbons

Polynuclear aromatic hydrocarbons (Chapter 1) are a class of compounds found throughout the environment in the air, in the soil, and in water. They are found naturally in crude oil, coal tar and coal, and are constituents of emissions produced during the incomplete combustion of hydrocarbons like coal, oil, gas, tobacco, and during forest fires.

Polynuclear aromatic hydrocarbons generally exist as colorless, pale yellow or white solids (Dias, 1987a, 1987b). Because they do not dissolve easily in water and generally do not burn, they can persist in the environment for months to years. It is difficult to isolate and analyze these hydrocarbons in the laboratory, due to the fact that they exist naturally as mixtures of many compounds.

Polynuclear aromatic hydrocarbons are formed by incomplete combustion of hydrocarbons, and can be isolated from the processing of fossil fuels. Many of these compounds have little use but there are some that are important in the making of pharmaceuticals, dyes, plastics, and pesticides.

Polynuclear aromatic hydrocarbons enter the body quickly and go to the fat-containing tissues.

There are few data available for the toxic effects of naphthalene on humans. Short-term low exposure to naphthalene may cause eye and skin irritation. At slightly higher levels (above 10 ppm), headaches, fatigue, and nausea occur. If naphthalene is ingested it has the potential to cause hemolytic anemia, a condition that involves the breakdown of red blood cells. Naphthalene is a suspected human carcinogen, and has been proven to cause damage to the kidneys and to the liver. Chronic exposure can lead to reproductive defects including fatal damage and decreasing fertility. Higher incidences of lung and skin tumors have been reported for people who have been occupationally exposed to naphthalene and other polynuclear aromatic hydrocarbons.

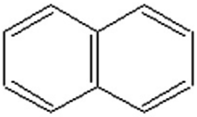
There are several hundred possible polynuclear aromatic hydrocarbons (Wise, 2003). As examples, and to illustrate the general properties of polynuclear aromatic hydrocarbons, naphthalene, anthracene, phenanthrene, and benzo[a]pyrene will be used here (Table 13.2).

Naphthalene is the smallest (lowest molecular weight) of the polynuclear aromatic hydrocarbons that contains two rings – synonyms for naphthalene

Table 13.2 Physical properties of selected polynuclear aromatic compounds

	Naphthalene	**Anthracene**	**Phenanthrene**	**Benzo[a] pyrene**
Molecular weight (g/mole)	128.16	178.23	178.23	252.3
Melting point (°C)	80.28	216.4	100.5	179
Boiling point (°C)	217.95	340	338	310–312
Solubility (aqueous, mg/L)	30	0.065	1.28	3.8×10^{-3}
Vapor pressure (Torr)	0.082	5.63×10^{-6}	1.250×10^{-4}	5.25×10^{-9}
Henry's constant (atm-m^3/mol)	4.27×10^{-4}	1.8×10^{-6}	2.800×10^{-4}	5.53×10^{-7}
Molar volume (cm^3/mole)	148	197	199	263
Heat of vaporization (kJ/mol)	43.2	52.4	52.7	71.7
Molecular volume (Angstroms^3)	26.9	170.3	169.5	228.6
Molecular surface area (Angstroms^2)	55.8	202.2	198	225.6

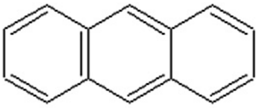
include *mothballs*, *white tar, tar camphor*, and *albo carbon*. It is a white, crystalline solid that can be found in the form of scales, balls, powder, or cakes. Naphthalene has the strong aromatic odor that is associated with mothballs.



naphthalene

Naphthalene is the most abundant distillate of coal tar. Its most common use is as a household fumigant against moths (hence the name mothballs). Naphthalene is an important hydrocarbon raw material used in the manufacture of phthalic anhydride (used in dye making), of celluloid and hydronaphthalenes (used in lubricants), and of motor fuels. At one time, it was used as an insecticide and vermicide. However, this use is decreasing due to the low toxicity of the vapor. Naphthalene is also of some use as an antiseptic and as a soil fumigant.

Anthracene (*anthracin*, *green oil*, and *para naphthalene*) is common in the natural environment. It has a crystalline structure, and is pale yellow in color. It exhibits a weak aromatic odor. It is a combustible solid.

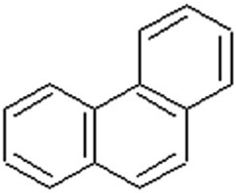


anthracene

Anthracene, like many polynuclear aromatic hydrocarbons, is used in the production of fast dyes as well as fibers and plastics. It is one of the most important feedstocks for the production of anthraquinone. Anthracene can also be used in insecticides and as a wood preservative. This compound is widely abundant. It is found in any type of coal or tar.

Anthracene exposure can cause skin and eye irritation, which can be aggravated by sunlight. Repeated exposure may cause alteration of skin pigments as well as cancerous growth, although there are no carcinogenic data for anthracene. Inhaled anthracene can cause bronchitis-like symptoms. There is limited information on human reproductive implications. Anthracene may cause genetic mutations in cells. Anthracene is not currently considered a toxic substance.

Phenanthrene is an isomer of anthracene and, as a result, many of the physical properties of the two are very similar.



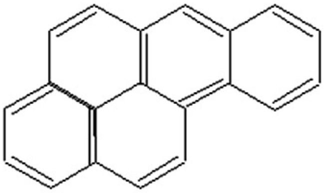
phenanthrene

The major differences between anthracene and phenanthrene lie in the melting point and the properties directly related to solubility (Table 13.2). Phenanthrene is purified as brown to white monoclinic crystals, and also has the characteristic faint aromatic smell.

Like anthracene, phenanthrene is used in the production of dyes. It is also used in the manufacture of explosives, and is an important starting material for phenanthrene-based drugs. This leads directly to use in biochemical research for the pharmaceutical industry. A mixture of phenanthrene and anthracene tar is used to coat water storage tanks to prevent rust.

Phenanthrene is also a skin and eye irritant, with increasing effects in sunlight due to photosensitization. There are currently no data available for human oral and inhalation exposure. It is, however, a suspected carcinogen and, although there are no data for humans, it is best to err on the side of caution and suspect carcinogenic effects will be present (Harvey, 1991).

Benzo[a]pyrene (3,4-benzpyrene) is the largest of the four compounds, with five rings. It also has the faint aromatic odor. Pure benzo[a]pyrene is pale yellow, and is found as monoclinic or orthorhombic crystals. These can be separated from a mixture of polynuclear aromatic hydrocarbons using various standard separation techniques, and recrystallized from benzene and methanol. Benzo[a]pyrene is one of several compounds that is a known human carcinogen.



benzo[a]pyrene

Benzo[a]pyrene is formed when gasoline, garbage, or any plant or animal materials are burned. So it is usually present in soot and smoke. It is found in the coal tar pitch industry, and is used to join electrical parts together. It is also found in creosote, a chemical used as a preservative for wood. It is used extensively as a positive control in a variety of laboratory mutagenic and carcinogenic short-term tests.

Benzo[a]pyrene has been found in various types of cereals, vegetables, fruits, and meats. High-temperature cooking processes, like charcoal grilling or charring, can increase the amount of benzo[a]pyrene found in food. It is also a component of tobacco products, and is one of the cancer-causing agents in cigarette smoke.

The greatest chance of high-level exposure to benzo[a]pyrene is likely to occur in the workplace. People who work in coal tar production plants, coking plants, asphalt production plants, coal gasification sites, and smoke houses receive higher doses than the general population.

Benzo[a]pyrene is a known precursor to cancer-causing metabolites in laboratory animals. Various studies have determined that this compound is toxic. It is converted by cytochrome P450 to a variety of oxides that react with DNA, making them highly mutagenic. The newborn animals of pregnant mice fed benzo[a]pyrene had other harmful effects including birth defects and low body weight. It is possible that similar effects could happen to humans exposed to benzo[a]pyrene.

Thus benzo[a]pyrene is a known carcinogen, and is regulated along with substances known as coal tar pitch 'volatiles'.

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