1
Medicinal Gases – Manufacturing

1.1
Where Do the Gases Come from?

Oxygen as the most prominent (medicinal) gas often lets us think that all other gases are of the same origin, coming right from the air. However, this is not the case. In addition to the very well-known oxygen, argon, and nitrogen, it might be advantageous to use other sources owing to technical or economic reasons. In addition, quite often specific methods of manufacturing or synthesis lead to specific types of impurities. In this chapter, we take a look at different gases, their sources, and the types of impurities that are characteristic of these different sources.

1.1.1
Gases Obtained from Air: Oxygen, Nitrogen, Argon, Xenon

Ambient air is a fascinating reservoir of numerous meteorological effects and has been known since the beginning of mankind. That atmospheric air is a gas and thus just a specific form of matter, and, moreover, that it not only contains water but is a mixture of different gases, was discovered only a few centuries ago.

Until the seventeenth century, it was a general opinion that air is an element, and as such indivisible. In laboratories as shown in the cover of the book (Figure 1), researchers like Jan Baptist van Helmont, (1577–1644) from the (then Spanish) Netherlands (Figure 1.1) recognized that gas is not a unique element but composed from different gases.

He noticed the difference between the chemical properties of hydrogen (developed by the reaction of hydrochloric acid and zinc) and carbon dioxide (developed by the fermentation of yeast) [1]. The two compounds had a physical property that was named "chaos" by van Helmont – a word that had the same pronunciation in Dutch as "gas," – and this became the term for this state of matter.

He discovered two gases, with almost similar physical properties as air, but with different chemical properties: hydrogen readily burned when ignited, while carbon dioxide remained chemically stable under most conditions, but giving a white precipitate with barium chloride solution.

Medical Gases: Production, Applications and Safety, First Edition. Hartwig Müller.

Figure 1.1 Jan Baptist van Helmont (1577–1644) [1].

Lavoisier *et al.* [2] discovered that air is composed of different gases in the late eighteenth century. They showed through chemical methods that there were at least two main components in the air, one being chemically reactive and the other one chemically inert [3]. Besides chemical absorption by specific reactions, air can be separated into its constituents by fractional distillation as with the liquids, to obtain its pure constituents, depending upon the knowledge of the art of fractionation.

As can be seen in Table 1.1, the major components of air have critical temperatures far below 0 °C. Above this temperature, no liquefaction of the gas is possible, indicating that the gas has to be cooled down first to below the critical temperature, before condensation starts, if the cooling is continued. Two well-known processes had been developed toward the end of the nineteenth and in the beginning twentieth century, respectively, by German (von Linde, 1895 [6]) and French (Claude, 1902 [7]) scientists.

While Linde's process works with a throttle to release the tension of the gas and to cool down the compressed gas (the Joule–Thomson effect), Claude's method uses an adiabatic expansion machine. The result is a "cryogenic" liquid with remarkable properties, having an average boiling point of about −194 to −185 °C. This liquid can be distilled in appropriate columns.

Table 1.1 Composition of ambient air, typical components [4].

Name of the gas	Content (approximately)	b.p. (°C)	b.p. (K)	
Nitrogen	78.1 vol%	−196	77.4	
Oxygen	20.8 vol%	−183	90.2	Σ 99.8 vol%
Argon	0.9 vol%	−186	87.3	
Carbon dioxide	390 ppm	−78	197.7	
Neon	18.2 ppm	−246	27.1	
Helium	5.2 ppm	−269	4.2	Σ 26 ppm
Methane	1.5 ppm	−162	111.6	
Krypton	1.14 ppm a)	−153	119.8 K	
Hydrogen	0.5 ppm	−253	20.4	
Carbon monoxide	0.2 ppm a)	−192	81.6	
Xenon	0.089 ppm	−108	165.1	Σ 1 ppm
Nitrous oxide	0.3 ppm	−88	184.7	
Sulfur dioxide	a)	−10	263.1	
Sulfur hexafluoride	a)	−63.9	209.2	
Carbon tetrafluoride	a)	−128	145.2	

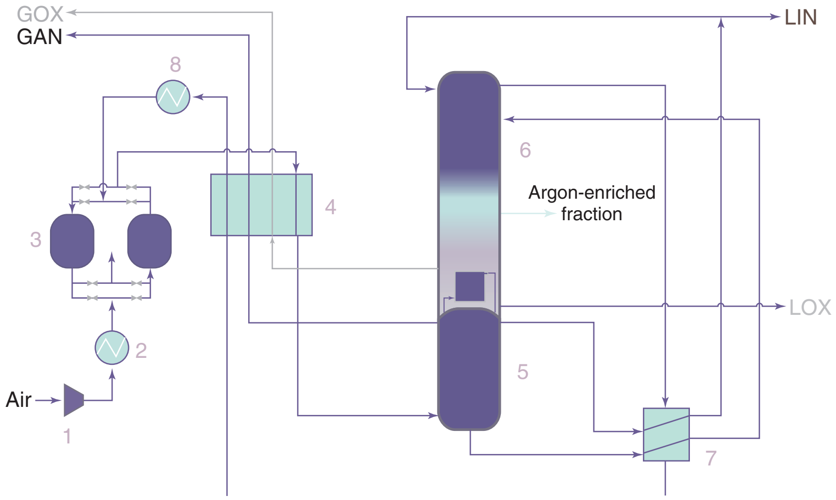
a) Under influence of human activities: depending upon localization of sampling, carbon monoxide and sulfur dioxide can be detected near industrial activities in considerable levels under specific conditions, sulfur hexafluoride and carbon tetrafluoride are gases that often escape during aluminum electrolysis, while krypton is contaminated with the radioactive isotope Kr-85, emanated during numerous nuclear processes [5].

Some of the low- or high-boiling components are emitted during human activities (industrial activities such as coal mining (methane), aluminum electrolysis (carbon tetrafluoride and sulfur hexafluoride)) or general activities such as those of traffic, power stations, and incineration plants (carbonmonoxide, carbon dioxide, nitric oxides).

On a technical scale, the air separation plant is a huge setup with separation columns reaching heights often of 20–50 m. A typical construction is shown in the Figure 1.2. The sequential steps of the air separation process of the incoming air can be described as follows:

Those contaminants that would precipitate under cryogenic temperatures have to be removed first (water, carbon dioxide, sulfur dioxide, higher hydrocarbons). The low-boiling pollutants, such as nitric oxides, sulfur hexafluoride, carbon tetrafluoride, methane, and acetylene accumulate in the oxygen fraction of the column. As a consequence, all these impurities show very clearly the increase in air pollution.

While the main constituents of ambient air (except water) remain constant in their concentration (although they are part of huge biological and microbiological cycles, such as the nitrogen and oxygen cycles), trace impurities present often are dependent on the specific localization, which is, the positioning of the air separation unit (ASU).



1 Compression
2–3 Purification. In the industrial environment the ambient air has first to be purified from dust, particles and high-boiling impurities, such as water, carbon dioxide, sulfur dioxide, and hydrocarbons, to prevent precipitation during the liquefaction process. Only the purified gas enters the liquefaction.
4 Liquefaction: Typically carried out at 5-6 bar (Linde-Fränkl process) to cool down the gas for liquefaction at about 100 K.
5 First stage of separation: 'high-pressure' column to separate oxygen from nitrogen. Nitrogen is sprayed into the top of the low pressure column to improve separation of pure oxygen in the
6 Second stage of separation: 'low-pressure' column to separate finally oxygen from nitrogen and to gain argon richh mixture.
7 Heat exchanger
Liquid Nitrogen (LIN)/Liquid Oxygen (LOX) Storage of the liquid product (oxygen, nitrogen)
The argon enriched mixture (GAN) is separated in an additional column, argon is purified by the reaction of hydrogen with oxygen and thus is pure argon created.

Figure 1.2 Air separation: schematic drawing [8].

Sometimes, these impurities undergo an increase or a decrease during a longer period of time, for example, since the 1950s, trace concentrations of carbon tetrafluoride and sulfur hexafluoride have shown continuous increase.

All nuclear events of the past released radioactive material into the atmosphere [8], krypton being the most prominent gas emanated. Radioactive isotopes of krypton kept changing in their concentration, depending on nuclear activities (atmospheric nuclear bomb tests in the 1950s, test ban in the 1960s, nuclear fallout following the Chernobyl disaster in the 1980s and the Fukushima blasts in the twenty-first century).

All these atmospheric ingredients, oxygen, nitrogen, and even the trace gases are integrated parts of appropriate cyclic equilibrium processes triggered by the dynamic chemical and meteorological phenomena of the atmosphere created by sunlight.

The fundamental starting point is that of cool gas sinking to the ground, while warm gas rises up in height; on the way upward, the warm gas is cooled down again and starts descending to the ground at another place. In addition, the possible content of water, as vapor or as droplets, which is directly linked to the temperature of the gas, is cause for many additional effects such as the generation of clouds and fog, as well as rain and snow.

Chemical effects are an integrated part of the meteorological effects in the air. Numerous reactive constituents forming reaction chains that are constantly stimulated by the UV part of sunlight, lightning in thunderstorms, and so on. All this depends on the height of the layer in the atmosphere.

Figure 1.3 shows the different layers schematically. Every layer has its own specific contribution to the chemistry of the atmosphere depending on the specific conditions (composition and physics, such as UV-radiation and water content). This leads to a gradient in the concentration of most trace gases at different heights above the ground.

The upper layers of the atmosphere being subject to high radiation (UV and shorter wavelengths) in some manner collect gases escaping from the lower layers, because of chemical inertness. Under the conditions prevalent in the stratosphere, these molecules react with other light gases such as ozone that collect there (Figure 1.3).

Owing to the emitted radiation, radioactive substances such as krypton-85 (Kr-85) can easily be traced down to a few atoms with appropriate counters. Kr-85 is one of the fragments created during nuclear fission. Since it is an inert gas, traces of Kr-85 are emitted at every nuclear activity. The radioactive half-life of Kr-85 being 10.7 years [11], nuclear disasters such as Chernobyl, Fukushima, and others lead to a temporary worldwide increase of the available Kr-85 in the atmosphere and thus to a change in the radioactive load of the krypton fraction in the ASU.

These global effects are more of academic than of practical interest. Krypton is isolated from the residual oxygen fraction in the ASU: even if Kr-85 can be detected owing to the high sensitivity of the measuring methods, the actual amounts remain below the threshold limit values in the gas phase. Oxygen generated in air separation plants all over the world is a unique product and contains no radioactive particles above the natural level. Owing to the physical properties of liquid air in the rectification column, the process of air fractionation is quite stable if the frame conditions are maintained such that other (chemical) contaminations are not present.

Any failure of compression, of pumps, or of valves leads to an instant interruption in the process and the column is transferred to a safe condition. Moreover,

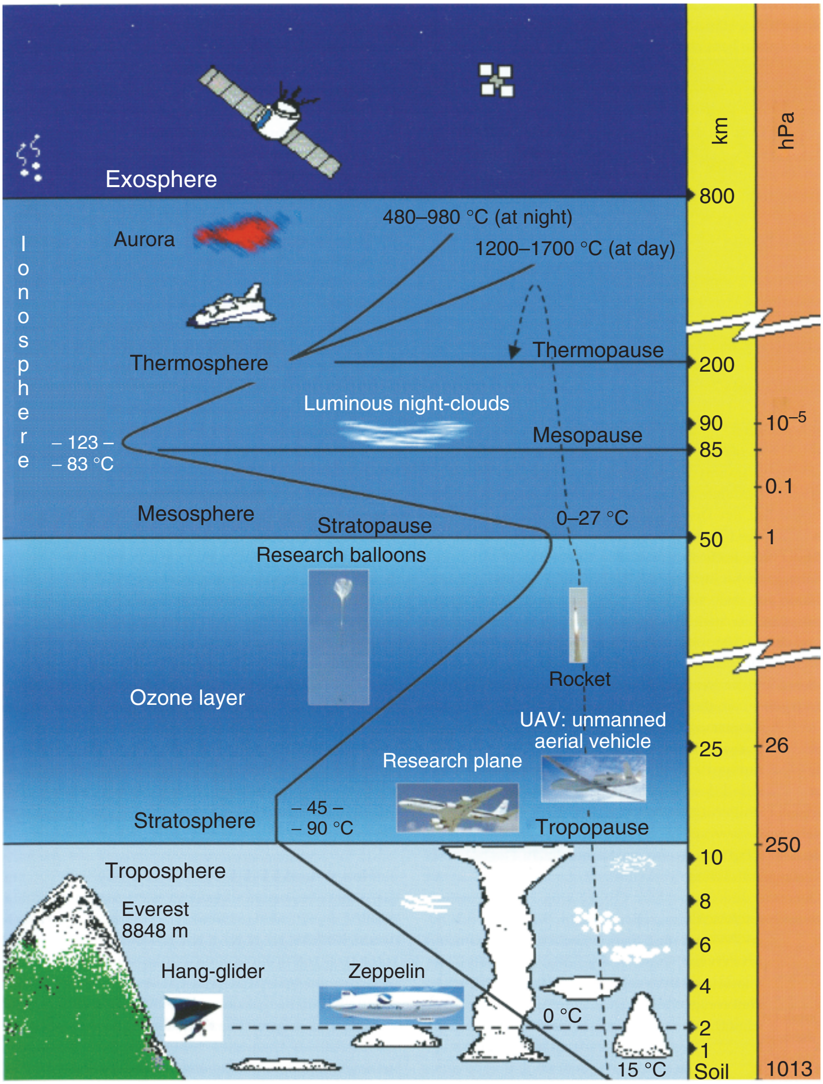


Figure 1.3 Different layers in the terrestrial atmosphere [10].

for reasons of safety, it is mandatory to check on-line the concentration of hydrocarbons in the oxygen (namely, acetylene that is collected) to avoid disastrous explosions.

1.1.1.1 Oxygen

Industrially generated oxygen contains argon as the main contaminant with the highest concentration of about 1 vol% maximum. The generated oxygen is suitable for big industrial needs of oxygen, namely, in the steel industry and, to some extent,

Figure 1.4 View of an air separation plant (Air Liquide).

the chemical industry, glass and ceramic industry, and finally the pulp and paper industry. The fraction of oxygen that remains for use as medicinal gas is thus only a small part of the overall oxygen consumption (Figure 1.4).

In spite of the importance of oxygen in medicine, there are only a few ASUs that work exclusively for the generation of medicinal oxygen. Medicinally used oxygen is just a by-product in the huge air separation process in most cases, which branches out beyond the plant, where it is then subject to further treatment following the GMP (good manufacturing practice)-rules.

Although consisting of the same molecules as industrial oxygen, medicinal oxygen is manufactured and processed as a drug, following the general GMP-Guidelines on the manufacturing of medicines for human use and also the specific GMP-Guidelines for medicinal gases, which will be explained in detail later in this book. In contrast to industrial oxygen, every batch of medicinal LOX and every cylinder of gaseous medicinal oxygen can be traced back to the generation and manufacturing process, because of an extended stepwise documentation of the manufacturing process including all checks and analysis made during generation.

Oxygen is marketed in Europe as a medicinal product both in liquid state as a cryogenic liquid or as a pressurized gas in steel cylinders (the pressure varying between 150, 200, and 300 bar). Although never administered to patients in its liquid form, the cryogenic liquid is also regarded in some countries as a medicinal product.

The cryogenic liquid itself requires some special care, as there are two main dangers inherent in this specific state of matter: the volume of gas generated even by small amounts of cryogenic liquid is quite considerable, one volume of LOX is vaporized forming a volume of gas that is almost 690-fold. This results in considerable oxygen enrichment, requiring a number of necessary precautions that are described later in this book.

The other main risk from a liquid at cryogenic temperature is the effect of the very low temperature on all sorts of materials, including human skin: on biological materials, a kind of cold burn is induced under sustained contact with the liquid (a few seconds are enough), while numerous materials show an effect called *cold embrittlement* when in contact with the very cold liquid and reaching cryogenic temperatures.

Owing to the low temperature, the material properties can be altered dramatically in a way that all mechanical strength is lost, and, for example, pipes lose their pressure resistance. All materials possibly or occasionally in contact have to be resistant to cryogenic temperatures, otherwise the access of cryogenic gas or liquid to such material parts has to be strictly prevented.

1.1.1.2 **Nitrogen**

The medicinal use of nitrogen is in most cases limited to application of its physical properties, namely, the transportation of cryogenic temperatures to any form of tissue to provide a sustainable conservation under low temperature, or, often under replacement of nitrogen by carbon dioxide of nitrous oxide, treatment of skin surfaces to clean up warts or similar irritations of the skin.

Although liquid nitrogen (LIN) is readily available, the handling of LIN, namely, the conservation of biological material requires sophisticated techniques to avoid destruction of the treated samples. Anyone who has already tried to freeze strawberries in a refrigerator would have experienced the difficulties of a proper freezing process, which is absolutely required so as to not to damage the cells by the sudden formation of ice crystals.

Special care has to be taken in the vicinity of storage containers to prevent hazards of LIN, especially in confined spaces.

The vaporizing liquid develops upon vaporization about the 850-fold volume of gas, creating a serious danger of asphyxiation, as the oxygen content of the air available for breathing will rapidly decrease in the vicinity of the container/s.

This risk is extremely high, when large amounts of substance are to be cooled down, thus warming up the liquid, generating large amounts of gaseous nitrogen, or during cooling down of “warm” containers, when all LIN in the containers has been removed by prior operations. Until the container has reached cryogenic temperatures again, LIN is vaporized in large quantities (Figure 1.5). The picture is showing on the left hand side a considerable flow of gazeous nitrogen leaving the receptacle, replacing oxygen in confined spaces.

Cryogenic temperatures on their own will create another risk, the danger of cold burns after contact with liquid or with cold parts of the piping or manifold. Cold burns are malicious, as because of an anesthetic effect of the cold, pain appears only after a while, when the burn has already taken place. It is a common practice to use the Leidenfrost phenomena for short contact with the hands or skin without any degradation of the skin: a thin layer of vapors isolates the exposed parts of the body, thus preventing for fractions of seconds deeper irritations such as burns or other such injuries.

Figure 1.5 Refilling LIN containers with cryogenic liquid (own picture).

In spite of a broad dissemination on the TV and Internet, this practice remains dangerous for two main reasons: bringing larger parts of the human body in contact with cryogenic liquid leads to accelerated vaporization of the cryogenic liquid, and the consequence is a highly possible oxygen deficiency of the environment, and last but not least, owing to contamination of the wetted skin, the generation of the isolating layer is not always the same, with possibly spots remaining with less or without isolation of the vapor layer, leading to severe burns of these parts.

1.1.1.3 **Argon**

Argon, being industrially the most widely used of the rare gases, finds use in a wide variety of applications, usually based on the ability of the gas to generate a stable electric discharge arc in an electric field. While this effect is used mainly for cutting and welding and in the lamp industry, it can be used also in the medicine under special conditions to close fissures in the tissue.

In clinical practice, this is done in surgery and at the dentist. The arc generates very high local temperatures leading to eschar at the edges of the cut or of the tissue.

1.1.1.4 **Xenon**

Xenon is present in air in orders of magnitude below the concentration of argon: it can be found only in trace concentrations, a generally accepted value of the content in ambient air is 0.08 ppm, meaning that a medium-sized presentation hall of 10 m length, 10 m width, and 5 m height containing roughly 500 m^3 of air contains about 40 ml xenon [12].

In specially equipped ASUs, a xenon-enriched liquid can be isolated, mainly consisting of krypton and oxygen. This liquid is often called the crude krypton.

Therefore, in a second additional process, this remaining enriched liquid is collected and processed again, to yield krypton and xenon in relevant quantities. This multistage enrichment process was originally developed for the isolation of krypton (see Figure 1.6, [13]). In a common layout, it first collects a fraction of crude krypton from one or more ASUs, which is liquefied again and then processed in liquid phase, separating the liquid into two gases: krypton and xenon. Xenon is kept back as a condensed liquid (Figure 1.6).

In the medicinal environment, xenon can be used in two different applications: for use as a contrasting medium in magnetic resonance tomography (MRT) (xenon affects the spin of the electrons). Xenon additionally has a market authorization in Europe as a mild anesthetic gas. In conjunction with other anesthetic agents, xenon gives a more tolerable anesthesia [13]. The narcotic effect can be supported with common liquid anesthetics to receive a very soft and smooth anesthetization, without some common, unwanted effects.

Technical applications not in the medical field include the filling of high-performance lamps (flashbulbs and headlights of cars) and extraterrestrial use as fuel in ion engines used for satellite movements in space.

Especially during anesthetization, large quantities of unwanted xenon would escape into the environment. As a consequence, an economic use of xenon in

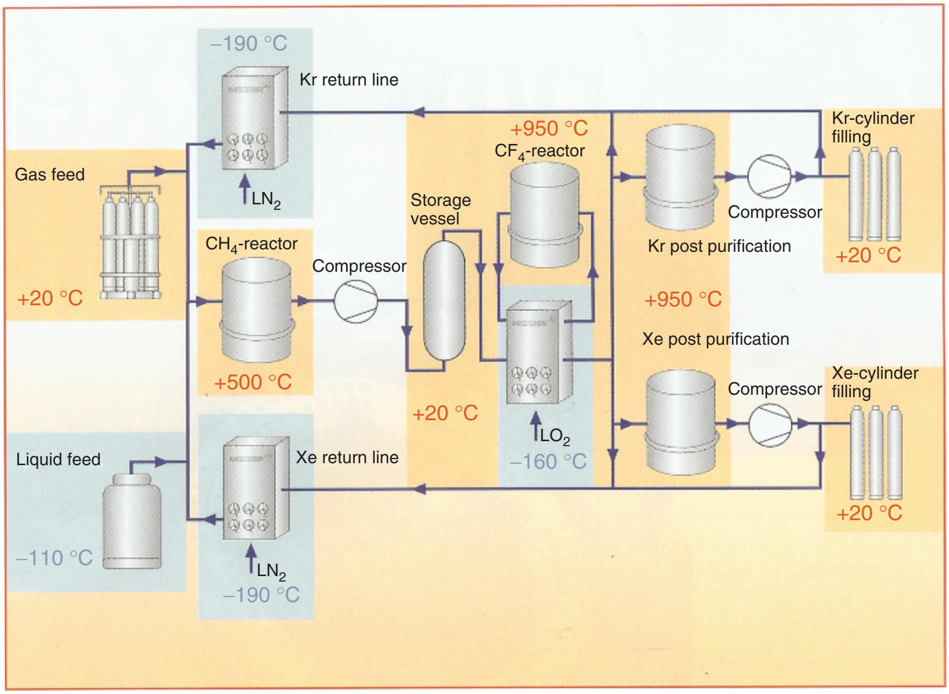


Figure 1.6 Separation of krypton and xenon [13].

Table 1.2 Physical properties of gases (I, [14]).

Name	Boiling point (°C)		Critical temperature (K)	Cylinder pressure (bar)	Status
Nitrogen	−196	77.4	126.26	200	Gas
Oxygen	−183	90.2	154.48	200	Gas
Argon	−186	87.3	150.86	200	Gas
Xenon	−108	165.1	289.74	52[a)]	Liq u pr

a) At 0 °C.

anesthetics is only possible with recirculation of nearly 100% of the used xenon in a closed-loop anesthetic device.

Xenon is marketed in cylinders liquefied under pressure. Some of the physical properties of xenon are listed in Table 1.2.

1.1.2
Gases Separated from Other Sources: Helium, Carbon Monoxide, Methane

Although most of the medicinal gases other than oxygen are present in traces in the ambient air, under the conditions of cryogenic air separation, the isolation, for example, of helium is not recommended: helium has a very low boiling point, thus it collects in the gas phase of the distillation column at a specific localization in the column. Larger quantities of helium (meaning here, a few liters) collected after appropriate periods of time form gas bubbles at the heat exchanger, thus decreasing the thermal conductivity and hence the efficiency of the unit. From this reason, helium (and hydrogen) has to be vented from time to time to eliminate the isolating gas, keeping the performance of the heat exchanger in the required range.

1.1.2.1 **Helium**

Helium was first identified on the sun, when, in the second half of the nineteenth century, Lockyer and Janssen discovered a new spectral line in the corona of the sun during an eclipse [14].

In the beginning of the twentieth century, it happened that helium came into the focus of military planning: lighter than air, it could be used to fill zeppelin-type airships and observation balloons. Helium is a rare gas and does not burn at all and so had been revealed to be a “safe” filling gas for airships at that time.

Military airships were not so common, because when filled with hydrogen, minimal sparks were sufficient to ignite the filling gas, creating a flash fire and causing the total burnout and loss of the ship. The disasters in the beginning of the twentieth century were legendary, but finally the crash of the “Hindenburg” during landing in Lakehurst, NJ, in 1937 brought an end to the filling of airships with hydrogen.

In our terrestrial environment, the amount of helium is limited. As no new sources of helium exist, it was decided that helium was a strategic war material. In consequence, a strategic reserve of helium was stocked. This “strategic” stock of helium in underground storages developed strong effects on the helium market in the world: by collecting or releasing amounts of the stored helium, the price development of the helium from third party sources [16] was strongly influenced.

With an average content of about 5 ppm in ambient air, helium is much easier to separate from natural gas, if this gas contains up to 0.1 vol% of helium, the method as such requiring about 0.04–0.3 vol% of helium. Isolating helium from gas wells with such low helium concentrations clearly needs a large quantity of natural gas to be processed, which is usually the case only in winter, when the consumption of natural gas rises.

Natural gas wells with a suitable concentration of helium and good productivity are quite well distributed all over the world, so helium needs very sophisticated logistics to be transported to the consumer. To save resources, helium is transported over long distances exclusively as a cryogenic liquid at the extraordinarily low temperature of approximately 4 K. This matches also quite well with the application of helium as cooling agent for superconducting magnets. Without the need for liquefaction on-site, helium only needs to be refilled as a liquid (Table 1.3).

At present, in large natural gas wells, when the main components of the gas (mainly methane and carbon dioxide) are liquefied, helium contained in the gas remains in the gas phase, is collected, purified, and also finally liquefied (Figure 1.7) [22].

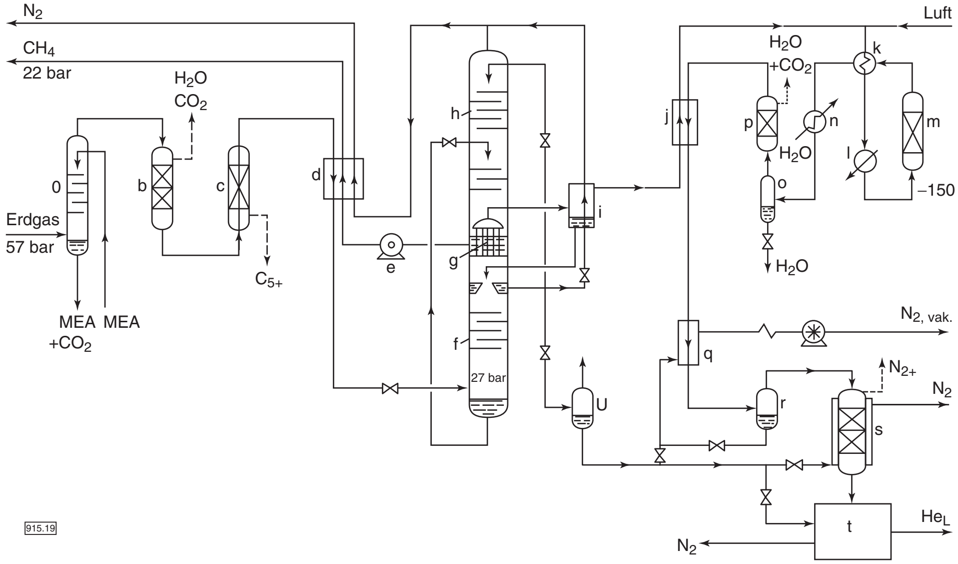


Figure 1.7 Separation of helium from natural gas [22].

Table 1.3 Exploitation of natural gas wells for helium [22].

Location	Liberal Kansas		Otis Kansas	Alfortville Frankreich	Ostrow Polen
Operator	n.a.		n.a.	n.a.	—
Manufacturer	n.a.		n.a.	n.a.	n.a.
On Stream since	1963		1966	1969	1975
Natural Gas	Kansas	Texas		Groningen	
Analyze (mol%)					
He	0.45	0.40	2	0.05	0.40
H_2	—	—	0.01	—	0.01
N_2	14.62	9.36	23	14.30	42.75
CH_4	72.74	79.26	68.5	81.15	56.01
C_2H_6	6.26	6.77	3.5	2.90	0.44
C_{3+}	5.73	4.01	2.5	0.70	0.99
CO_2/H_2S	0.20		0.5–1	0.90	0.30
Pressure (bar) abs.	45		20	41	57
Quantity ($m^3 h^{-1}$)	950 000		25 000	65 000	137 000
Helium-Product					
Quantity ($m^3 h^{-1}$)	6500		500	25	480
Purity (mol%)	65		>99 995	99 999	99 999
State of matter	gas		liquid	gas	liquid
Pressure (bar)	124		—	350	—

Figure 1.8 Helium tank trailer (own picture).

Helium is distributed in liquid phase in tank trailers (Figure 1.8), which are transported over sea by ship or by truck tractors over land. Large helium-containing natural gas wells are situated, for example, in the United States (Wyoming), in Russia (Sibiria), and in Qatar. The main consumers are concentrated in Western Europe, the United States, Russia, Canada, and Japan.

As mentioned above, helium is liquefied to optimize the transport. After liquefaction very pure helium gas is obtained when vaporized from the −269 °C cold liquid. The transport is managed with a kind of standardized tank trailers, each with a capacity of approximately 40000 l of liquid helium. Helium is transported in these tanks from the source to the customers everywhere in the world.

Helium is used as a refrigerant for superconducting magnets, as used in the medicinal MRT. To yield high resolution imaging, the magnetic field must be very strong. This is only possible using superconducting magnets. The solenoids are cooled down by liquid helium (temperature 4.2 K) to reach a superconducting state (Figure 1.9).

Before going onstream, the magnet is precooled with LIN, then nitrogen is removed by purging with helium, and finally, the cooling chamber is flooded with liquid helium. During normal operation, helium is gasified and evaporates in small quantities, depending on the efficiency of the isolation of the magnet.

An unwanted incident is the so-called “quenching” of the magnet. If the helium filling has fallen under a limit, parts of the solenoid can reach a temperature, where the superconducting property is lost. The resistance heats the solenoid very quickly and leads to a total warming of the solenoid, while more than 50% of the liquid helium filling is vaporized (as also the LIN shielding). The huge amount of gas generated must be safely vented.

Figure 1.9 Superconducting MRT (magnetic resonance tomography) (15).

1.1.2.2 Carbon Monoxide

The old coke-oven processes disappeared in Europe parallel to the end of extended coal mining. Town gas has been substituted widely by natural gas, which is not as toxic and thus easier to handle. Carbon monoxide, therefore, nowadays is generated in the steam-reforming process, mainly used for the generation of hydrogen from natural gas. After removal of the sulfur components in natural gas (reduction to hydrogen sulfide and absorption with zinc oxide), the natural gas is mixed with hot water vapor and passed over a catalytic reactor in two stages to form a mixture of carbon monoxide and hydrogen.

According to the applied temperature, a mixture of hydrogen, carbon monoxide, carbon dioxide, and methane is generated, leaving the reactor at about 850–950 °C. The ratio H_2/CO can be varied according to the need of the application or hydrogen and carbon monoxide will be separated to yield pure hydrogen and pure carbon monoxide[1] (Figure 1.10).

Carbon monoxide is purified from carbon dioxide by absorbers and then liquefied and rectified for high-purity carbon monoxide. The typical impurities in carbon monoxide are hydrogen, methane, and nitrogen under specific conditions (high pressure, steel cylinder) also iron-penta-carbonyl and nickel-tetra-carbonyl

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[1] Steam-reforming is a process used to generate hydrogen and carbon monoxide from natural gas or from higher hydrocarbons. The reformer contains a nickel catalyst, which transforms the steam–gas mixture into synthesis gas (H_2-CO·CO_2-CH_4), which is then processed again to yield either a mixture of hydrogen and CO or hydrogen and CO_2 (Air Liquide).

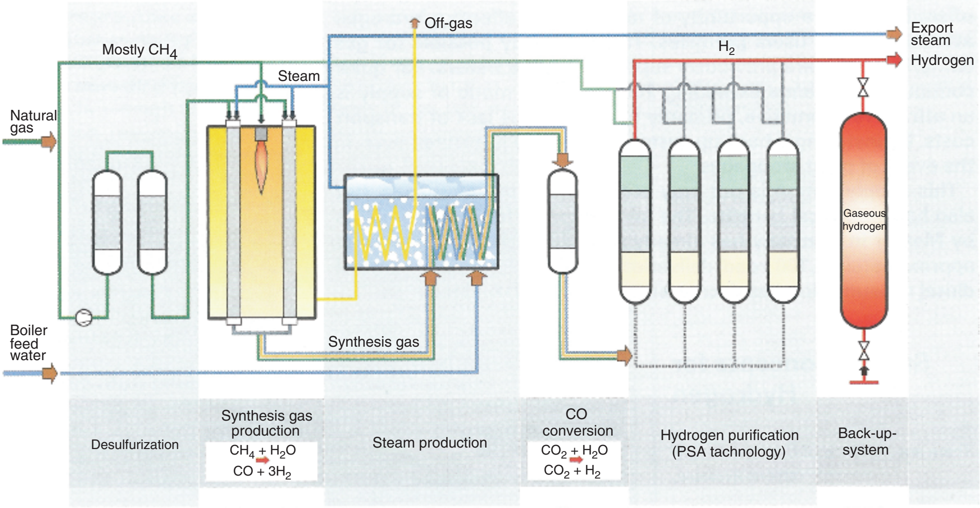


Figure 1.10 Schematic of the steam reforming process (1).

can be formed. Before medicinal use, all these compounds have to be completely removed.

A further purification can be done by liquefaction of carbon monoxide at cryogenic temperatures followed by a rectification. Cryogenic rectification is most often used to purify carbon monoxide beyond technical grades. Figure 1.11 shows a separation column from the outside.

Figure 1.11 Separation column for the purification of carbon monoxide [24].

1.1.2.3 Methane

Methane is a very common reaction product in various types of biodegradation. Natural gas, one of the most important sources of energy all over the world, contains up to 95% methane. It is liquefied and rectified to yield high-purity methane, suitable for all sorts of chemical syntheses.

Being a very stable molecule, methane can be found as a trace gas all over the world with an average concentration of about 1 ppm in the atmosphere. For industrial use, in most cases, pure methane is used. This is either generated by the reaction of carbon monoxide or carbon dioxide with hydrogen or separated from natural gas.

Natural gas consists of methane and carbon dioxide, in changing ratios, depending on its source. The composition of natural gas ranges widely from "dry gas," containing only methane and water in changing quantities, up to methane hydrates, "wet gas," accompanying oil wells and containing higher hydrocarbons up to C7 and carbon dioxide and sulfur compounds, and natural gas coming from condensate sources, containing hydrocarbons higher than C7 [24] (Table 1.4).

1.1.3
Gases from Chemical Synthesis: Carbon Dioxide, Nitric Oxide, Nitrous Oxide

1.1.3.1 Carbon Dioxide

Carbon dioxide is the stable residual of many exhaust gas purification processes in the chemical industry or a stable by-product of many chemical synthesis reactions. To yield higher purity, all contaminations (hydrocarbons, sulfur compounds, others) are oxidized in a catalytic converter under addition of oxygen and then separated (sulfur dioxide, nitric oxides, etc.) from the gas. From this reason a stable source with known composition should be used if the carbon dioxide is intended for medicinal use.

The fundamental steps for obtaining pure carbon dioxide are shown in Figure 1.12.

Table 1.4 Physical properties of gases (II) [14].

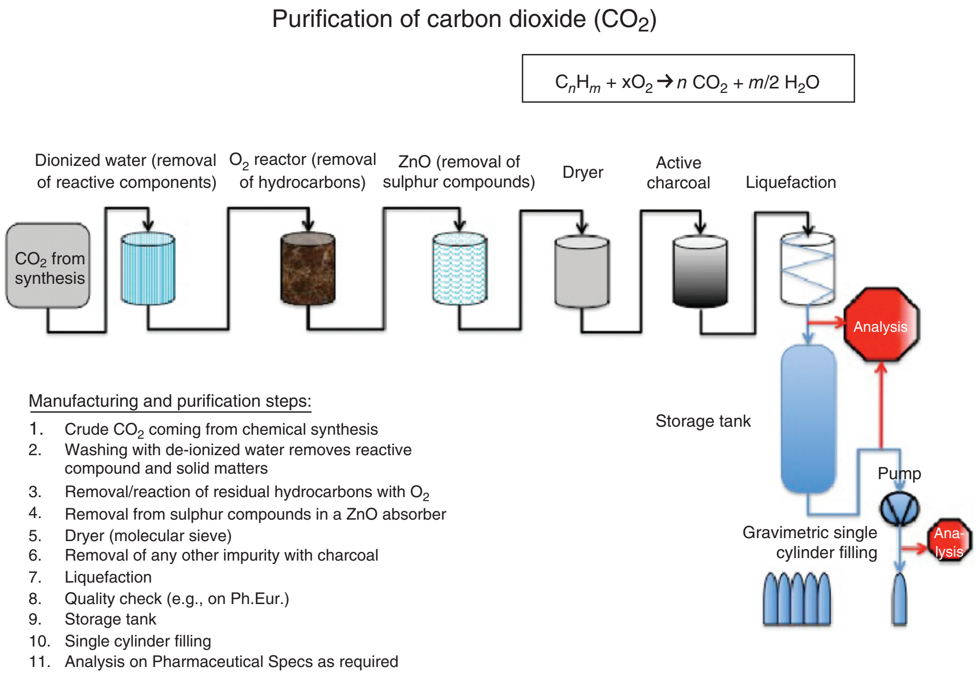
Name	Boiling point (°C)		Critical temperature (K)	Cylinder pressure (bar)	Status
Methane	−162	111.6	190.56	200	Gas
Carbon monoxide	−192	81.6	132.85	200[b)]	Gas
Helium	−269	4.2	5.20	200	Gas

a) At 0 °C.

b) Reduced for quality.

Although carbon dioxide is not toxic, breathing of higher concentrations than 8 vol% result very quickly in reactions within the body as carbon dioxide triggers a breathing reflex, and higher concentrations induce headaches, dizziness, and rising blood pressure.

Carbon dioxide is easily liquefied under pressure, filled in cylinders, and is marketed in steel cylinders of different volumes.



Manufacturing and purification steps:

1. Crude CO_2 coming from chemical synthesis
2. Washing with de-ionized water removes reactive compound and solid matters
3. Removal/reaction of residual hydrocarbons with O_2
4. Removal from sulphur compounds in a ZnO absorber
5. Dryer (molecular sieve)
6. Removal of any other impurity with charcoal
7. Liquefaction
8. Quality check (e.g., on Ph.Eur.)
9. Storage tank
10. Single cylinder filling
11. Analysis on Pharmaceutical Specs as required

Figure 1.12 Purification of carbon dioxide.

1.1.3.2 **Nitric Oxide**

Nitric oxide is produced by the reaction of an aqueous solution of sodium nitrite and sulfuric acid or as an intermediate during combustion of ammonia for the synthesis of nitric acid (Figure 1.13). The generated gas is washed and dried in several stages and finally dried with a molecular sieve, compressed, and filled in steel cylinders. As nitric oxide is not stable under pressure, cylinders for highly pure nitric oxide are filled only to a pressure of approximately 50 bar, to keep the self-decomposition low, as this would contaminate the gas with other nitrogen oxides.

Nitric oxide must not be used undiluted. In lower concentration, nitric oxide can support specific breathing activities.

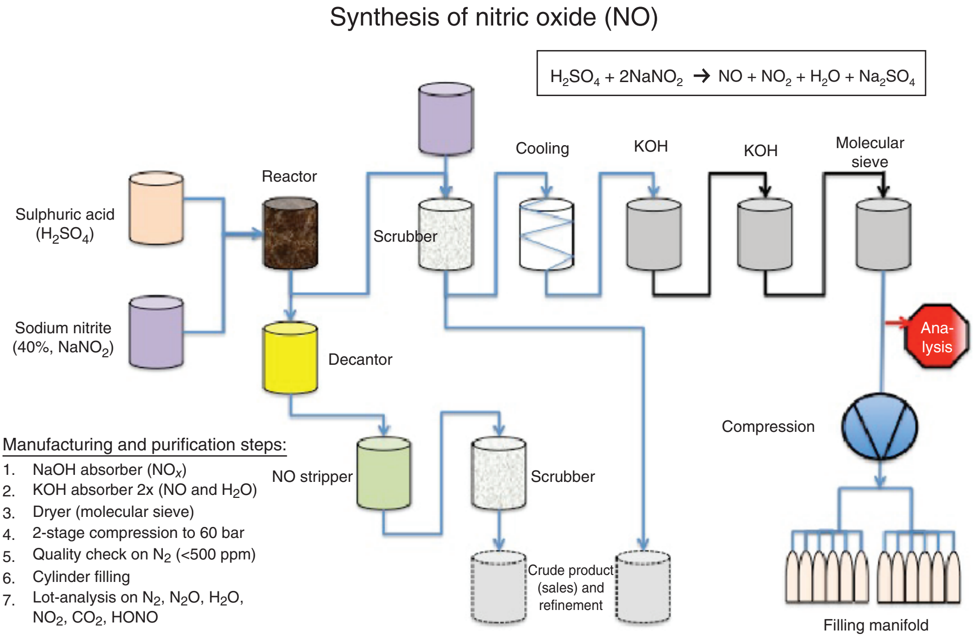


Figure 1.13 Synthesis of nitric oxide.

1.1.3.3 Nitrous Oxide

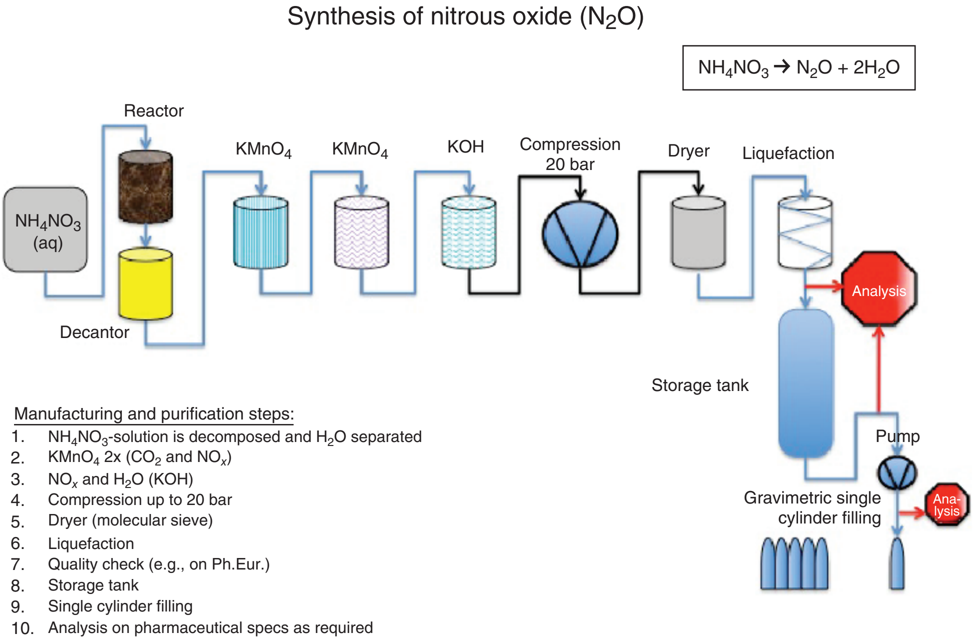
Although nitrous oxide is generated by numerous microbiological reactions in the soil, depending on the content of nitrogen and hydrocarbons [10] and thus released in the atmosphere, it is not separated from the air during fractional distillation.

Nitrous oxide is related to the fertilizer industry. Careful heating decomposes a concentrated solution of ammonia nitrate and the generated gas is nitrous oxide with trace impurities of nitrogen oxides and carbon dioxide (Figure 1.14).

Once these impurities are removed by washing, the gas is dried and liquefied and filled into appropriate steel cylinders as a gas liquefied under pressure. Nitrous oxide is stable under ambient conditions, but it supports fire and decomposes under high temperatures with tremendous release of energy.

The physical properties of nitrous oxide are similar to those of carbon dioxide, being a very efficient solvent in the supercritical state and liquefying/solidifying when the pressure decreases below a limiting value. The gas is liquefied under pressure and stored in cylinders (Table 1.5).

In the early days of gas therapy, it was Humphrey Davy, in about the year 1800, who first described the analgesic effect of nitrous oxide or laughing gas [28].



Manufacturing and purification steps:

1. NH_4NO_3-solution is decomposed and H_2O separated
2. $KMnO_4$ 2x (CO_2 and NO_x)
3. NO_x and H_2O (KOH)
4. Compression up to 20 bar
5. Dryer (molecular sieve)
6. Liquefaction
7. Quality check (e.g., on Ph.Eur.)
8. Storage tank
9. Single cylinder filling
10. Analysis on pharmaceutical specs as required

Figure 1.14 Synthesis of nitrous oxide (N_2O).

Table 1.5 Physical properties of gases (III) [14].

Name	Boiling point (°C)		Critical temperature (K)	Cylinder pressure (bar)	Status
Carbon dioxide	−78	197.7	304.21	55[a)]	Liq u pr
Nitric oxide	−152	121.4	180	200[b)]	Gas
Nitrous oxide	−88	184.7	309.56	55[a)]	Liq u pr

a) At 0 °C.
b) Reduced for stability.

1.1.4
Gas Mixtures for Inhalation

Except for oxygen, most of the described gases are not administered to the patient as pure gases, the reason being that any patient needs at least 20.9 vol% of oxygen in the gas he breathes in order to survive.

Any lack of oxygen is dangerous for the patient as all the organs, namely the brain, are very sensitive to oxygen deficit. Within a few moments, the level of oxygen in the blood is reduced to very low concentrations as the remaining oxygen in the blood vessels is further reduced by continued inhalation of gas without oxygen or with low oxygen levels.

So for reasons of safety, it is recommended that reliable breathing machines are used to mix gases at the operation theater or near the patient. In most of the European countries, gases for inhalation need a manufacturing license, as legally they are drugs because of their intended use for medicinal or diagnostic purposes so the breathing machines are medical devices acc. 93/42/EEC conso. 2007/47/EC [164]. Other gases are legally treated as medical devices, when they do not have a pharmaceutical effect on the patient, for example, carbon dioxide and some fluorohydrocarbons are used for dilatation purposes in diagnosis and micro-invasive surgery or for dilatation of the eye-ball often their application includes the appropriate medical device to facilitate the technical exercise.

Mixing gases is a matter for experts, as the gases have complicated physical properties, depending on their boiling, critical, and triple points. Wrong operation during the mixing procedure can lead to completely erroneous results, lack of preparation of cylinders can lead, for example, with reactive components, to instable mixtures, and, last but not least, mixing of oxygen and organic gases without thorough safety precautions can lead to serious explosions [29], often with drastic consequences.

In principle, the mixing of gases can be done either by weight (“gravimetric”) or by volume (“volumetric”) of the gases. Both methods having inherent difficulties in practice: while gravimetric methods suffer from the low weight of the gases (so 1 m^3 of nitrogen weighs only $\approx$ 1 kg) because of temperature-effects the volumetric methods are difficult to handle, because they need extraordinarily exact measurements, not only of the volume but also of pressure and temperature.

The fundamentals of how to prepare mixtures and perform measurements according to the Pharmacopoeia is laid down in the Annex 6 of the GMP and will be explained later. In fact, determination of the exact amount of the active ingredient is an important step during production of gas mixtures and puts high demands on the purity of the gases, the quality of the analytical methods used, in terms of stability and traceability of the calibration gases used, and in terms of the handling of the sample.

In other words, the use of ready-made gas mixtures, prepared and secured in their composition by reliable gas manufacturers, is recommended. This is true even for the simplest of all gas mixtures, recombined or synthetic air: in some European countries, recombined air is used as a substitute for compressed medical air.

For the substitution of mixing gases near the patient, ready-made mixtures for inhalation typically include the following:

1.1.4.1 **Reconstituted (Synthetic) Air**

It might be recommended to use recombined air when ambient air is polluted or loaded with contaminants, which is sometimes the case in summer in warmer regions. When mixing oxygen and nitrogen, the final mixture has to be analytically verified to be in the right concentration range of oxygen (between 20 and 22 vol% as defined in the appropriate Pharmacopoeia) to avoid any difficulty due to wrong oxygen concentration: an oxygen deficiency would create serious deterioration in the breathing of patients, an oxygen enrichment would create serious danger to the environment around the patient, as oxygen enrichment would cause a fulminate acceleration of fire if present.

1.1.4.2 Compressed Medical Air

Although a mixture, ambient air is usually regarded as a single gas, because during purification and compression, ambient air behaves like a single gas, by not demixing or decomposing during ordinary operations. The use of compressed medical air is only restricted by the quality of the ambient air, its contaminations, and water load. To remove these contaminations, information about the ambient air quality at the inlet of the compressor is needed, for example, if there are incinerator plants, heating installations, or laundries, in the neighborhood.

1.1.4.3 Nitrous Oxide 50 vol% in Oxygen

The mixture is used as a substitute to mixing gas with a breathing machine in cases where the application of breathing machines would be too complicated owing to the nature of the anesthesia required. This gas mixture is often used by practitioners or dentists. The use of the mixture is prevalent because it obviously breaks Dalton's law [30]: in a cylinder at room temperature, a unique and permanent gas phase with a pressure of up to 200 bar is available for use.

1.1.4.4 Nitric Oxide Approximately 1000 ppm in Nitrogen

This gas is used for inhalation to support dilatation of blood vessels in the lung environment. This gas must be used only with appropriate application devices to provide reliable mixtures with oxygen and to minimize formation of nitrogen dioxide by contaminated hoses or adapters.

1.1.4.5 Mixtures with the General Composition Carbon Monoxide, Helium in Synthetic Air (Carbon Monoxide Ranging between 0.2 and 0.3 vol%, Helium between 8 and 18 vol%)

These mixtures are used for diagnosis of lung functions. Depending on the type of instrument and the manufacturer of the device, they are used to measure the capacity of the patients' lungs by (blood) analysis during or after inhalation. Carbon monoxide is readily absorbed by erythrocytes, thus showing the equilibrium between offer of carbon monoxide and the value of occupied erythrocytes [25], equal to the absorption potential for oxygen.

1.1.4.6 Carbogen (5 vol% Carbon Dioxide in Oxygen)

In some mixtures, the positive effect of carbon dioxide on the breathing center is supported by adding small amounts of carbon dioxide to the gas (e.g., Carbogen is a mixture of 95 vol% oxygen and 5 vol% of carbon dioxide [26]). This concentration accelerates breathing which is in some cases of administering oxygen, a wanted effect [27]. Carbogen is used to facilitate exchange of gas molecules occupying erythrocytes. By the offer of a large excess of oxygen it is ensured that occupied erythrocytes are liberated by oxygen in very short time. As the exhalated gas contains only little carbon dioxide, this component has been added to support the breathing center, triggering deeper and more frequent breathing.

1.1.5
Gas Mixtures for Reference – Calibration Gas Mixtures

While all tests of the human and animal breathing functions rely on exact analysis of the composition of the exhalated gas in comparison to the inhalated ambient gas, reliable calibration gases are crucial to the determination of the concentrations.

As described above, Addition of carbon monoxide to the inhalation gas allows calculating the lung capacity via the calculation of the capacity to absorb carbon monoxide. Analytically, the ratio between inhalated and exhalated carbon monoxide is estimated and calculated.

Adding helium to the inhaled gas, the ratio of inhaled volume to lung volume can be calculated, thus the total active lung volume is estimated. Specialized analytical mass spectrometers are used to carry out all dilution and diffusion measurements simultaneously [31].

All electronically based analytical instrumentation needs gaseous standards to connect the reading of the instrument with the concentrations of the components. To accomplish this, all sorts of gases with carbon dioxide (often between 2 and 10 vol%) and oxygen (between 2 and 20 vol%) in nitrogen are now in clinical use.

The final determination of the ingredients of a gas mixture is as important as the determination of the concentration of the active ingredient. As a consequence, the manufacture of the gas mixture (preparing of the starting materials, mixing, and exact determination of the product's composition) needs thorough planning and exact handling.

The first step is to find the right material for the cylinder: this is needed to keep a stable composition of the gas mixture over the time. It is obvious that reactive components in the cylinder can react either with the cylinder wall or with other components in the mixture. This would alter the composition of the gas mixture over time, giving either incorrect analysis when used as a standard, or in case of therapeutic mixtures, one would be afraid of decreasing levels of, for example, the active ingredient. Often used materials for cylinders containing gas mixtures are either steel or aluminum, with specially treated surfaces that avoid chemical reactions with the components of the gas mixture.

To prepare gas mixtures, most often the components are prepared in a very pure state and then the mixture is prepared statically by adding one component after the other into the cylinders. For most of the gases with low boiling points, the composition is straightly depending on the partial pressures of the gases in the cylinder adding up to the total pressure.

For gases with higher boiling points, the so called "real gases," this simple equation has to be extended with correction factors to calculate the correct or required concentration. Namely, for carbon dioxide, nitrous oxide, and hydrocarbons, things turn out to be rather complicated and the mixture calculation is experts' knowledge.

Figure 1.15 shows the equations for a real gas, carbon dioxide, and the very obvious deviation from a linear plot as it is for "ideal" gases.

After the components are mixed and the balance added to the mixture, a thorough analysis is of utmost importance for a working standard. The calibration gas mixtures are used as calibration standards for any sort of analysis to establish a connection between the reading of the instrument and the concentration of one or more components in the mixture. This connection must be traceable to the SI System of weights and measures, to be robust enough to establish true analytical values of the subsequent analyses. These calibration gas mixtures thus are directly comparable to standard (volumetric) solutions used throughout the quantitative wet chemical analysis.

Figure 1.16 shows a typical linear calibration function with five calibration gases and one certified reference gas. Although the calibration gases are analytically connected to each other and to the reference gas, the effect is clear to see: the farther the value from the reference gas, the higher the analytical tolerance. Things

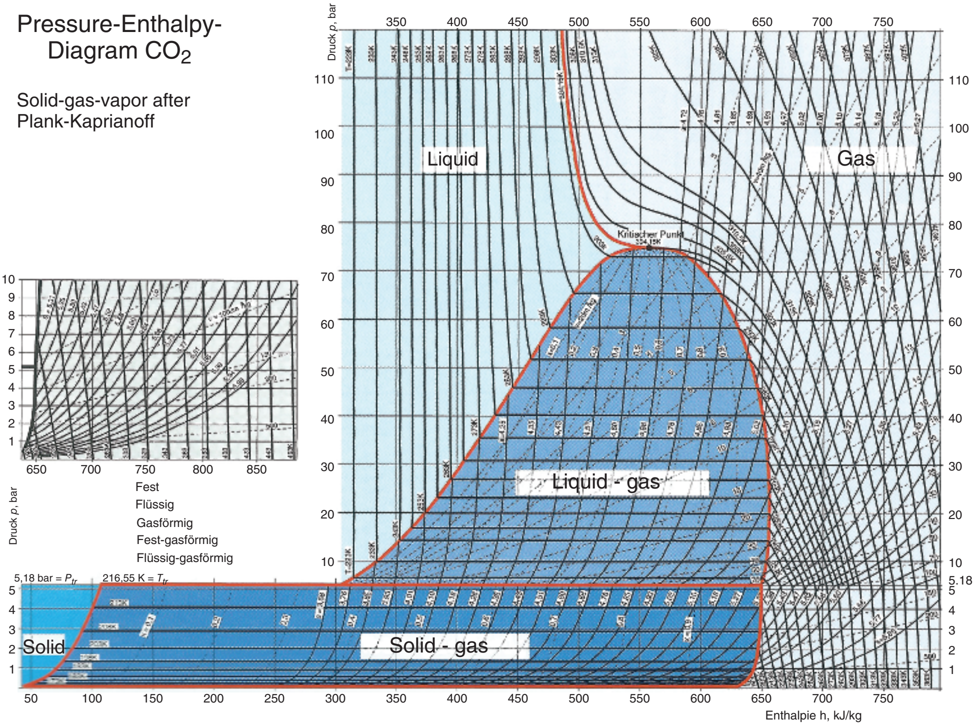


Figure 1.15 Equations of state for carbon dioxide [32].

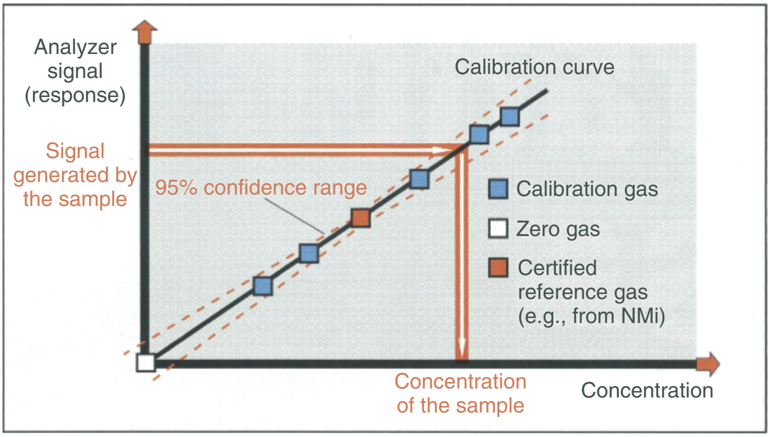


Figure 1.16 Calibration of instruments with calibration gases [33].

become more complicated, when the analyzer produces functions other than linear calibration functions.

For the measurement and good calibration of the instrument, the crucial factor is the withdrawal of the gas from the storage cylinder and the transfer to the instrument. All components of the mixture have to be transferred unaltered into the analytical instrument.

The use of a pressure-regulating device is mandatory from safety reasons: to avoid any damage to the instrument or even of the operators, there is no alternative to the use of a pressure-regulating device. Owing to their inner surface design, the instruments have to be purged several times by pressure buildup/venting cycles before the gas is led to the instrument for measurement [28].