Chemical Warfare—A Chemical and Toxicological Review*

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IN reviewing very briefly the chemistry and toxicology of the war gases, military secrecy demands that my remarks be confined to chemical warfare agents already known to our enemies, and to data about these known agents which will not give them aid or comfort. This, of course, precludes discussion of newer developments, but there is much unrestricted information which may be unfamiliar and of interest.

Of the many thousands of poisonous substances known, only a few have the necessary toxicity, and chemical and physical properties to qualify them as effective war gases.

CLASSIFICATION OF WAR GASES

The chemical and physical properties of the war gases are of primary importance in determining how and when they may be effectively employed, and in predicting what the enemy may do with them. A simple but important classification of gases in this respect refers to the length of time they are effective. If they persist in toxic concentrations at the point of attack less than ten minutes, they are called *non-persistent* gases; if they are effective for a longer time, they are *persistent* gases.

The toxicological properties of the war gases must be known in great detail in order that the proper gas may be selected to produce a particular effect, and in order to know what concentration of the gas must be put down on the target.

The war gases are classified according to their primary toxicological effects, as follows:

WAR GASES

1. Harassing gases
   a. Tear gas (lacrimator)
   b. Vomiting gas (nose gas; sternutator)
2. Casualty gases
   a. Choking gas (lung irritant)
   b. Blister gas (vesicant)
   c. Blood and nerve poisons (systemic poisons)

The harassing gases are used to force the enemy to put on gas masks and to interfere at a crucial time with his effectiveness. These agents have only temporary effects and they do not kill, or even produce dangerous symptoms. The casualty gases are used to injure or kill.

TEAR GASES

The tear gases are all effective in very low concentrations. The most widely employed are the following:

1. Chloroacetophenone, C_6H_5–CO–CH_2Cl, is a white crystalline solid, which is volatilized either from burning or explosive munitions or sprayed as a solution in chloroform, generally mixed with chloropicrin. Once volatilized it is essentially non-persistent. It has a faint odor, somewhat like apple blossoms.

2. Brombenzyl cyanide, C_6H_5–CH–BrCN, is a liquid, which volatilizes slowly. The

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commercial product is light brown in color. It is used as a liquid spray or in explosive munitions. It is moderately persistent and has a fruity odor.

3. Ethyl iodoacetate, CH_2I–COO–C_2H_5, a brown liquid, is less used. It smells like pear oil.

4. Recently, chloropicrin, C–NO_2–Cl_3, or nitro-chloroform, a pale yellow, volatile liquid, has been reclassified as a tear gas. It also causes vomiting and in high concentration it is an effective lung irritant, making it difficult to classify. It is often used in solution with chloroacetophenone. It is very irritating to the nose and has an odor somewhat like flypaper or anise.

The tear gases (or lacrimators) in low concentrations act almost exclusively upon the eyes to produce pain, blepharospasm, a flow of tears and temporary interference with vision. In high concentrations some also irritate and redden the hot sweaty skin.

VOMITING GASES

The vomiting gases are all crystalline solids and are usually dispersed as fine particulate smokes from burning munitions. They are effective in very small concentrations, but their smokes are non-persistent. They all smell somewhat like burning fireworks.

1. Adamsite, or diphenylamine chloroarsine, $HN{=}(C_6H_4)_2{=}AsCl$ produces a canary yellow smoke which fades to colorless as it is diluted by air

2. Diphenylchlorarsine, $(C_6H_5)_2{=}AsCl$

3. Diphenylcyanarsine, $(C_6H_5)_2{=}AsCN$, which produce white smokes, which become colorless on dilution with air

The vomiting gases induce at first a strong sensory irritation of the respiratory tract. The symptoms may be delayed a few minutes in their onset, so the victim may get a good dose of the gas before he knows anything is wrong. He then begins rather suddenly to cough, and in the course of a minute or so this becomes quite violent and uncontrollable. He feels as though his trachea was about the size of a balloon and as raw and irritated as a full blown acute tracheitis. He may sneeze some and soon his nose begins to drip a watery secretion. He is quickly salivated, and feels depressed, weak, and ill. If he is severely affected, he will have nausea and vomiting and pain in his teeth and sinuses, particularly the frontal sinuses. These effects, as you may well imagine, make it difficult for the victim to wear a gas mask. A man fully affected by a vomiting gas looks and feels about as miserable as a human specimen can. Fortunately, however, in spite of his alarming symptoms, he is not seriously injured, and it has been demonstrated many times that he is still capable of strenuous physical exertion. If he can be induced by inspiring leadership to carry on, he can do so without injury to himself, and the effects pass off in an hour or two.

CHOKING GASES

The most important choking gases are phosgene and chlorine, both gases at ordinary temperatures and pressures, but are generally liquefied under pressure for storage in cylinders, shells or bombs. On opening the cylinders or bursting the explosive munitions, they rapidly evaporate to form a gas cloud, heavier than air. If conditions are right, that is, the ground as cool or cooler than the air and the wind very gentle, these clouds will drift along the ground in effective concentrations for several miles.

Phosgene, $COCl_2$, is a colorless gas which irritates the eyes, nose, and throat. Its odor is difficult to describe, but it is probably nearer like that of very musty hay or crushed green cornsilk than anything else.

Chlorine, Cl_2, is a greenish-yellow gas with a very pungent, irritating odor familiar to all.

The effects of these gases are predominantly upon the lower parts of the respiratory tract, particularly upon the terminal bronchioles. Their immediate action is to induce coughing, due to

sensory irritation, and a feeling of constriction in the chest and shortness of breath, due to bronchoconstriction. The heart is slowed and there begins very early a deficiency of oxygen in the circulation. The victim is usually uncomfortable, restless, and apprehensive. He develops a moderate temperature and may sweat profusely. A fair percentage of cases of poisoning by phosgene, however, recover from their initial symptoms after the first few minutes, and may then experience a feeling of well-being for possibly several hours, provided strenuous exercise and deep breathing are avoided. The bronchospasm, bronchiolar edema, and loosening of bronchiolar epithelium bring on a curious mixture of emphysema and atelectasis of the air sacs and cut down the functional capacity of the lungs. There follows, after a few hours, an outpouring of fluid into the alveoli, which seriously interferes with gaseous exchange and enormously accelerates the developing anoxia. The fluid lost into this lung edema causes a serious progressive hemoconcentration and slowing of the circulation. Some of the subjects during these stages exhibit a dusky cyanosis, peripheral venous congestion, and a rising blood pressure, known as the " blue stage." It is particularly common in chlorine poisoning. The " blue stage " may subside gradually and eventuate in recovery, or it may gradually or suddenly pass into the " grey stage " of circulatory collapse. Many cases of phosgene poisoning fail to go through a " blue stage," but pass directly into the " grey stage " of falling blood pressure and a series of symptoms closely resembling shock. The skin appears pale and waxy and is cold and dry. Breathing is hurried and shallow, and the pulse is weak and rapid. The victim is extremely weak, and fearful of impending death, until unconsciousness supervenes. Death is due to an intense want of oxygen by the body tissues and a widespread interference with metabolic processes, which culminates in circulatory failure.

BLISTER GASES

The blister gases are all liquids which vaporize slowly to highly toxic vapors. There are three main classes of these gases:

1. The sulfur mustards, which are compounds, containing sulfur
2. The nitrogen mustards, which contain nitrogen
3. The arsenical vesicants, which are compounds of arsenic

Either the liquids or the vapors burn and injure any part of the body they contact. The eyes and respiratory tract are particularly susceptible, but the skin as well is reddened, burned, and blistered. When they are ingested in food or water, they violently irritate the gastrointestinal tract and produce all the attendant symptoms of pain, nausea, vomiting, and collapse. They attack any part of the respiratory tract, but the predominant effect is on the upper portion, particularly the pharynx, larynx, trachea, and bronchii. The ciliated cells of the respiratory epithelium are quickly killed and the whole bronchial tree is laid wide open to infection. Secondary bronchopneumonia is very common in the severe cases, and is responsible for most of the deaths. Direct injury may, however, be severe enough to cause death. Respiratory epithelium, exuded serum and leukocytic cells are shed from the surface of the trachea and bronchii as a coagulated, continuous, tenacious cast extending deep into, and plugging, the smaller bronchii and bronchioles. This plugging may so completely block the smaller air passages that the victim is suffocated. The term " cooked " best describes the appearance of the upper respiratory tract. Intense congestion of the lungs with moderate edema completes the terminal picture.

MUSTARD GASES

The only sulfur mustard which has yet been used is mustard gas itself, $S=(C_2H_4Cl)_2$. This was by all odds the king of war gases in World War I. It caused three-quarters of all AEF gas casualties, and three-quarters of the gas deaths.

It is an oily liquid, colorless when pure, but usually brown as employed in the field. Its odor is variously stated to resemble horseradish or garlic, but it stretches the imagination to note the resemblance. Its odor is quite characteristic and resembles nothing else very closely. It can be dispersed in a wide variety of explosive munitions, sprayed from airplanes, sprinkled on the ground from watering carts, or simply dropped from planes in large tin cans. It contaminates everything it touches and in heavy contaminations slowly gives off its poisonous, blistering vapors for days.

The chemistry of the nitrogen mustards is secret. They are all colorless or pale yellow liquids. Some are less persistent and some are more persistent than mustard gas. Their odors vary from fishy to practically odorless. They do not damage the skin as much as mustard gas, but do a first-class job on the eyes and respiratory tract.

Two great tactical assets possessed by the sulfur and nitrogen mustards are their insidious action and persistence. They produce no immediate pain or effects of any kind, and some have almost no odor. The victim may be severely or even fatally injured without knowing he is being exposed.

The degree of injury produced by a casualty gas is dependent upon the product of time and concentration of gas. Since the blister gases vaporize slowly and persist for a long time, they are effective in extremely low concentrations, provided the victim remains in the contaminated area long enough.

In investigating industrial and laboratory accidents due to the mustards, one cannot help being impressed with the fact that the vast majority of the cases had no idea they were contaminated and being burned. Pain and reddening of the skin do not begin for some hours, long after the damage is done. Even liquid mustard in the eye is only mildly irritating for the first hour, yet the damage is irreparably done in the first five minutes.

Some of the nitrogen mustards are quite toxic by skin absorption and readily cause fatalities in animals. The bone marrow, spleen, thymus and lymphoid tissue in general are severely attacked and an almost complete leukopenia develops. This has not yet been observed in man from skin burns.

ARSENICAL VESICANTS

The arsenical vesicants are all organic dichlorarsines, and all are colorless to brown liquids. They all have sharp irritating odors, and lewisite smells strongly like geraniums. They all hydrolyze easily in contact with water or moist surfaces to yield the corresponding arsine oxide.

Lewisite, $Cl—CH=CH—AsCl_2$, or chlorvinyldichlorarsine, has been widely studied, but has not yet had war experience, unless the Japanese employed it against the Chinese. It is more volatile than mustard, and very damaging to the skin and eyes as liquid drops. It has a very low freezing point and can be used in cold weather when mustard would freeze. It can also be mixed with mustard gas to form a low freezing point mixture. It can be dispersed from explosive munitions or sprayed from airplanes.

The other three arsenical vesicants, called Dicks by the Germans and British, methyl Dick, ethyl Dick, and phenyl Dick, have all had limited war service in World War I. Methyldichlorarsine, $CH_3—AsCl_2$, and ethyldichlorarsine, $C_2H_5—AsCl_2$, are fairly volatile,

and are usually dispersed as a vapor from explosive munitions. Phenyldichlorarsine, $C_6H_5—AsCl_2$, is a heavy oily liquid and quite persistent. Like lewisite, it forms an effective low melting point mixture with mustard gas.

In contrast to the insidious action of the mustards, the arsenical vesicants cause instantaneous excruciating pain upon striking the eye, with immediate blepharospasm. Stinging pain is felt by most subjects within 10 to 30 seconds after a liquid arsenical vesicant contacts the skin. Their vapors are likewise very irritating to the eyes and respiratory tract, which compels wearing of the gas mask. Their presence is therefore quickly obvious, and serious injury from them is proportionately less likely, if defensive measures are available.

The arsenical vesicants can cause very deep burns into the muscle and serious or fatal systemic poisoning by absorption through the skin in animals, because the animal is prevented from doing anything about it. No human subject has yet been so seriously burned or poisoned, however, nor does it seem likely to occur unless the victim is unconscious or defenseless.

BLOOD AND NERVE GASES

The third group of casualty agents is known as the blood and nerve poisons (or systemic poisons). Their local effects are minimal, and their poisonous properties are manifest only after absorption into the general circulation. There are a great many possible compounds in this class, and many have been investigated. I shall, however, refer to only two which have a record of war service.

The only one employed to any extent in World War I was arsine gas, AsH_3. It is a colorless, inflammable, diffusible gas. In its highest purity it is odorless, but the commercial item smells strongly like garlic. It can be liquefied in munitions but special precautions are required to prevent it inflaming upon explosion of the shell. It can be generated at the target in wet weather by dispersing a suitable powdered arsenide, which reacts with water to liberate the arsine.

It acts in a number of ways in the body, widely inhibiting enzyme systems, but it manifests itself clinically chiefly by its striking effect upon the red blood cells. In severe cases it causes widespread hemolysis and much of the liberated hemoglobin is passed in the urine. Coagulated debris collects in the kidney tubules, stained almost black by the hemoglobin, and may eventuate in kidney failure, anuria and a uremic death. During the stage of hemolysis, the victim suffers chills, nervousness, exhaustion, and collapse. He soon develops anemia, and in the course of a few hours jaundice begins to appear. This may progress until he is deeply jaundiced. If he survives the hemolytic stage, he may then develop the typical symptoms of arsenic poisoning. As the gas was employed in World War I, however, there were not so many severe cases, and the mortality was very low—only one-half per cent.

Hydrocyanic acid gas was tried abortively in World War I and given up as ineffective. It was then technically difficult to build up crash concentrations of any gas, and this was particularly difficult to accomplish with a light diffusible gas like HCN.

It is a colorless, highly volatile liquid, boiling at 26.5° C. It is dispersed from explosive munitions as a colorless gas having a faint odor of bitter almonds or peach kernels.

Very low concentrations of HCN can be detoxified and eliminated without the development of any symptoms, but high concentrations are more rapidly lethal than those of any other known gas. The rapidity of onset of symptoms is practically identical with the

circulation time from lungs, through the heart, to the brain. The subject becomes confused, befuddled and dizzy in a few seconds. He is seized with an uncontrollable hyperpnea, the depth of respiration being particularly increased. Great weakness and muscular incoördination come on simultaneously and in 10 to 20 seconds the victim is unconscious and beginning to be seized with convulsions. Respiration stops in a half to three-quarters of a minute, except for an occasional gasp, but the heart continues to beat for several minutes. The chances of survival after respiration ceases are small indeed. HCN is almost wholly an " all or none " gas. The subject is either rapidly killed or he quickly recovers. There are, however, a few borderline cases who, as a result of prolonged anoxia of nervous tissue during the poisoning, either die slowly, or recover slowly, and may be left with permanent neurological damage quite analogous to that which sometimes follows carbon monoxide poisoning. The gas acts primarily to inactivate the cytochrome oxidase enzymes. Thus the blood, while itself fully oxygenated, is unable to supply the tissues, because the tissue cytochromes cannot utilize the oxygen. The venous blood is returned to the heart bright red in color and nearly as fully oxygenated as arterial blood. At autopsy these cases have a pink hue to the skin strongly reminding of carbon monoxide poisoning.

There are two other classes of chemical agents, the incendiaries and screening smokes, which may cause incidental injury to troops, but they are not used for that purpose. There are also other gases incident to war, such as carbon monoxide and the nitric oxides, which may cause injuries or fatalities among troops, but they are not employed as war gases.

I should not like this brief discussion of the war gases to give the impression that these agents as employed in war are extremely lethal. On the contrary, the injuries they cause are many times less lethal than those due to other weapons of war. While they caused nearly one-third of all the AEF battle casualties hospitalized in France, they caused less than 10 per cent of the hospital deaths, the mortality being only 1.75 per cent, compared with a mortality of 8.1 per cent due to other weapons.

A very striking comparison is obtained if all those killed in action or dying before reaching hospital are included. The gas warfare mortality is then almost exactly 2 per cent, while that due to other weapons is 24 per cent, a ratio of 1:12.

Large numbers of wounded are a very serious encumbrance to an army. One of the chief tactical values of chemical weapons is their ability to produce large numbers of casualties with relatively few fatalities.

In closing, I should like to stress that there are no super-colossal war gases, of the variety that one drop on a dog's tongue will kill ten men. It takes very definite and large amounts of chemicals to build up casualty producing concentrations in open spaces. This requirement is so great that it seems most unlikely that our enemies could make more than a small nuisance chemical raid against the continental United States. The most likely supposition is that they will consider the benefits to be derived from such a raid not worth the cost and effort.