

## NERVE AGENTS

Nerve agents, such as sarin, are considered primary agents of weapons of mass destruction threat to humans because of their high toxicity and effectiveness through multiple routes of entry into the human body. Nerve agents are absorbed through the eyes, respiratory tract, and skin.

### Nerve Agents, The Beginning

The first group of nerve agents, the G-Series, was developed in Germany in December 1936 by a research group directed by Dr. Gerhard Schrader at IG Farben. The Schrader research group was working to develop new insecticides for IG Farben. During their research they developed the nerve agent tabun. The group found that tabun was extremely powerful, and 5 ppm of tabun killed all insects dosed. In January 1937, Dr. Schrader and his colleague personally experienced effects of tabun as a nerve agent when a drop of tabun spilled onto the lab bench. Within minutes, he and his colleague experienced miosis (constriction of the pupils of the eyes), dizziness, and severe shortness of breath. It was three weeks before they recovered.

In 1935, the Nazi government had a law requiring all inventions of possible military significance to be reported to the Ministry of War. In May 1937, Schrader sent a sample of tabun to the chemical warfare section of the Army Weapons Office in Berlin-Spandau. Dr. Schrader presented the tabun to the German government administrators in the Wehrmacht chemical lab in Berlin. After the presentation, Schrader's patent application, and all related research, were classified as secret. Schrader and a number of his group went to a new laboratory at Wuppertal-Elberfeld in the Ruhr valley where their research was conducted in secret throughout World War II. Tabun was initially given the code name Le-100 and later Trilon-83.

Schrader's group discovered Sarin in 1938 and used their initials to name the chemical: Schrader, Ambrose, Rüdiger and van der Linde. It was code named T-144 or Trilon-46. Sarin was found to be ten times more potent than tabun. Soman was discovered by Dr. Richard Kuhn in 1944 as he worked with the existing compounds, it was codenamed T-300. Cyclosarin was also discovered during WWII but the details were lost and it was 'discovered' again in 1949. The G-series naming system was created by the United States when it uncovered the German research, labeling tabun as GA (German Agent A), sarin as GB and soman as GD. Ethyl sarin was called GE and cyclosarin called GF.

## TOXICITY

The nerve agents considered for use today are Tabun (GA), Sarin (GB), Soman (GD), GF, and VX.

Tables 1 and 2 show the toxicities of the nerve agents by inhalation exposure and skin exposure.

The Ct is the product of the concentration (C) of a vapor or aerosol to which one is exposed and the time (t) over which one is exposed to that concentration (C). The units are usually mg/m<sup>3</sup> for C and minutes for t. One can be exposed to a Ct of 100 mg-min/m<sup>3</sup> by staying in a concentration of 10 mg/m<sup>3</sup> for 10 minutes (10x10=100), 20 mg/m<sup>3</sup> for 5 minutes (20x5=100), or 5 mg/m<sup>3</sup> for 20 minutes (5x20=100). The Ct that will cause a biological effect is constant over a range of C and t. Therefore, if a Ct of 100 mg-min/m<sup>3</sup> of nerve agent causes shortness of breath, it would be a result of any combination of C and t that produces a product of 100.

The LCt<sub>50</sub> is the Ct of agent vapor that will be lethal (L) to half of the population exposed to it. The ICt<sub>50</sub> is the Ct that will incapacitate (I) half of those exposed to it. The word "incapacitate" must be defined. For example, dim vision might incapacitate a person for some tasks, in which case the ICt<sub>50</sub> will be the Ct dosing to cause dim vision. More seriously, incapacitation might be defined as loss of consciousness and twitching, in which case the ICt<sub>50</sub> will be the Ct needed to produce these effects. The ICt<sub>50</sub> in Table 2 shown is that causing severe effects, including convulsions.

Table I shows the estimated LCt<sub>50</sub>, estimated ICt<sub>50</sub>, and estimated Ct that will cause pinpointing of the pupils (miosis) in half of the population (MCt<sub>50</sub>). Units of the Cts are in milligrams minutes per cubic meter (mg-min/m<sup>3</sup>).

Table 2 shows the estimated amounts that will cause lethality in half of the population when placed on

the skin.

The LD50 is the dose (D) of agent liquid or solid that is lethal (L) to half of the population exposed to it. The LD50 of VX, when placed on human skin, is the size of a droplet that will cover the width of two columns of the Lincoln Memorial on a Lincoln penny.

TABLE 1. Nerve Agent Vapor Toxicity mg-min/m<sup>3</sup>

Agent	LCt50	ICt50	MCt50
GA	400	300	2-3
GB	100	75	3.0
GD	70	UNK	<1.0
GF	UNK	UNK	<1.0
VX	50	35	0.04

TABLE 2. Nerve Agent LD50 on Skin

Agent Amount	Agent Amount mg
GA	1000
GB	1700
GD	50
GF	30
VX	10

#### MECHANISM OF ACTION

Acetylcholinesterase (AChE) is found in many types of conducting tissue such as: nerve and muscle, central and peripheral tissues, motor and sensory fibers, and cholinergic and noncholinergic fibers. The activity of AChE is higher in motor neurons than in sensory neurons.

Acetylcholinesterase is also found on the red blood cell membranes, where different forms constitute the Yt blood group antigens. Acetylcholinesterase exists in multiple molecular forms, which possess similar catalytic properties, but differ in their molecular complex assembly and mode of attachment to the cell surface.

When a person is poisoned by a nerve agent, the function of the enzyme acetylcholinesterase is blocked. The normal function of acetylcholinesterase is to break down or hydrolyze the chemical, acetylcholine. Acetylcholine is a neurotransmitter, or messenger chemical in the nervous system. Nerve paths, which are divided into sections with gaps between the nerve endings and between the nerve ending and the target organ, are used to pass a signal from the central nervous system to various organs. These gaps are crossed by acetylcholine, the messenger, which relays the signal on to the next step and finally to the target. Under normal conditions, when the signaled action at each step is completed, the acetylcholine is broken down by the acetylcholinesterase, stopping the action. However, when a nerve agent inhibits the acetylcholinesterase, this enzyme cannot do its normal function of hydrolyzing the acetylcholine. Acetylcholine then accumulates along the nerve path, and the target organ's action continues

uncontrolled. The nerves continue to send signals, or continue to “fire”. As the nerves continue to “fire” muscles and organs become hyperactive and twitch uncontrollably, and glands secrete copiously.

## NERVE AGENT EFFECTS

The nerve agent’s mechanism of action is to inhibit the enzyme acetylcholinesterase. Inhibition of this enzyme allows the neurotransmitter, acetylcholine, to accumulate at the nerve endings where it causes excessive stimulation of the target organ. The parts of the body that are affected by excessive acetylcholine accumulation are as follows:

- Eyes
- Nose (glands)
- Mouth (glands)
- Respiratory tract
- Gastrointestinal tract
- Cardiac muscle
- Sweat glands
- Skeletal muscle
- Central nervous system

The primary concern of the medical team when treating the nerve agent poisoned person is to provide correct, timely, and lifesaving care. The first step in providing this care is to understand the effects that a vapor or liquid nerve agent exposure has on the person.

**Eyes.** The eyes are affected by direct contact with a nerve agent vapor or aerosol. When the route of entry of the agent is through the skin or by ingestion, the effect on the eyes is delayed or may not occur. The main effect of the agent is to cause miosis, or pinpointing, of the pupils. One or both pupils may be pinpointed and unresponsive to light or darkness. Pinpointing causes a complaint of dim vision that is more pronounced in low light conditions. Frontal headache, mild aching around the eye, or severe pains are common complaints in a person exposed to a moderate concentration of agent. Twitching of the eyelids may be observed, and the eyes may be reddened. When a pen light is used to test for pupillary response, the person may complain of an increase in aching behind the eyes due to light sensitivity.

**Nose and Mouth.** The secretory glands of the nose and mouth are as sensitive or more sensitive to nerve agent vapor or aerosol than the eyes are. When the person is poisoned by nerve agent liquid on the skin or by ingestion, the nose will become affected, but only in response to the whole body (systemic) involvement. When exposed to a nerve agent vapor or aerosol, the nose will begin to run. The nose discharge effect has been described by patients recovering from accidental nerve agent vapor exposure as “worse than a cold or hay fever” and “like a leaking faucet.” Even after low concentrations of agent, rhinorrhea may be severe. The mouth will secrete such excessive amounts of saliva that watery secretions run out the corners of the mouth.

**Respiratory Tract.** Inhalation of a small amount of nerve agent vapor will cause the person to complain of tightness in the chest or shortness of breath (dyspnea). This occurs because the excessive acetylcholine stimulates the muscles in the airways to contract and constrict the airways (bronchoconstriction). As the concentration increases, breathing difficulty will become severe. One or two breaths of a high concentration of nerve agent vapor will cause gasping and irregular respirations within seconds to a minute or two. Cessation of breathing (apnea) can occur within minutes after exposure to a large amount of nerve agent, either by liquid on the skin or vapor. Excessive bronchial and upper airway secretions caused by stimulation of the airway glands by the excessive acetylcholine will compound breathing difficulty. These secretions can be thick, mucoid, “ropy,” and plug and obstruct the airway and cause difficulty in moving air into and out of the lungs with prolonged expiration a noticeable effect.

***Gastrointestinal (GI) Tract.*** After exposure to a large but sublethal concentration of vapor, the person will complain of nausea and may vomit. Also, nausea and vomiting may be the first effects from liquid nerve agent exposure on the skin. The person may complain of nausea followed by vomiting, “heartburn,” and pain in his abdomen. In addition, the person may belch frequently and have diarrhea or involuntary defecation and urination. These effects usually occur within several minutes after vapor exposure. However, after liquid agent exposure on the skin, these effects may not begin for as long as 18 hours after exposure.

***Cardiac.*** The heart rate may increase or decrease after nerve agent exposure. Usually, blood pressure will increase. The heart rate in nerve agent poisoning will not aid the medical team in choosing the care needed.

***Sweat Glands.*** The skin is very permeable to nerve agent. When penetration occurs after liquid or vapor exposure, localized sweating occurs and progressively spreads over the surrounding skin area as nerve agent is absorbed. The likelihood that the medical team will be able to observe this sweating is minimal.

***Skeletal Muscles.*** After exposure to a moderate or large amount of nerve agent, the person will complain of weakness and twitching of muscle groups. Twitching can first be noticed at the site of a liquid droplet on the skin. The muscles may show a rippling effect (fasciculations). As the nerve agent effect progresses, muscles can go into a prolonged contraction. However, instead of a prolonged contraction, the large muscle groups may begin unsynchronized contractions that cause the arms and legs to flail about. The hyperactivity of the muscles in these instances leads to muscle fatigue and flaccid paralysis (limp, unable to move). Unless the medical team aggressively cares for this casualty, he/she will not survive.

***Central Nervous System (CNS).*** When large inhalation doses or liquid doses occur, the effects are rapid and usually fatal. The person almost immediately loses consciousness, followed seconds later by seizure activity. Several minutes later, respiration ceases. Without immediate care, this person will not survive. When exposed systemically to low amounts of nerve agent, the person may complain of generalized weakness. Understanding when these effects can most occur is critical for the medical team.