Chapter 28

EXPLOSIVES AND PROPELLANTS

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INTRODUCTION

This chapter is an update to Chapter 9, Military Energetic Materials, Explosives, and Propellants, in the previous edition of this book.[1] Much of the chapter has been revised to reflect new policies related to workplace exposure limits, and the references have been updated as well. The US military is both a producer and consumer of explosives and propellants. Although the toxic effects of most of these compounds have been recognized for many years, and data on their effects on human health have been published since World War I and World War II, many gaps remain in the understanding of their human and ecological toxicity. The database on the health effects (especially human) is evolving as research continues. Newly discovered carcinogenic and reproductive effects are especially concerning. However, lack of exposure data in human occupational epidemiology studies, and lack of route-specific toxicity data (especially inhalation and dermal absorption) in animal studies, hampers the ability to make dose-response estimates for most explosives. Therefore, judgments about human exposures to these chemicals must err on the side of safety, and data on structurally similar chemicals must be included in assessments of the health hazards of explosives.

The production of most of these explosives parallels US military activity. Peacetime production is usually sufficient only for research and training needs. During wartime, the manufacture of these compounds increases; the workforce increases (thereby increasing the number of inexperienced workers who are unfamiliar with these compounds); and providers who are inexperienced with the unique hazards posed by these chemicals are suddenly charged with the care of explosives workers. The rapid increase in production during wartime has tended to result in far higher exposures, with correspondingly more numerous and more severe adverse effects, than the few mild adverse reactions that occur during peacetime.[1-4] Furthermore, the regulatory environment that surrounds these and other industrial exposures to hazardous substances is constantly evolving.

This chapter focuses exclusively on military explosives and propellants, and is structured according to the chemical family of the compounds: (*a*) aliphatic nitrate esters, (*b*) nitroaromatics, (*c*) nitramines, (*d*) initiating explosives, (*e*) composite propellants, and (*f*) liquid propellants. Most munitions, however, are mixtures of chemicals. Medical professionals need to learn about these propellants and explosives and understand the steps in the manufacturing process to identify where chemical exposures are likely to occur. Occupational health clinic personnel need to expect, in addition to exposures among plant workers, sporadic exposures among ammunition quality-assurance specialists, explosive ordnance-disposal specialists, and personnel who test or use explosives in enclosed spaces.

HISTORY

The Chinese are generally credited with inventing explosives—in the form of fireworks—before 1,000 CE. Black powder was not introduced to the Western world until approximately 1225. Roger Bacon, an English monk, conducted and described some of the first scientific experiments with this explosive mixture of saltpeter, charcoal, and sulfur in 1249. The age of gunpowder began nearly simultaneously in Europe and China with the invention of cannons early in the 14th century. However, the development of explosives was limited mainly to improvements in the manufacture and application of black powder until 1800. Modern explosive technology was developed during the 19th century with increased research on and development of propellants, high explosives, and weapons technology.[5]

Because of their ready natural availability, inorganic nitrate-based explosives were the first to gain importance. (Today, the most important inorganic nitrate explosive is ammonium nitrate, which is used in demolition and construction.) Inorganic nitrates formed the basis of black powder, which was the predominant explosive used in the United States before 1900.[5] Its last major military use was during the Spanish-American War of 1898. Black powder is an easily produced physical mixture of sulfur, charcoal, and potassium nitrate, but it is not well suited for most modern military uses: it produces excessive smoke and flash (which could alert the enemy to the position of the gun) and has a dangerous tendency to cake and misfire. However, it is still used in primers, safety fuses, flares, grenades, practice munitions, blanks, fireworks, signals, and specialized quarry work.[5]

During the opening years of the 20th century, faster, cheaper, and higher-volume methods for producing explosives were developed. Numerous compounds were synthesized and used as detonators, boosters, and flash suppressors; dynamite almost completely supplanted black powder in commercial use, and trinitrotoluene (TNT) became the most commonly used military explosive.[5]

With these developments, attention became focused on organic nitrate explosives. The aliphatic nitrates were the first group to achieve importance because cel-

lulose, glycerol, sugars, and coal-tar derivatives were readily available for use as raw materials. Later, as cost-effective bulk synthesis of ammonia and formaldehyde became possible, the aromatic nitrates became important militarily. The most recent group to achieve prominence is the nitramines.[5]

In the early years of World War II, low production capacity for most explosives and propellants plagued the United States, and numerous changes in manufacturing processes were made in attempts to increase production. Adaptation to the shortages of raw materials, in addition to the unique requirements of each type of weapon, led to the increasing complexity of munitions design. Inadequate resources in rocket propellants led to the addition of nitroguanidine to nitrocellulose to form nitroglycerin-based propellants, which increased production capability and met exacting requirements for new weapons systems.[5] Additional weapons research after World War II has further expanded the uses of these compounds. The plethora of explosives and propellants currently in use and under development has resulted from continued research into the properties, cost, safety, stability, and reliability of explosives.

The British were the first to respond to the threat posed by the manufacture of explosive materials. In 1875, they passed the Explosives Act after an industrial explosion killed 53 people.[5] This law established "inspectors of explosives," who were authorized to inspect all magazines and factories to ensure that operations were accomplished safely.

At the beginning of World War I, TNT was generally believed to be nontoxic in all its stages of production, but this belief changed.[4] During the course of the war, the major powers used approximately 5 billion pounds of high explosives, primarily TNT, resulting in millions of battlefield casualties.[5] In the United States, at least 17,000 cases of TNT poisoning occurred during the war, resulting in more than 475 deaths.[4,6,7] Efforts to reduce the burden of disease included job rotation, medical examinations, and workplace ventilation and hygiene. These efforts were only marginally effective. Successful control of worker exposure was finally achieved through the automation of many operations during shell loading, and the application of strict standards of workplace hygiene.[5,8]

The World War I experience demonstrated that ammunition-loading plants were among the most dangerous industrial operations, due to the open handling of dusty and fuming compounds. Beginning in 1938, the Ordnance Department and the US Public Health Service coordinated an intensive effort to forge an integrated health and hygiene program in ordnance plants to reduce the burden of worker death and disability.[4] This effort was the first large-scale demonstration of what can be accomplished in a large industry with many serious health hazards by a vigorous medical and engineering program.[2] Consequently, the successes of and lessons learned from this effort led to the establishment of the occupational medicine field in the Army, in which providers monitor the health of over 100,000 civilian employees at depots, arsenals, and ammunition plants.

ENERGETIC MATERIALS

An energetic material is a compound that can undergo rapid, self-sustaining, exothermic reduction-oxidation reactions. Energetic materials may be categorized according to their intended uses: (*a*) explosives, (*b*) propellants, and (*c*) pyrotechnics. Explosives and propellants evolve large volumes of hot gas when burned; they differ primarily in their rates of reaction.[5] Pyrotechnics (powder or ammunition used for igniting a rocket or producing an explosion; the term is also used in the military to designate flares and signals) generate large amounts of heat but much less gas than explosives or propellants.[5] Energetic materials may also be grouped according to their rate of reaction. Both propellants and pyrotechnics are considered to be low explosives. The velocity at which the combustion proceeds through these materials is usually 400 m/sec or slower. In comparison, high explosives are detonated by a process in which the very rapid rate of the combustion reaction itself produces a shock wave, capable of shattering objects, in the surrounding medium.[5] The shock wave moving through the explosive material causes further explosive decomposition of that material, and the reaction rate is determined by the speed of the shock wave. The shock wave's velocity ranges from 1,000 to 9,000 m/sec.[5] In addition to being used as explosive charges, many high explosives are also used in propellant formulations.[5] For purposes of this discussion, the term "explosive" is used generically to indicate any energetic material.

Explosives

Modern explosive devices employ an explosive train that takes advantage of the specific explosive properties of its components: the initiator, the detonator, the booster charge, and the main charge.[5] The initiator, or primary explosive, consists of a small quantity of material that is very sensitive to heat, spark, impact, or friction. Primary explosives may intensify the energy up to 10 million times that of the initiating stimulus.[5]

Geometric arrangement of the explosive device directs either the flame or the detonation wave of the initiator toward the detonator charge. The detonator, a larger amount of less sensitive but more powerful explosive material, then detonates either the booster charge or the main charge. The booster charge is an optional component that further magnifies the explosive impulse. The main explosive (or bursting) charge contains the largest amount of an insensitive but powerful explosive. Explosives used as booster and main charges are usually not capable of being initiated by impact, friction, or the brief application of heat, and are known as secondary explosives.[5]

The secondary explosives used currently in most military explosive devices are physical mixtures of one or more high explosives with various additives. The use of mixtures provides for greater flexibility in explosive design, and additives extend the range of performance. Melt-loading, commonly used with TNT mixtures, is a process in which a molten explosive mixture is introduced into an empty shell casing and allowed to cool and harden. Secondary explosive mixtures are used to facilitate the melt-loading process to optimize oxygen balance, explosive characteristics of blast and fragmentation, and metal properties of malleability and strength.[5]

Explosives and explosive-actuated devices are used widely in both industry and the military. Explosives are used in construction, mining, quarrying, demolition, welding, and cladding. Explosive-actuated devices are used to drive turbines, move pistons, operate rocket vanes, start aircraft engines, eject pilots, and provide heat. Between 1972 and 2016, domestic industrial explosive consumption has fluctuated with the US involvement in the wars in Vietnam, Iraq, and Afghanistan. For example, TNT consumption was 500,000 pounds in 1972, increased to 1 million pounds in 1985, and rose to 10 million pounds in the Persian Gulf War, remaining at that level until the Operation Iraqi Freedom surge ended in 2010. Since then consumption has fallen off considerably.[5–7] The specific military uses of explosives are numerous and include the production of fragments, air blasts, and underwater shock; armor penetration; demolition; the ejection of personnel from aircraft; and components of nuclear weapons.[5–7]

Propellants

Propellants are explosive materials formulated and engineered to react at carefully controlled rates, producing a sustained pressure effect over a longer period of time than high explosives. In contrast to the detonation of high explosives, the process of propellant burning is referred to as deflagration, wherein the rate of heat transfer determines the rate of the reaction, which proceeds at subsonic speeds.[5–7]

Like explosives, propellants utilize a series of materials in an ignition train. An electrical or mechanical impulse impinges on the sensitive primer material. This ignites the igniter, a pyrotechnic, which in turn ignites the main propellant grain. Propellants may be formulated either as solids or as liquids. Solid propellants are used more frequently in guns, cannons, and smaller rockets, while liquid propellants are used in high-performance missile systems and certain other applications.

Solid propellants may be classified by their chemical composition. Each class has unique properties that render it useful in certain applications. All solid propellants may contain additives similar to those used in explosive mixtures. The additives can be more toxic than the principal components of the propellant and must be considered in occupational hazard analysis. Regardless of the composition class, the chief advantages of solid propellants include their compactness, safety, ease of storage, tolerance of temperature extremes, and ease of handling. In comparison, liquid propellant systems permit greater thrust control and deliver higher specific impulses.[5–7] Liquid propellants have been limited to use in high-performance missile systems until recently, when research focused on using liquid gun propellants for howitzers. Several liquid gun propellants are discussed later in this chapter.

Pyrotechnics

Pyrotechnic materials are relatively slow-burning, nonexplosive powders such as metals, alloys, and hydrocarbon mixtures.[5] The only pyrotechnic compounds discussed in this chapter are those used in initiating compositions and propellants. However, pyrotechnics are also widely used in the military as flares, signals, relays, delays, and fuses.

EXPOSURE

Ammunition plants operated by the US Army for the Department of Defense are the primary sites of occupational exposure to military explosives.[5–8] The types of ammunition plants include (*a*) propellant- and explosive-manufacturing plants, (*b*) metal-parts plants, (*c*) small-arms plants, and (*d*) shell loading, assembly, and packing (LAP) plants. Private companies have operated most of these ammunition plants under government contracts since the late 1950s.

In addition to the work at ammunition plants, workplace exposures occur at other types of facilities: munitions are manufactured (in limited quantities), tested, and stored at arsenals; munitions are tested at proving grounds; and munitions are maintained, stored, and demilitarized at depots. Unique operations are conducted at each type of facility. Workers may perform duties that expose them to toxic hazards, and occupational medicine providers must be aware of these potential exposures.

Furthermore, propellant and explosive manufacturing plants produce a limited number of specialized products, but workers can be exposed to feedstock and process chemicals as well as the finished explosives. Feedstock chemicals include toluene and nitric acid used in the synthesis of TNT, and chemical salts and acids in the synthesis of nitrocellulose. Exposures are usually controlled by enclosing the manufacturing process and the feedstock chemicals.

LAP plants pose the greatest exposure potential for employees, due to their use of a wide variety of explosive compounds during labor-intensive loading operations.[5–8] Comparatively few employees are exposed to explosives at small-arms plants, arsenals, or depots. Workers at metal-parts plants can be exposed to a variety of industrial chemicals including carbon monoxide, lead, nitrogen oxides, solvents, paints, and cutting oils.[2] Metal-parts plant workers manufacture the hardware in which explosives are loaded and used, such as rocket tubes, shell casings, bomb casings, and trigger assemblies. Cutting oils (usually mineral oil) are used to lubricate and cool the saws and machining tools used to shape the metal parts. Cutting oils have been found to be contaminated with nitrosamines, a class of potent carcinogens. Machinists exposed to these contaminated oils via the dermal and inhalational routes may be at high risk for cancer.[7,9]

Exposure Controls

Several types of workplace standards have been established to regulate employee exposure. Army policy follows the most stringent of the Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL)[10] or the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV).[11] In addition, because dermal absorption is a significant route of exposure for explosives, OSHA has given a skin designation to these chemicals. Skin exposure to chemicals with significant dermal absorption should be avoided. However, where published limits from OSHA and the ACGIH are either unavailable or inadequate to meet Army requirements, the US Army Public Health Command established military exposure guidelines to protect service members (published in Technical Guide 230[12]).

General Safety Practices

Safety is of paramount importance when personnel handle explosives and propellants. The accidental detonation or deflagration of these materials poses serious hazards to employees, other people nearby, and property, including blast overpressure, fragmentation, and burns. Creating a safe workplace around explosives demands that cardinal principles of safety be followed:

- Separate each handling operation to prevent fires, blasts, or fragmentation.
- Use the minimum number of personnel necessary for each operation.
- Stockpile only the minimum amount of explosive or hazardous material necessary for efficient operation.

The Department of Defense has established uniform safety standards applicable to ammunition and explosives,[13] which the Army implemented in Army Regulation 385-64.[14] Most of these address factors such as the sensitivity of explosive materials to accidental initiation; the quantity of material available to be detonated or deflagrated; the heat that would be generated; the rate of burning; the potential sources of accidental ignition and initiation; and the protection capabilities of shields, clothing, and fire-protection systems. Other health-focused standards address the potential toxicity of the explosive materials and control measures that must be in place to ensure that worker exposure is within acceptable limits.

Industrial Hygiene Principles

Applying industrial hygiene principles such as (*a*) engineering controls, (*b*) administrative controls, and (*c*) personal protective equipment (PPE) in the workplace will further limit potential worker exposures.

Engineering Controls

The preferred method of control for industrial hazards is through design changes or product substitution involving a safer or less toxic process or material. However, substitution as a long-term solution is not always possible. For example, finding a substitute for dinitrotoluene (DNT), which is toxic to humans, mutagenic in animal systems, and classified as suspect carcinogen,[15] has been difficult. Qualified industrial hygiene and safety personnel should work closely

together during any workplace modification. Some controls have endured the test of time. Methods in use today include

- enclosure of processes (eg, the melt unit used in TNT melt-loading operations);
- general exhaust ventilation (eg, the type used in rooms where poured TNT munitions are cooled);
- local exhaust ventilation (eg, the type used in dusty operations such as screening flaked DNT or TNT);
- temperature control to reduce vapor generation (used in rolling operations with propellants containing nitroglycerin); and
- remote-controlled operations (eg, the modern continuous-flow nitrator used to produce nitroglycerin).[16,17]

Administrative Controls

Administrative controls have consistently emphasized work and sanitation practices that involve more than just rotating employees in and out of areas with high-exposure potential. These controls include essential measures such as (*a*) educating workers about the safety hazards of the materials; (*b*) enforcing strict work practice guidelines to minimize dust and vapor production and prevent dermal contact; (*c*) adhering to sanitation practices with strict attention paid to preventing explosive contamination of workers' bodies or clothing; and (*d*) providing changing and shower rooms with separate locker facilities to segregate street and work clothing. Contaminated clothing must be removed immediately and placed in closed containers until laundered or discarded. Contaminated skin should be washed promptly with soap and water. Furthermore, workers must wash their face, hands, and forearms thoroughly with soap and water before eating, drinking, smoking, or using toilet facilities.[16–18] In work areas, employees must also be prohibited from storing, preparing, dispensing, or consuming food or beverages; storing or applying cosmetics; using tobacco products; and storing or using chewing gum.

Personal Protective Equipment

PPE to control exposure should be used only when engineering and administrative controls are inadequate. Using changing rooms and wearing coveralls continue to be widespread practices. Respiratory protection and gloves must be used where indicated; the National Institute for Occupational Safety and Health (NIOSH) has published guidance on the types available.[15–19] Some respirators, especially those with air supplied (by a tank or compressor and hose), can create sparks and therefore pose an unacceptable risk of igniting an explosion.[10]

GENERAL MEDICAL CONSIDERATIONS

The challenge facing a provider beginning work in an industrial environment is to understand the hazards faced by employees. Military ammunition plants are no exception: each type of projectile and munition contains a unique combination of explosives. A careful occupational history might reveal exposures. The provider must be able to interpret this information in terms of specific chemical exposures, just as he or she would interpret chemical trade names in civilian practice. Those who work with composition C4 should be assessed for RDX (hexahydro-1,3,5-trinitro-1,3,5-triazine) toxicity, or given medical surveillance for RDX; cyclotol workers should be assessed for both TNT and RDX toxicity; amatol workers should be assessed for both TNT and ammonium nitrate toxicity; and base propellant workers should be assessed for both nitroglycerin and nitrocellulose toxicity. Sources of information include Material Safety Data Sheets and military specifications of ammunition products. Often the best information is available from a safety officer, industrial hygienist, or plant commander.

Preplacement Considerations

Preplacement examinations establish work ability and baselines for hearing, vision, pulmonary function, and various blood indices for comparisons over time. The 1990 Americans with Disabilities Act, as amended in 2008,[20] precludes preemployment examinations from being applied as discriminatory tools and requires that they be used only to assess critical aspects of job performance.

Preplacement medical examinations remain part of the foundation of a medical surveillance program for workers exposed to hazardous agents. They are done to (*a*) identify preexisting conditions, (*b*) identify hypersusceptible individuals, and (*c*) establish preexposure baseline values. Preplacement examinations must identify preexisting conditions to ensure the worker's safe performance of critical job tasks (eg, blindness would preclude a worker's being assigned as a forklift operator, and certain neurobehavioral conditions such as epilepsy and severe psychiatric disorders may not be appropriate among explosives workers).[21] In addition, susceptible individuals must

be identified because they may be at higher risk for developing diseases related to specific occupational exposures. For example, individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency may have a hemolytic crisis when exposed to methemoglobin-inducing agents.

Examples of preexposure baseline values include erythrocyte counts and liver-function tests for workers who are exposed to agents capable of inducing anemia or hepatotoxicity. Thorough details of prior occupational exposure should be documented. In addition, recreational activities or hobbies that could expose an individual to chemicals should be documented.

Acute Exposure Decontamination

First aid measures and treatment procedures for individuals who have been exposed to explosives and propellants are similar to those for exposure to other toxic substances. Rescue procedures follow those dictated for most emergencies, but personnel must guard against additional exposures among would-be rescuers. The main goals of initial treatment are to prevent further absorption and enhance excretion, which may be achieved by first removing the victim from exposure and then removing contaminated clothing. Rescuers should thoroughly cleanse victims' skin with soap and copious quantities of water, paying attention to hair and nails. Contaminated clothing should be either laundered carefully or discarded. Eyewash fountains should be placed throughout the workplace to provide copious irrigation of the eyes in the event of a splash. The treatment of mild, asymptomatic cases may require nothing more than removal from exposure and decontamination.

COMMON MANIFESTATIONS OF EXPOSURE

Commonly, organic nitrates share these major toxic effects: allergic contact dermatitis (ACD), methemoglobinemia, vasodilation, and carcinogenesis. Nitrates used in explosives are no exception. Each of these effects can occur separately or in combination; however, not every organic nitrate causes all four effects. The prevalence of each effect varies with the specific chemical. For example, tetryl causes ACD almost exclusively, nitroglycerin causes vasodilation, and DNT is a mutagen and probable carcinogen. The International Agency for Research on Cancer classifies 2,4- and 2,6-DNT as Group 2B carcinogens (possibly carcinogenic to humans).[21] Many organic nitrates are potent vasodilators, but few have found therapeutic uses in clinical medicine.

Dermatitis

ACD is a type IV delayed hypersensitivity reaction mediated by the immune system and caused by cutaneous exposure to a chemical. The other major occupational dermatitis is irritant contact dermatitis, which is a nonallergic reaction of skin exposed to a chemical. The immune system is not involved in irritant contact dermatitis, but is involved in the allergic form. Dermatitis caused by exposure to organonitrates has no characteristics to distinguish it from other irritant or allergic reactions.

Both allergic and irritant contact dermatitis have been seen in explosives workers.[22] The agents most responsible are tetryl, TNT, amatol, ammonium picrate, picric acid, and mercury fulminate. However, the role of other ingredients and exposures must not be overlooked: industrial exposures to solvents, cutting oils, and degreasers all occur in the munitions industry and can also induce dermatitis.

Occupationally induced dermatitis is considered to be the most prevalent occupational disease in workers.[23] During World War I and World War II, morbidity from TNT exposure was a major cause of time lost from work. Fortunately, these effects resolve after the worker has been removed from exposure, and they generally do not sensitize the individual to other chemicals.

Methemoglobinemia

Methemoglobinemia has been recognized as an adverse occupational effect. Many drugs and chemicals exert an oxidant stress on hemoglobin, which oxidizes the iron in the heme portion of the molecule from the ferrous to the ferric form, thus rendering the hemoglobin molecule incapable of binding oxygen. The body spontaneously produces small amounts of methemoglobin, but enzymatic reducing systems within the erythrocyte normally maintain that concentration below 1% of the total hemoglobin. Clinical effects of methemoglobinemia may develop when more than 10% to 15% of the total hemoglobin is converted to methemoglobin. The acute signs and symptoms of methemoglobinemia include persistent, slate-gray cyanosis; fatigue; malaise; headache; and reddish-brown discoloration of the peripheral blood, which does not become bright red when exposed to oxygen. Massive exposure may cause 60% to 70% of the hemoglobin to convert to methemoglobin, which can produce collapse, coma, and death.

Chemicals that induce methemoglobinemia tend to cause chronic anemia, which may develop even in the absence of cyanosis.[24] This anemia usually occurs when erythrocytes that contain methemoglobin hemolyze. Patients with mild chronic methemoglobinemia due to enzyme deficiencies may be treated with oral medications in an attempt to decrease cyanosis. These medications include methylene blue, ascorbic acid, and riboflavin. The methylene blue dosage in this situation is 100 to 300 mg/day, which may turn the urine blue in color. The ascorbic acid dosage is 200 to 500 mg/day; however, long-term oral ascorbic acid therapy can cause the formation of sodium oxalate stones. The riboflavin dosage is 20 mg/day.[24]

As with many toxic exposures, individuals have a wide range of sensitivity to methemoglobin-inducing chemicals. For example, individuals with G6PD deficiency and other hemoglobinopathies are uniquely sensitive to the hemolytic effects of exposure to these agents. Preemployment screening should identify individuals with G6PD deficiency and sickle-cell trait. Aggressive medical surveillance of workers at high risk has effectively reduced such exposures and health effects. Methemoglobin can be measured directly, but this must occur within just a few hours of sample collection because methemoglobin in erythrocytes reduces rapidly to hemoglobin. All cases of cyanosis and abnormal blood findings should trigger exposure-control action.[22]

Individuals with mild to moderate cases of methemoglobinemia will recover spontaneously within 2 to 3 days. In more severe symptomatic cases, methylene blue (administered intravenously as a 1% solution in saline at 1–2 mg/kg over 10 min) is an effective therapy. A second dose may be administered after 1 hour, if necessary.[24,25] The US Food and Drug Administration warns against using methylene blue concurrently with serotonergic psychiatric drugs, unless such usage is indicated for life-threatening or urgent conditions.[24,25]

Hyperbaric oxygen treatment is another option for situations in which methylene blue therapy is ineffective or contraindicated. This approach permits tissue oxygenation to occur through oxygen dissolved in plasma, rather than through hemoglobin-bound oxygen.[25]

Vasodilation and Carcinogenesis

Although organic nitrates as a class cause both dermatological and hematological effects, specific explosives such as nitroglycerin and DNT are vasodilatory and mutagenic, respectively. These substance-unique effects are discussed below.

THE ALIPHATIC NITRATE ESTERS

The aliphatic nitrate ester class of compounds includes many members with explosive properties, some of which are militarily significant. With the exception of nitrocellulose, members of this class are manufactured similarly and are similarly toxic. The physical properties and uses of the individual compounds vary, as does the amount of toxicological data available.

Nitroglycerin

Nitroglycerin was the first organic nitrate to be used as an explosive. Although Ascanio Sobrero, an Italian chemist, first synthesized nitroglycerin in 1847, it was not widely appreciated until 1863, when Alfred Nobel began to use it as a blasting compound.[26] To make nitroglycerin safer to work with, Nobel began using solid materials to adsorb liquid nitroglycerin, from which dynamite was formed.

In 1888, Nobel demonstrated that, by using nitroglycerin to gelatinize nitrocellulose, the explosive properties of nitroglycerin could be converted to propellant uses; as a result, he developed not only the earliest of the smokeless powders, but also the first double-base propellant. Until then, all propellants had nitrocellulose alone as the explosive component—now called single-base propellants. Double-base propellants are those with nitroglycerin in addition to nitrocellulose. Triple-base propellants have nitroguanidine as the third explosive component.[5] Military use of nitroglycerin is almost exclusively in combination with nitrocellulose in double- and triple-base propellants.

The freezing point of nitroglycerin (55.4°F) caused a major safety problem with early dynamite.[27] Explosions were not uncommon when munitions or dynamite were accidentally frozen during winter. Nitroglycerin in the solid state is much less sensitive than in the liquid. But while thawing, nitroglycerin is much more sensitive to detonation than while either a solid or a liquid. Decomposed nitroglycerin is especially dangerous. Not only is it more sensitive to accidental detonation than when pure, but the formation of nitrogen oxides may also constitute a separate toxicity hazard.[6] However, because military use of nitroglycerin is limited to the double- and triple-base propellants, which are stable colloidal mixtures with lower freezing points, the instability of nitroglycerin at its freezing point is no longer a problem.

Other aliphatic nitrate esters have limited, specialized uses. In 1905, ethylene glycol dinitrate (EGDN; freezing point -8°F) was introduced as an additive to lower the freezing point of nitroglycerin, and since 1920 EGDN has been a major component of most civilian dynamite formulations.[27] EGDN has little current military use. However, another aliphatic nitrate ester, propylene glycol dinitrate (PGDN), is used as a torpedo propellant.[5]

Manufacture and Exposure Hazards

Nitroglycerin is manufactured by one of three closed, continuous-flow processes known as the Biazzi, Schmid-Meissner, and Nobel nitrator processes, in which glycerin is mixed with concentrated nitric acid.[5] A closed process is one in which liquid chemicals are piped from one closed container to another—from the beginning of the process, where feedstock is introduced, to the end, where finished product is packed for shipping or storage. A continuous-flow process is one in which the reactions occur constantly, not in batches. The product is subjected to a series of purifying washes and then transported by gravity flow to storage tanks. The nitration and purification processes—controlled remotely via closed-circuit television—are conducted in small, heavily revetted buildings. Other liquid aliphatic nitrates may be prepared by similar methods using other aliphatic polyols instead of glycerin.

Liquid nitroglycerin, together with nitrocellulose and other ingredients, is manufactured into double- and triple-base propellants by two methods.[5] In general, the solvent process is used for propellants that contain less than 40% nitroglycerin, and the solventless process is used for compositions that contain more than 40% nitroglycerin. The solvent process begins with the addition of a solvent such as ether or acetone to water-wet nitrocellulose in a dough-type mixer. Nitroglycerin and other ingredients are added and mixed until a dry colloid forms. The mixture is then subjected to a series of presses to remove the solvent and complete the colloiding process. Finally, the mixture is extruded through a die, cut to length, and dried in an oven to form the finished propellant. The solventless process begins with mixing a slurry of nitrocellulose and nitroglycerin in a tank of water. Other ingredients are added, and the excess water is removed by centrifugation. The process is completed by extruding the dried colloid through a die and drying it in an oven.

Occupational exposure to nitroglycerin can occur during any of these operations. In the solventless process, dermal exposure is especially significant among roller-press operators, and can be detected in blood samples that have concentrations of nitroglycerin in blood. Due to the widespread use of engineering controls, exposure to vapors is minor during nitration, but inhalational exposure can be significant for press operators and drying-room attendants. During World War II, nitroglycerin toxicity caused at least 78 reported cases of lost time among propellant workers, several of whom required transfers to different worksites.[2] Almost certainly, other cases of nitroglycerin toxicity occurred during World War II, but they either went unreported, were unrecognized, or did not result in time lost from work.

Human Exposure and Health Effects

The effects on human health from exposure to nitroglycerin have been observed since its discovery. Because of its vasodilating properties, nitroglycerin has been a mainstay of antianginal therapy since it was introduced to medicine in 1879. Reports of effects that appeared in nitroglycerin workers and their families were described in the literature as early as 1890.[28–31]

Toxicokinetics. The toxicokinetics of nitroglycerin have been studied and reviewed intensively.[32–37] Nitroglycerin is readily absorbed through intact skin, as well as via the respiratory and gastrointestinal tracts. Vascular-tissue uptake and local metabolism are extensive, thus explaining the rapid systemic clearance of nitroglycerin. Once nitroglycerin is absorbed, it is rapidly metabolized by hydrolysis and glutathione-dependent organic nitrate ester reductase.

Because of their rapid hydrolyses, nitroglycerin and the other aliphatic nitrates have shorter biological half-lives than other classes of explosives.[36] Variations among individuals in sensitivity, plasma levels, time of onset of symptoms, and duration of effects are extremely wide. Metabolites may alter the toxicokinetics of the parent compound during chronic dosing.[37]

Acute effects. Acute or intermittent exposure to nitroglycerin may cause a constellation of symptoms in sensitive individuals. Vasodilatory effects can occur with inhalation of airborne concentrations as low as 0.1 mg/m^3. Symptoms due to vasodilation include headache, dizziness, nausea, palpitations, hypotension, flushing, and abdominal pain. Most of these symptoms are due to direct vasodilation of the meningeal, cutaneous, and systemic blood vessels. Other effects of acute exposure appear to be mediated by other mechanisms and include methemoglobinemia, reflex tachycardia, and increased respiratory rate. Hyperthyroidism has been reported to potentiate the acute toxicity of the organic nitrates.[30] Inhalation exposure at levels as low as 14 mg/m^3 have led to more severe effects such as electrocardiogram (ECG) changes, chest pain, and palpitation. Massive acute exposure may cause cyanosis, coma, and death.

Other acute effects have been described but are less well documented. Central nervous system (CNS) symptoms, such as confusion and hallucinations, and psychotic episodes, including homicidal violence, have been reported in patients after they handled nitroglycerin. Peripheral nervous system effects such as paresthesias have also been reported.

Ingestion of nitroglycerin is an industrial hygiene problem. It can occur via contamination of food or smoking materials in the workplace. However, the use of sublingual nitrates is a common form of therapy for coronary artery disease, taking advantage of the transdermal and transmucosal absorption and the vasodilatory effect of some nitrates.

Chronic effects. Most workers become tolerant to the vasodilatory effects of nitroglycerin within 1 week after their exposure has begun and develop compensatory vasoconstriction. This effect has also been described in patients who receive therapeutic nitroglycerin.[37] The tolerance persists for approximately 1 week after the worker is removed from the exposure.

Evidence of a withdrawal syndrome or sudden death in chronic users has been controversial, and more study of the long-term effects is needed. Withdrawal may precipitate angina pectoris, myocardial infarction, and sudden death. The condition has been called "Monday morning angina" because the symptoms appear after a 48- to 72-hour absence from work. Anecdotal reports of these effects have appeared since the early 1900s, but the first medical case series was reported in 1952.[38] Some evidence of withdrawal has been found in a small cohort of patients taking nitroglycerine,[39] and a recent epidemiological study found evidence of sudden death in long-term nitroglycerine users.[40]

The mechanism associated with angina and sudden death appears to be a series of events starting with habituation to the hypotensive effects of chronic nitrate exposure. When removed from exposure, the employee develops rebound hypertension, which may be followed by coronary insufficiency.[22] Coronary insufficiency is, therefore, a secondary effect due to rebound coronary vasoconstriction, making the heart less able to compensate for the additional strain caused by systemic hypertension. Studies done with animals have shown that nitroglycerin-tolerant subjects become more sensitive to vasoconstrictors after they are withdrawn from nitroglycerin. Some have shown electrocardiographic ST segment changes and ventricular arrhythmias suggestive of coronary artery spasm.[31] Evidence shows that withdrawal from nitroglycerin increases the sensitivity of α_1 adrenergic receptors in the coronary arteries to endogenous and exogenous vasoconstrictive agents.[31]

The chronic cardiac effects of nitroglycerin withdrawal appear to be latent for 6 to 10 years before the onset of symptoms.[40] Several studies of Swedish dynamite workers have demonstrated excess mortality from cardiovascular and cerebrovascular disease. This excess mortality was only significant for workers with long-term employment and had a latency of 20 years.[37] A more recent retrospective cohort-mortality study of workers at a US Army ammunition plant showed an excess of mortality from ischemic heart disease among workers younger than 35 years of age.[31] Pathological examinations of nitroglycerin workers who experienced cardiac events have failed to reveal coronary artery disease, strengthening the conclusion that rebound vasospasm is responsible.[31,41]

A 1965 review of earlier case reports revealed complaints of digestive troubles, tremors, neuralgia, and, in rare cases, ACD among nitroglycerin workers.[42] Decreased alcohol tolerance is common and may be caused by nitroglycerin's interference with liver alcohol dehydrogenase. Simultaneous exposure to ethanol and nitroglycerin can cause manic behavior.[43]

Numerous other chronic effects of nitroglycerin exposure have been reported but, as with some acute effects, are poorly documented. Research has been conducted on other chronic effects in mammals, but the results have not been substantiated in humans. Chronic oral administration of nitroglycerin in rats has produced liver cancer. Other research with mammals has indicated the possibility of male reproductive, fetotoxic, and teratogenic effects.[29,44] Recent evidence has shown that nitroglycerin does not increase intraocular pressure to cause glaucoma.[36]

Medical Surveillance

Early identification of cardiovascular disease is the primary goal of medical surveillance of nitroglycerin workers. A preplacement examination must be administered to all new employees, and should consist of both medical and occupational histories, a physical examination, and indicated laboratory tests. When their employment begins, nitroglycerin workers should maintain a daily record of their pulse rates. Periodic examinations should be conducted semiannually, with the same focus as the preplacement examination. During the periodic examination, the provider should be aware that headaches occurring during work shifts can indicate skin absorption of nitroglycerin, even if air concentrations of nitroglycerin are below the PEL. Similar examinations are necessary when exposure to nitroglycerin has been terminated, although surveillance should perhaps extend beyond employment due to the latency of the withdrawal effects.[18]

In addition to performing medical surveillance examinations, the plant provider should follow these procedures to safeguard the workers' health:

1. The provider should alert the worker's private provider to the effects of exposure to and withdrawal from nitroglycerin.
2. Workers who leave the plant due to any kind of illness should be cleared through the medical department.
3. Workers should also be examined before they return to work after lengthy absences.

This procedure, common in all types of industries, is a management tool used as an administrative control measure. When workers leave the plant with any illness, a medical examination can help determine if that illness is due to an acute overexposure to nitroglycerin (or any other toxic agent). By early detection of a sentinel event, plant managers can intervene at the worksite and thus protect other workers in the area, as well as the ill individual on his or her return to work. An examination is necessary whenever a nitroglycerin worker returns from an illness to ensure that the worker's health status has not changed in such a way that he or she will be placed at risk. Specifically, the occupational provider should look for changes in cardiovascular status, such as a recent myocardial infarction or new-onset hypertension.

A biological marker of exposure would be a useful aid to the occupational health provider, but none are reliable. Blood methemoglobin levels increase after high exposures, but these are not sufficiently sensitive to monitor exposure to nitroglycerin.[45,46] Nitroglycerin can be detected in blood, but because cubital venous blood samples reflect almost exclusively the locally absorbed compound from the distal part of the arm, they are unreliable indicators of systemic exposure.[45–47]

Primary Prevention

The most efficacious method to control occupational nitroglycerin toxicity is to prevent exposure using engineering controls and hygienic work practices. This is especially true because adverse effects occur at exposure levels below the odor and eye-irritation thresholds that could warn workers of potentially hazardous environments.[29,48]

Several types of engineering controls have proven to be effective in reducing inhalational exposure, including automation, closed-circuit television, and ample work-area ventilation. Volatilization of the aliphatic nitrates can be minimized by processing these materials at the lowest practicable temperatures. Operations that require heating should be controlled remotely.[16,22] Maintaining a water seal over liquid nitroglycerin will prevent its evaporation and reduce its concentration in air.

When necessary, PPE should be worn to prevent dermal contact and to reduce airborne levels to an acceptable range. Particular attention must be devoted to the type of gloves worn. Polyethylene gloves may be the best choice, because nitroglycerin easily penetrates neoprene, leather, and rubber. Cotton or canvas gloves, frequently changed, are also preferable to rubber gloves. A face shield or splash-proof safety goggles may also be necessary to protect the eyes. An organic vapor respirator may also be required to prevent headache, especially at concentrations higher than 0.02 ppm.[15]

The selection of a respirator should be consistent with NIOSH guidance and be approved for use in explosives manufacture to avoid potential safety hazards.[10,15] To date, the only respirators that have been demonstrated to provide a sufficiently high protection factor are full-face, supplied-air respirators. However, even these are yet to be proven safe in the potentially explosive atmospheres that may exist in nitroglycerin manufacturing operations. Therefore, the only way to ensure that workers are protected is to lower the airborne level through engineering controls. However, this is not feasible in all cases. Both the government and industry are aggressively pursuing a resolution to this problem to comply with the lower OSHA PEL for nitroglycerin.[10]

Careful attention to personal hygiene is necessary to prevent workers from contaminating their street apparel and, as a result, possibly poisoning their family members. At a minimum, manufacturing plants should provide changing facilities that contain an adequate number of coveralls, gloves, and caps for use during the shift and shower facilities for use at the end of the shift.[48] Indicator soaps are available that turn red in the presence of residual nitroglycerin not removed from the skin (sodium sulfite in the soap reacts with nitrate groups in nitroglycerin to form sodium sulfonate).[48]

The treatment for nitroglycerin poisoning consists of removing the patient from the source of exposure, thoroughly cleansing the skin and mucous membranes of nitroglycerin contamination, and providing cardiovascular support. Washing the skin with aqueous sodium thiosulfate will assist in neutralizing any nitroglycerin that remains. The use of oral nitrates and calcium channel-blocking agents has been somewhat efficacious in the treatment of nitroglycerin withdrawal. Both reduce reflex vasospasm; oral nitrates work by drug replacement (analogous to using nicotine gum

in tobacco cessation to overcome the physiological effects of withdrawal), and calcium channel blockers relax and widen blood vessels by affecting the muscle cells in the arterial walls.[49]

Nitrocellulose

Nitrocellulose is a nonvolatile, fibrous white solid consisting of chains of glucoside units in which the hydroxyl groups have reacted to form nitrate esters. The molecular weight depends on the chain length and the degree of polymerization, which in turn depend on the source of the cellulose. Many sources of cellulose are used, including paper rolls, cotton linters, wood pulp, and waste cotton.[5]

Manufacture and Exposure Hazards

Nitrocellulose was first produced in 1838, but practical difficulties in manufacturing and using the material were not overcome until 1865. Since that time, it has become the basic component of single-base solid propellants**.** Nitrocellulose is the principal ingredient in gun and mortar propellants, smokeless powder, and ball powder**.** The military's production of nitrocellulose is second only to its production of TNT. Nitrocellulose is also a component of combustible cartridge cases, and in the civilian sector is used in manufacturing blasting fuses and mining charges.

In explosive applications, nitrocellulose requires a higher degree of nitration than that produced for its nonexplosive uses (such as lacquers, medical collodion, ink bases, or filter membranes). Military-grade nitrocellulose is produced at various Army ammunition plants in a process wherein cellulose is nitrated with concentrated nitric and sulfuric acids. The only significant byproducts of manufacture are the spent acids, which are concentrated and then reused.

Human Exposure and Health Effects

Insoluble in water and resistant to biological degradation, nitrocellulose per se has a very low potential as a hazard to human health. As an insoluble polymer, nitrocellulose is not absorbed in the gut, and in fact does not appear to be absorbed by any route. The only effects of ingestion are due to the bulk of fiber, which may occlude the intestinal lumen, and are no different than effects of non-nitrated cellulose. Nitrocellulose is not irritating to the skin, and no mutagenic activity has been detected.[50]

Other exposures during the manufacture of nitrocellulose are of greater significance to workers. These include exposures to acids and acid vapors during the initial nitration process, which may lead to dental erosion and chemical burns. Uncontrolled exposure to raw cotton dust from the linters before nitration can cause byssinosis, an allergic, occupational respiratory disease of cotton, flax, and hemp workers characterized by symptoms—especially wheezing—that are most severe at the beginning of each work week (because the lack of exposure over the weekend allows large quantities of the mediators of allergy, such as histamine, to accumulate).

The potential hazards encountered during the manufacturing process necessitate that precautions be taken. Adequate ventilation during both preparation of linters and nitration is essential. It is recommended that PPE be worn by employees who work near the acids. No special medical surveillance for exposure to nitrocellulose is necessary, and treatment for the sequelae of acid contact is not unique. No exposure limits have been established for nitrocellulose.

THE NITROAROMATICS

The nitroaromatics were the second class of organic nitrates to become important as explosive compounds, and they continue to be represented prominently in the world's arsenals. These chemicals are well absorbed by all routes and tend to rapidly penetrate the dermis. The major effects of these chemicals include methemoglobinemia, cancers of the urinary tract, anemia, and ACD.[51,52]

Trinitrotoluene

The best known of the aromatic nitrate explosives, TNT was first prepared in Germany in 1863. It was manufactured industrially starting in 1891 and rapidly became the premier high explosive.[27] Major military powers adopted TNT as their major high explosive in 1901, and the first significant military use of TNT was during the Russo-Japanese War of 1905. Many factors, including its low cost, safety in handling, compatibility with other explosives, low melting point, moderate toxicity, and low sensitivity, made TNT the most widely used military explosive. Before 1940, its manufacture was limited by the availability of toluene, but advances in petroleum chemistry during World War II permitted the synthesis of large quantities of inexpensive toluene, which greatly enhanced TNT production capacity in the United States.[27]

TNT can be found in virtually all military applications and is frequently mixed with aluminum and other high explosives to form binary or ternary

explosives. Its easy availability during World War II made TNT a perfect suspension agent for more powerful explosives such as RDX, and made melt-loading methods feasible.[51]

Manufacture and Exposure Hazard

TNT manufacturing methods are based on continuous stepwise nitration of toluene, with a mixture of concentrated nitric and sulfuric acids flowing countercurrent to the toluene. Anhydrous sodium carbonate and sodium sulfite are used in the washing and crystallization processes to purify the crude TNT solution. The purified TNT is then dried in a steam-jacketed pan before being flaked and packed. Occupational exposure to acids, toluene, and impure TNT have been reduced during the continuous-manufacture process.[53,54]

The most significant risk of exposure to TNT occurs during shell-loading operations. Exposure can occur during several of the steps, most of which involve the melt-loading process. In this process, dry flakes of TNT are poured into a steam-heated melting kettle and heated to approximately 212°F. Other high-temperature melting, nonmetallic additives such as RDX are added at this point. Continued heating drives off the water, and flaked aluminum may be added at this point. The mixture is then cooled until the established pouring consistency is reached. After the mixture is poured, the loaded shells are cooled under controlled conditions.

Exposure to TNT dust, fumes, and vapor can occur during any of these operations. TNT exposure is considered high when the levels are above the OSHA PEL of 1.5 mg/m^3, which is based on an 8-hour time-weighted average (TWA).[55] Moderate levels of exposure occur below the OSHA PEL and above the ACGIH TLV of 0.1 mg/m^3 (also based on an 8-hour TWA).[56] Exposure levels below the ACGIH TLV are considered low, but even low exposure levels cause hemolytic anemia in workers.

Exposure to TNT can occur during numerous work processes in addition to shell loading. Some of the highest TNT dust levels occur during screening operations (passing TNT flakes through a sieve), where concentrations up to 75 mg/m^3 have been measured in breathing zones.[16,57] Workers can also be exposed to TNT fumes and vapors during demilitarization, when munitions may be steam-cleaned to melt and remove the high-explosive charge.

Significant amounts of TNT and its manufacturing byproducts have been released into the environment in huge volumes of liquid waste from factories and LAP plants, and as a result, people living near these facilities have been exposed to TNT. The liquid wastes (known as "pink water") contain TNT isomers, DNT isomers, and mononitrotoluenes. Due to the difficulty and expense of disposing of this waste, the United States currently imports most of the TNT it uses.[53]

Human Exposure and Health Effects

TNT's toxicity to animals and humans has been recognized for at least 75 years.[58–63] Most of this knowledge results directly from work performed during the two world wars. From 1914 to 1918, approximately 24,000 people were poisoned with TNT in the United States, fatally in 580 instances. Similar experiences were described in other combatant nations. In Great Britain, 475 cases of TNT poisoning were reported between 1916 and 1941, of which 125 were fatal.[64] During World War II, TNT poisoning was a factor at US manufacturing and loading plants and arsenals, although the case rates at arsenals and manufacturing plants were less than half that at loading plants. Of the 21 deaths that occurred, 18 were at loading plants, 2 at arsenals, and 1 at a TNT-manufacturing facility.[2] Progressively more people were exposed to more chemicals as the war continued, yet the morbidity was much lower. Case rates for all locations fell dramatically despite the marked increase in TNT production, demonstrating the effectiveness of occupational health and industrial hygiene interventions.

Researchers have analyzed the 21 TNT fatalities of World War II, together with a later death of a former TNT worker. Of this series, 8 died of toxic hepatitis and 13 of aplastic anemia. The late death occurred in a worker who apparently had recovered from hepatitis but later succumbed to aplastic anemia. Only one-third of these fatalities had been exposed to average airborne concentrations higher than the maximum allowable concentration of 1.5 mg/m^3, which reflects the contribution of dermal absorption. Workers who died of toxic hepatitis were younger than those who died of aplastic anemia (the median ages were 35 and 45 years, respectively). In both conditions, the median period of exposure was quite short: 63 days for hepatitis, and 216 days for anemia.[8]

Other cohort studies of TNT workers have shown that virtually all cases of toxic hepatitis have occurred within the first 3 months of exposure; however, cross-sectional studies have not shown significant signs of hepatotoxicity.[65] This may indicate that a sensitive subgroup of individuals is at risk for this effect.

Another World War II–era study evaluated the effects of TNT intoxication in 250 male and 103 female workers in a bomb- and shell-loading facility.[66] No

cases of severe TNT intoxication were seen; however, adverse effects of TNT exposure were found in 32 workers (30 of whom were males), of whom 21 had either gastritis or hepatitis; 14 had anemia; and 3 had systemic manifestations of intoxication.[66]

More recent workplace occupational exposures involving TNT have been substantially lower than levels seen in World War I and II.[67–69] Several researchers who examined workplace medical surveillance results observed workplace anemias and altered liver function tests in workers exposed at levels below the PEL and, to some extent, below the TLV.

Toxicokinetics. TNT is readily absorbed by all routes of exposure. Approximately 60% to 70% of oral doses are absorbed; inhaled TNT appears not only to be absorbed faster than oral doses, but it also reaches higher concentrations in the blood. Dermal absorption is less efficient, but its significance must not be underestimated. TNT dissolved in water is particularly well absorbed through the dermis. This effect is greater in hot weather when workers wear cotton coveralls that become saturated with sweat, which increases TNT skin absorption. Workers' coincident exposure to hygroscopic chemicals such as ammonium nitrate further promotes dermal absorption by keeping the skin moist.[26] Consequently, measuring only airborne levels may significantly underestimate the workers' total systemic exposure.[62,65]

TNT is metabolized primarily by a two-step process: the reduction of the nitro group and its conjugation to glucuronide. Some enterohepatic recycling occurs, but urinary clearance of the glucuronides occurs fairly rapidly, preventing bioaccumulation. The urine of humans who have been exposed to TNT becomes discolored with a red metabolite.

Dermatitis and systemic effects do not correlate well.[62] Hematological effects appear to occur at lower doses than hepatic effects, but susceptible individuals will develop hepatotoxicity sooner after initiation of exposure.

Acute effects. Acute exposure to airborne TNT can cause irritation of the upper respiratory tract and skin; symptoms include sneezing, coughing, rhinitis, and erythematous dermatitis. The onset of acute systemic toxicity is frequently heralded by gastrointestinal symptoms such as nausea, anorexia, and epigastric pain.[64] Systemic symptoms may progress to include headache, fatigue, malaise, palpitations, loss of memory, and cyanosis.[65]

Chronic effects. The most serious chronic manifestations of TNT toxicity are (*a*) anemia and other hematological changes and (*b*) hepatitis; chronic effects may also include dermatitis, ocular effects, neurological effects, and cancer.

Hematological effects result from the action of TNT on both the bone marrow and mature erythrocytes. Although virtually every cell series in the marrow is affected, the most significant hematological effects occur in the erythrocytic series, and may result in anemia with both aplastic and hemolytic components. TNT depresses erythropoiesis and induces aplastic anemia by suppressing two enzymes that catalyze heme synthesis: δ-aminolevulinic acid synthase and heme synthase. This suppression has been demonstrated even in the clinical absence of anemia.

Hemolysis in TNT toxicity occurs as a result of methemoglobinemia. This is a dose-related effect, with low-grade anemia and compensatory reticulocytosis noted at airborne TNT concentrations lower than 0.5 mg/m^3. Exposures of 0.2 to 0.5 mg/m^3 appear to have minimal and well-compensated effects on erythrocytes. Poikilocytosis may occur, as well as hepatic and splenic congestion related to hemolysis. Early signs and symptoms of fatal anemia—even in the absence of G6PD deficiency—include weakness, anorexia, weight loss, cough, epistaxis, elevated bilirubin, decreased hemoglobin, and decreased leukocyte counts. Survival in the case reports of fatal anemia varied from 6 to 185 days, but the median was only 40 days.[6] Hemolytic crisis has been seen in G6PD deficiency within the first few days after exposure.

Other hematological effects include both leukocytosis and leukopenia. Transitory leukocytosis and moderate eosinophilia have been described at airborne levels lower than 2.5 mg/m^3. Leukopenia develops late, well after the hemoglobin level and erythrocyte count fall, in contrast to other chemically induced aplastic anemias. Exposure to TNT causes the monocyte count to increase, regardless of the presence of symptoms, and neither the extent of dermal contact nor the length of inhalational exposure influences the intensity of the hematological response.[59]

TNT poisoning can induce both massive hepatic necrosis and cirrhosis. As with most hepatotoxic agents, the hepatitis manifests with increases in the concentrations of serum transaminases and lactate dehydrogenase (LDH). Researchers found no liver function abnormalities at a TWA lower than 0.5 mg/m^3, but they found elevated aspartate aminotransferase (AST) and LDH at airborne concentrations of 0.8 mg/m^3, which persisted even at 0.6 mg/m^3.[67] Early symptoms of TNT-induced hepatitis include nausea, vomiting, malaise, and hepatic tenderness. Jaundice, although a late symptom of TNT hepatitis, develops rapidly as the liver atrophies and indicates a poor prognosis. In a study of TNT-induced hepatitis fatalities from World War II, the average elapsed time from the first definite symptom to death was 34 days, with a range of 12 to 53 days.[6]

Dermatitis is the most common chronic effect of exposure to TNT. Yellow-orange staining of the skin, hair, and nails is a common sign, and irritant contact dermatitis may occur. Dermatitis requires at least 5 days of exposure to develop, and most patients become tolerant to mild cases.[20,70] Palmar lesions with deep vesicles are characteristic. Allergic contact dermatitis with classic eczematous lesions have been reported, and may rarely appear as an erythema-multiforme-like eruption. ACD usually affects the upper limb, but the skin at friction points such as the collar line, belt line, and ankles may also be involved.[18] Workers exposed to high levels of TNT dust are especially at risk for dermatitis, although it may occur in workers throughout the manufacturing process.

Several studies performed in Europe noted that exposure to TNT was associated with cataracts, but at undefined levels of exposure. TNT workers in Finland developed equatorial cataracts at concentrations of airborne TNT of 0.14 to 0.5 mg/m^3. These characteristic cataracts are insidious in their development and are present only at the lens periphery; consequently, they do not affect vision. They may not be noted on a routine ophthalmological examination, although they are easily observed when the affected eyes are dilated and examined with a slitlamp.[71] Most affected subjects in these studies had normal liver function tests. The duration of exposure to TNT was 1.2 to 17.0 years, with a mean of nearly 7 years. Older workers were more commonly affected, and the lens changes appear to be irreversible. Cataract formation may result from direct action of TNT on the lens via lipid peroxidation and production of superoxide anions.[72]

Research into whether neurological signs develop from TNT exposure has yielded controversial results. Some studies of TNT exposure report neurasthenia and polyneuritis.[5] While some accounts of TNT exposure in the United States support these findings, at least one investigator has concluded that symptoms of peripheral neuritis among workers were not solely due to TNT exposure.[73] This study found that, when present, symptoms were limited to mild sensory disturbances, with no objective evidence of the disease.

TNT has been implicated in carcinogenesis in studies done with laboratory animals. The results of studies performed on rodents have shown increased incidence of bladder papilloma and carcinoma, and statistically insignificant increases in leukemia and lymphoma. In 1996 the International Agency for the Review of Cancer found little evidence in humans and animals and concluded that the carcinogenicity of TNT was not classifiable.[60] However, the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area classified TNT as a class 2 carcinogen in 1991.[61] TNT might be genotoxic; it has given positive results in Ames assays both with and without metabolic activation.[62,63] Many studies published on TNT since 1996 have found an association between TNT and cancer. In 2008 both the US and California environmental protection agencies reviewed the carcinogenicity of TNT. The US Environmental Protection Agency classified TNT as a possible human carcinogen.[62] The California Environmental Protection Agency ruled that through scientifically valid testing according to generally accepted principles, TNT causes cancer.[63]

Numerous other manifestations that have been attributed to TNT exposure include myalgia, cardiac dysrhythmia, nephritis, increased vascular permeability, cardiotoxicity, pancreatic exocrine abnormalities, increased capillary fragility, menstrual disorders, and testicular atrophy and hyperplasia.[64]

Primary Prevention and Medical Surveillance

Historically, control of TNT exposure has been accomplished through general safety and hygiene measures, yet specific additional measures are necessary. For example, hazard communication programs at each facility should instruct workers about the need for strict personal and shop hygiene, and about the hazards of particular operations conducted in that plant. In addition, soap that contains 5% to 10% potassium sulfite not only helps remove TNT dust from the skin, but suds that turn red also indicate any remaining contamination.[54] Furthermore, respiratory protective equipment, selected according to NIOSH guidance, should be worn during operations that release dust, vapor, or fumes.

Because TNT interacts with certain medications, including those that cause intrahepatic cholestasis, hepatocellular necrosis, and bone marrow depression, patients taking medications such as isoniazid, halothane, phenylbutazone, phenytoin, and methotrexate, and whose exposures to TNT cannot be prevented, should be closely followed by an occupational health provider.

The US Army currently recommends preplacement and periodic (semiannual) examinations of TNT workers. The occupational health provider should determine on a case-by-case basis the elements of examinations to use in periodic surveillance. However, to identify workers with higher than normal sensitivity to TNT toxicity, workers should undergo monthly hemoglobin, LDH, and AST determinations during the first 3 months of exposure to TNT.[65] One study demonstrated that assaying for AST, LDH, and hemoglobin in combination detected all abnormal cases,

whereas if the assays were performed alone or in pairs, many cases were missed.[67,73] Periodic examinations provide inadequate warning of impending aplastic anemia.[74] Workers who have abnormal results should be removed from exposure and evaluated further.[73,75]

Bioassays for TNT exposure began during World War II with the use of the Webster test for urinary TNT.[76] This qualitative test was based on the reaction of alcoholic potassium hydroxide with an ether extract of acidified urine, wherein colors are produced when TNT and other polynitro compounds are present in urine.[77] In comparison to the qualitative Webster test, a quantitative test for urinary aminodinitrotoluene (ADNT), a metabolite, can be related to TNT absorption within 24 hours of exposure. Urinary ADNT is measured via gas chromatography with electron-capture detection.[77] Most individuals excrete the highest concentrations of ADNT within a few hours after exposure, but some continue excreting significant amounts many hours later. This prolonged excretion time may indicate that TNT or a metabolite has been retained, or may indicate delayed skin absorption. Prolonged dermal absorption has been indicated in a group of explosives workers whose urinary concentrations of ADNT indicated higher total exposures than were predicted from the concentrations in ambient air.[58,78]

Dinitrotoluene

Toluene is converted to DNT, which is widely used in military applications. DNT is used in the synthesis of toluene diamine, an intermediate in the production of toluene diisocyanate. DNT may comprise up to 10% of commercial dynamite formulations as well. Military uses of DNT are similarly broad; it is most often used as an additive to modify the properties of other explosives. For example, DNT may function as a combustion modifier in propellants, as a gelatinizer, or as a waterproofing agent in explosives.[5]

Manufacture and Exposure Hazard

Due to the serious safety and health hazards inherent in the manufacture of DNT (it is a carcinogen and even more hazardous than TNT), current practices for technical-grade DNT production uses continuous, closed systems that are highly automated and remotely controlled. Technical-grade DNT is a greasy liquid comprised of approximately 80% 2,4-DNT and 20% 2,6-DNT, but military-grade DNT requires highly purified 2,4-DNT flakes. Significant occupational exposure is possible during purification and flaking, as well as during mixing and shell-loading operations. Because DNT is also present in the waste water of TNT manufacturing and shell-loading plants, significant environmental contamination and environmental exposure can also occur.

Human Exposure and Health Effects

DNT is readily absorbed via all routes of exposure, but absorption through the dermis is probably the most significant. In rats, both the 2,4- and 2,6-isomers are extensively metabolized by the liver and then excreted in bile.[79] Intestinal nitroreductase-active bacteria further metabolize the product, which is resorbed and metabolized in the liver to a genotoxin.[80] The excretion of 2,4-DNT metabolites in humans is qualitatively similar to that in rats; however, humans do not excrete the reduced metabolite of 2,6-DNT. This qualitative difference in metabolism makes interspecies extrapolation of the carcinogenic risks difficult.[81,82]

Acute effects. The most characteristic sign of acute DNT toxicity is methemoglobinemia. Associated symptoms include headache, fatigue, cyanosis, irritability, and nausea. Moderate exposures may cause ataxia, respiratory depression, and arthralgias, while severe exposure may lead to progressive CNS depression and death.[80,81]

Chronic effects. Anemia and ischemic heart disease are the most commonly recognized chronic effects of exposure to DNT.[80] The anemia, which occurs when erythrocytes that contain methemoglobin hemolyze, is typically low grade and partially compensated.[81] Increased mortality from ischemic heart disease has been seen in munitions workers who were exposed to DNT during the 1940s and 1950s.[83,84] Unfortunately, a lack of adequate exposure data prevents making accurate dose-response estimates for these effects.

Concerns about DNT's carcinogenicity have been expressed for several years, and have recently focused on incompletely burned DNT in propellant residue at waste propellant disposal sites. Anyone exposed is at risk for carcinogenesis, including workers at the disposal sites and all who are environmentally exposed via dust, groundwater, or direct contact with contaminated soil. DNT isomers exhibited only weak mutagenic activity in Ames assays[81] and no activity in various mammalian cell culture genotoxicity assays. However, studies in rats using technical-grade 2,4-DNT and 2,6-DNT showed a high incidence of hepatocellular carcinomas produced by 2,6-DNT, with a lower incidence in females compared to males. Enterohepatic recirculation with hepatic and intestinal microfloral metabolism are necessary for the production of the carcinogen. Three major mammalian carcinogenicity studies have indicated that 2,6-DNT is both an initiator and a promoter, while 2,4-DNT is only a promoter.[24,81] Evidence of carcinogenicity in

humans is lacking, however. Two occupational cohort studies have been completed on workers exposed to DNT. Neither study showed any excessive incidence of cancer, but both demonstrated elevated cardiovascular and cerebrovascular mortality.[83]

Deleterious effects on the reproductive system have been reported in rats given large doses of DNT (≥ 34.5 mg/kg/d), but such effects were not seen in a NIOSH study of workers at a DNT-toluene diamine plant.[85] Testicular atrophy, decreased spermatogenesis, and nonfunctioning ovaries have been seen in rats, mice, and dogs in feeding studies performed to assess chronic exposures. Results of multigenerational reproductive studies in animals have been negative. Only one of three epidemiological studies has shown effects on the human reproductive system, and these were limited to decreased sperm counts, minor morphologic changes in sperm, and a small increase in spontaneous abortions among wives of exposed workers.[80,81] Studies done on animals and humans have failed to identify teratogenic effects.

Other chronic effects noted in animal studies include neurotoxicity and hepatotoxicity, with histological changes in both organs noted at autopsy. ACD may also occur, but not as frequently as with exposure to TNT. Friction sites are frequently affected by DNT dermatitis.

Primary Prevention and Medical Surveillance

As with all potential carcinogens, prevention of exposure is essential with DNT. Workers who could potentially be exposed to DNT should be informed of its deleterious health effects, including the possible reproductive system effects. In addition to the safety and hygiene measures previously mentioned, occupational health personnel should monitor for residual buildup of DNT on clothing, boot linings, and hardhat liners. Respiratory protection is usually unnecessary because DNT has low vapor pressure.

Medical surveillance should consist of the same protocol as that for TNT, with the addition of a reproductive history and measurement of urinary DNT. The preplacement evaluation should include a baseline sperm count and morphology assessment for workers who intend to have children. Semen analysis is not necessary during routine periodic medical surveillance of exposed workers.

THE NITRAMINES

The nitramines are the most recently introduced class of organic nitrate explosives. The most prominent member of this class is RDX (hexahydro-1,3,5-trinitro-1,3,5-triazine, known as *r*esearch *d*epartment *ex*plosive); HMX (octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine, known as *h*igh-*m*elting *ex*plosive); nitroguanidine; tetryl; and IMX, or *i*nsensitive *m*unitions e*x*plosive.

Hexahydro-1,3,5-trinitro-1,3,5-triazine

Although RDX was first prepared in 1899, its explosive properties were not appreciated until 1920. RDX was used widely during World War II because, unlike other explosives, petroleum was not needed as a raw ingredient.[27] After World War II, RDX became the second most widely used high explosive in the military, exceeded only by TNT. As with most military explosives, RDX is rarely used alone; it is widely used as a component of plastic explosives, detonators, high explosives in artillery rounds, Claymore mines, and demolition kits. RDX has limited civilian use as a rat poison.

Manufacture and Exposure Hazard

RDX is manufactured using the continuous Bachman process, in which hexamine is nitrated with ammonium nitrate and nitric acid in a solvent mixture of acetic acid and acetic anhydride. The byproducts of RDX manufacture include nitrogen oxides, sulfur oxides, acid mists, and unreacted ingredients. In 1964, during mobilization for the Vietnam War, the Holston Army Ammunition Plant alone produced approximately 750,000 pounds per day of RDX and HMX combined.[86]

Soldiers and other workers have been exposed to RDX during its manufacture, in the field, and through environmental contamination. The main occupational exposure to RDX during its manufacture is through the inhalation of fine dust particles. Ingestion is possible, but it is poorly absorbed through the skin.[87]

The greatest potential for occupational exposure to RDX occurs at ammunition plants with LAP operations, among workers involved with melt-loading and maintenance operations.[87] During World War II, there were no fatalities and little morbidity at RDX manufacturing plants. Small numbers of Italian and German workers, who handled powdered RDX in the drying, cooling, screening, and packing processes, were reported to have experienced RDX toxicity, but all recovered completely.[88]

In 1962, five cases of convulsions, unconsciousness, or both occurred at a US RDX manufacturing plant. In four of these cases, exposure was from inhaled dust during cleanup of a mixing area. The fifth employee screened and blended dried RDX from different

batches; gross skin and air contamination occurred because no mechanical ventilation was used and the individual did not follow hand-washing and hygiene precautions. All five employees had convulsions during their work shifts or within a few hours after their shifts were over. These patients exhibited little or no prodrome, and the postictal phase lasted up to 24 hours. No abnormal laboratory or physical findings were noted.[88]

Troops have also become intoxicated during field operations from exposure to composition C4 plastic explosive, which contains 91% RDX. These field exposures occurred because the C4 was either chewed as an intoxicant or used as a fuel for cooking; thus, the route of exposure was ingestion or inhalation. At least 40 American soldiers experienced convulsions due to RDX ingestion during the Vietnam War.[89,90]

RDX in waste water from manufacturing and loading operations has also contaminated the environment. Although contamination has appeared in soil and groundwater near some ammunition plants, RDX's low solubility in water has limited its migration in most cases.

Human Exposure and Health Effects

The mainstay of treatment for RDX exposure is removal from exposure. Patients who are experiencing seizure activity should be given phenobarbital. Phenytoin is ineffective in controlling RDX-induced seizures.[89]

Toxicokinetics. Gastrointestinal absorption of RDX in humans is slow but complete; serum levels peak approximately 12 hours after ingestion. Clearance of RDX from the serum occurs in approximately 15 hours. The highest tissue levels of RDX occur in the kidneys, with slightly lower levels in the liver, brain, and heart. RDX is metabolized by the liver, and the metabolites are excreted primarily in the urine.[90] Unlike most other nitrated explosives, RDX does not metabolize to form nitrite in the blood.

Acute effects. RDX has relatively low acute toxicity. After acute exposure by inhalation or ingestion, there is a latent period of a few hours, followed by a general sequence of intoxication that begins with a prodromal period of irritability. Neurological symptoms predominate and include restlessness and hyperirritability; headache; weakness; dizziness; hyperactive reflexes; nausea and vomiting; prolonged and recurrent generalized convulsions; muscle twitching and soreness; and stupor, delirium, and disorientation.[91]

Clinical findings in acute exposures may also include fever, tachycardia, hematuria, proteinuria, azotemia, mild anemia, neutrophilic leukocytosis, elevated AST, and electroencephalogram abnormalities.[5] These abnormal effects, transient and unreliable for diagnostic purposes, last at most a few days. In fact, all physical and laboratory tests may remain normal, even in the presence of seizures.[5,88,90] Electroencephalograms made at the time of convulsions may show bilateral synchronous spike and wave complexes (2–3/sec) in the frontal areas with diffuse slow wave activity; normalization occurs within 1 to 3 months.[89] Patients will recover from acute RDX exposure within days to months, gradually but completely, and they may experience amnesia early in the process.

Several case reports of RDX ingestion have been documented. In one instance, a 3-year-old child ingested plasticized RDX that had adhered to the boots and clothing of the child's mother, who worked in a munitions plant. The child presented with status epilepticus, but recovered without sequelae. Laboratory tests were essentially normal, and the dose of RDX ingested by the child was estimated to be 84 mg/kg.[92] In the instances of convulsions that occurred among American soldiers in Vietnam, signs and symptoms usually began 8 to 12 hours after ingestion. Renal toxicity was observed in 3 of 18 patients (16%) in one series.[89] The sequence of symptoms was similar to that which occurs after occupational exposures, proceeding from confusion and hyperirritability to myoclonic contractions, severe prolonged generalized seizures, prolonged postictal confusion, and amnesia.[5,89,90]

The effects of acute exposure to RDX have also been studied in animals. In rats, the median lethal dose of orally administered RDX was approximately 200 mg/kg. Groups of 20 rats at each dose level were administered 25 mg/kg, 50 mg/kg, or 100 mg/kg; all doses produced hyperirritability, convulsions, and mortality up to 86.6%.[91]

Chronic effects. Although intensive research with animals has revealed some effects, few effects of chronic human exposure to RDX have been reported. One study reported that occupational exposure to TWAs of 0.28 mg/m^3 to 1.57 mg/m^3 did not cause hematological, hepatic, or renal abnormalities. This study also failed to substantiate a suspected association of RDX exposure with systemic lupus erythematosus. Moderate reductions of the erythrocyte count and hemoglobin occur during the first month of exposure, but these values return to normal by the end of the second month.[90]

Tests done on animals have supplemented the knowledge of the chronic effects of RDX in humans. Dogs fed 50 mg/kg of RDX daily for 90 days developed hyperirritability, convulsions, and weight loss, with no alterations of their blood chemistries or cytology. No histological lesions have been found in animals that have had RDX-induced seizures. In addition to the effects noted in humans, several others have been

seen in animal tests: cancer, weight loss, anemia, hepatotoxicity, testicular degeneration, and suppurative inflammation of the prostate.[90]

Investigations into the mutagenicity and carcinogenicity of RDX have yielded conflicting results. RDX does not appear to be a mutagen, based on negative results in the Ames test, the dominant lethal test, and the unscheduled deoxyribonucleic acid synthesis assay. RDX has not been found to be carcinogenic in gavage studies performed on rats, but increased hepatocellular carcinoma and adenoma were noted in females of one strain of mice. Due to this finding, the US Environmental Protection Agency has classified RDX as a possible human carcinogen.[90]

Reproductive effects have been noted in rabbits and rats. A study performed on rabbits showed teratogenic effects at 2 mg/kg/day (10% of the dose that caused maternal toxicity).[90] Similarly, a teratology study performed on pregnant rats exposed to RDX resulted in offspring with lower body weights and shorter body lengths than were found in the control group. These researchers therefore recommended that workers desiring children be protected from exposure to RDX.

Primary Prevention and Medical Surveillance

Despite the low toxicity of RDX, exposure should be maintained at the lowest levels possible due to its possible carcinogenicity and reproductive effects. Sound industrial hygiene and preventive medicine measures, such as those used in the handling of TNT, should suffice to protect workers.

General medical surveillance examinations may be conducted, but specific testing for the effects of low-level occupational exposure does not appear warranted, given the absence of abnormal results even in patients with RDX-induced seizures. Surveillance for both males and females should also include a screening questionnaire for reproductive history.

Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine

HMX is the highest energy solid explosive produced on a large scale in the United States. It is used exclusively for military purposes to implode fissionable material in nuclear devices, as a component of plastic-bonded explosives, as a component of rocket propellant, and as a high-explosive burster charge.[5]

Manufacture and Exposure Hazards

Exposure to HMX can occur during the manufacture and filling of munitions or through the environmental contamination of groundwater and soil. HMX, like RDX, is manufactured using the continuous Bachman process. Although its solubility in water is very low, HMX can be present in particulate form in water effluent from manufacturing, LAP, and demilitarization operations.

Human Exposure and Health Effects

Data on the effects on human health of exposure to HMX are very limited. HMX causes CNS effects similar to those of RDX, but at considerably higher doses.[93] In one study, volunteers submitted to patch testing, which produced skin irritation. Another study of a cohort of 93 workers at an ammunition plant found no hematological, hepatic, autoimmune, or renal diseases. However, the study did not quantify the levels of exposure to HMX.

HMX exposure has been investigated in several studies on animals. Overall, its toxicity appears quite low. HMX is poorly absorbed by ingestion. When applied to the dermis, it induces mild skin irritation but not ACD. Various acute and subchronic neurobehavioral effects have been reported in rabbits and rodents, including ataxia, sedation, hyperkinesia, and convulsions. Chronic effects of HMX documented in animal studies include decreased hemoglobin, increased serum alkaline phosphatase, and decreased albumin. Pathological changes were also observed in the animals' livers and kidneys.[94] No data are available concerning the possible reproductive, developmental, or carcinogenic effects of HMX.

Primary Prevention and Medical Surveillance

Both primary prevention and medical surveillance for HMX exposure should be conducted as they would be for exposure to RDX.

Nitroguanidine

Nitroguanidine was first prepared in 1877, but was not used as an explosive until World War II. Today, it is a major component of triple-base solid propellants. The properties that give nitroguanidine an advantage over nitrocellulose or nitroglycerin include cooler burning, greater production of gas, less flash, less smoke, and less corrosion in gun barrels.

Manufacture and Exposure Hazards

Nitroguanidine is produced using the British aqueous fusion process, which does not depend on either coal or petroleum for raw ingredients. The ingredients

and process chemicals used in nitroguanidine production include calcium carbide, nitrogen, calcium cyanamide, ammonium nitrate, guanidine nitrate, ammonia, and sulfuric acid.[5]

Workers can be exposed to nitroguanidine during the manufacturing process or during its incorporation into propellants. Nitroguanidine is moderately soluble in water and is rapidly absorbed in the gastrointestinal tract. It is only negligibly metabolized, however, and the body rapidly excretes unaltered nitroguanidine in the urine.

Human Exposure and Health Effects

Although no studies of the effects of nitroguanidine on humans have been done, studies performed on animals have indicated generally low toxicity. The oral median lethal dose (LD_{50}) is 3.9 g/kg in mice and 10.2 g/kg in rats. Direct contact with nitroguanidine may burn the skin and eyes. Single sublethal doses of nitroguanidine in rodents have caused respiratory effects (epistaxis and dyspnea), gastrointestinal effects (diarrhea and hemorrhage), and CNS effects (depression, hyperactivity, ataxia, and tremors). Chronic exposure to nitroguanidine may result in osmotic diuresis and modest hematological and liver function changes.[95] Results of studies of the reproductive and teratogenic effects of nitroguanidine appear to be negative, as do results of testing for mutagenicity.[96]

Primary Prevention and Medical Surveillance

Employees who work with nitroguanidine should avoid exposing skin, eyes, and the respiratory tract, and should wear PPE (safety glasses and respiratory protective equipment) when exposure to nitroguanidine exceeds the permissible exposure limit. Preplacement examinations should focus on the kidneys, liver, and blood and include renal and liver function tests and complete blood counts (CBCs). Because the toxic effects are subtle and the long-term implication of alterations in these clinical tests results is unclear, occupational health providers should use an interim medical history to determine the contents of periodic examinations on a case-by-case basis. Abnormal test results may indicate the need for improved exposure control in the workplace and additional medical follow-up.

Insensitive Munitions

Since explosives were first used by the military, accidental fires and munitions explosions have led to death of service members and destruction of military equipment. In July 1967, a rocket accidentally discharged on the flight deck of the aircraft carrier *USS Forrestal*. The chain reaction of exploding bombs and ordnance resulted in 134 fatalities, and the aircraft carrier was out of commission for several years. A similar incident occurred at US Army Camp Doha in Kuwait, where fire led to a chain reaction of explosions from stored artillery. These incidents underscore the need for insensitive munitions. The munition IMX is harder to explode in thermal, mechanical, and electrical tests than conventional military energetics such as TNT.[97] IMX is more stable and less reactive to shocks from gunfire, fire, and bombs. Although IMX is a high explosive, it cannot be detonated unintentionally, and IMX-filled rounds, mortar, projectiles, shells, and rockets are designed to be safer for soldiers to handle and transport.

Manufacture and Exposure Hazard

IMX is a high-performance insensitive energetic compound developed as a direct replacement for TNT in 155-mm M795 and M122 rounds.[97] IMX is composed of three compounds: 2,4-dinitoanisole (DNAN), nitrotriazolone (NTO), and nitroguanidine.[97]

IMX-101 is manufactured by a stepwise melt-pour manufacturing process. During manufacturing, DNAN is added to the nitroguanidine in a large stainless, steel steam-jacketed melt kettle. The kettle's temperature is increased to a point above DNAN's melting point, allowing it to melt (known as "charging" the melt kettle) and the residual moisture to evaporate. When this is complete, the temperature is adjusted https://frederick.craigslist.org/zip/d/free-chairs/6743884097.html to allow the nitroguanidine to melt. Once all the residual moisture of the DNAN-nitroguanidine mixture is removed, NTO is slowly added to the melt kettle and charged as well. Strips of the molten explosive mixture are then transferred from the melt kettle onto a flaker belt, where they are cooled and solidified while traveling along the belt. At the end of the flaker belt, the IMX-101 flakes are packaged.[98] The flakes are then shipped to a "load and pack" facility, re-melted, and poured into the explosive cavities of ammunition rounds.

Workers are exposed to IMX-101 during several of the steps in the manufacturing process, mostly during the melt-pour and shell loading operations. During these operations, exposure to IMX-101 dust, fumes, and vapor can occur. Exposure to IMX-101 can also occur through environmental contamination of the ground and surface water.

Human Exposure and Health Effects

There is limited information in the literature regarding human toxicity and adverse health effects of

IMX-101. Nitroguanidine animal studies show no toxic effects. The US Army Public Health Center (USAPHC) conducted several studies to examine the health effects of the other two components of IMX-101. A study of oral toxicity was conducted in rats that noted several health effects including testicular atrophy, low sperm count, decreased sperm density and motility, splenomegaly, tubular degeneration, and lethality at high doses of DNAN (> 500 mg/kg/d). The LD_{50} in male and female rats was 1,237 mg/kg and 924 mg/kg, respectively, and the combined LD_{50} value was 1,100 mg/kg.[99]

The lethality and splenomegaly are suspected to be due to the DNAN because these effects are observed at similar concentrations of DNAN alone. The reproductive effects of the IMX-101 are likely due to NTO, which has a similar effect. However, in the IMX-101 mixture, the effect is seen at much lower levels, indicating there may be some synergistic effects. In a 2012 study, a 14-day oral administration of IMX-101 caused reductions in testicular mass at a daily dose of 100 mg/kg. This is a 10-fold lower concentration than the concentration when similar reproductive effects are seen in NTO alone, which caused a reduction in testicular mass at a daily dose of 1,000 mg/kg per day.[99]

The USAPHC studies on IMX-101 components showed that IMX-101 can affect blood, liver, eyes, skin, and endocrine function. DNAN is a nitroaromatic, and one of the main health concerns are hematopoietic effects. DNAN causes a reduction in red blood cell count, hematocrit, and hemoglobin levels. It also causes increased spleen mass and extramedullary hematopoiesis in rats, according to a 90-day oral gavage USAPHC toxicology study.[99] DNAN seems to have some dermal effects as well. Rabbits exposed to DNAN exhibited slight dermal irritation that was reversible within 24 to 48 hours. However, studies in guinea pigs indicated otherwise, showing that DNAN was not a sensitizer.[99] Other researchers have observed ophthalmologic effects after exposure in multiple species that is thought to be due to the DNAN metabolite, DNP.[100]

In a 2012 USAPHC study,[101] rodents given oral doses of DNAN had increased liver mass, which was observed at lower dose levels in male rodents compared to females. In addition, alanine transaminase and bilirubin became elevated in rats given DNAN at 50 and 100 mg/kg per day due to hepatocellular injury.[102]

A 2010 USAPHC study investigating oral exposure to NTO showed elevated AST levels and hepatocellular hyperplasia in male rodents at high doses. However, the main health effect of NTO is on the reproductive system. NTO is associated with decreased sperm count, testicular atrophy, and decreased epididymis mass in rats. These effects suggest that NTO might be an endocrine disruptor, but NTO does not appear to affect testosterone or estrogen-mediated signaling pathways. NTO targeting of reproductive organs was also tested in vivo using Hershberger bioassays, which provided no evidence that NTO acts as an estrogenic or antiandrogenic endocrine disruptor. Biologically significant effects on organ mass were limited to reductions in testes and epididymis mass. The study also noted that NTO does not act as an estrogen- or thyroid-active compound.[101] NTO may cause mild dermal irritation according to the safety data sheet produced by the IMX-101 manufacturer.

Primary Prevention and Medical Surveillance

In September 2011, the Joint Munitions Command surgeon, in conjunction with USAPHC, convened an expert panel to provide recommendations regarding medical surveillance of IMX-101. The panel included experts from academia and the surgeon general's consultants for occupational medicine, endocrinology, hematology, and oncology. The panel's recommendations were adopted for worker medical surveillance for IMX-101 (Exhibit 28-1).

In 2013, the Joint Munitions Command surgeon reviewed the medical surveillance data obtained from clinics performing IMX surveillance. Hemolytic anemia was the most prevalent health effect observed in IMX workers.[102] DNAN has similar effects on hemoglobin levels as other nitrogen-based explosives, such as TNT. Monitoring hemoglobin levels has been standard practice for the medical surveillance of workers exposed to TNT, and the same monitoring is required for IMX-101 workers. The primary laboratory test for the hematopoietic effects of IMX-101 is a CBC. Diagnosis of hemolytic anemia includes obtaining a health history, family history, occupational history, clinical presentation, and special laboratory testing including electrophoresis. Work-up of IMX-101 workers for hemolytic anemia should rule out other causes of hemolytic anemia, including blood loss, intravascular hemolysis, metabolic defects, membrane abnormalities, hemoglobinopathy, autoimmune defects, and fragmentation hemolysis.

Preliminary Exposure Level

The USAPHC established a preliminary occupational exposure limit (OEL) for two of the compounds in IMX-101 using the data from the multiple USAPHC animal studies. The OEL for DNAN was established at 0.10 mg/m^3. An OEL for NTO was established at 1.6 $mg/m.^3$ An OEL for nitroguanidine has not yet been

EXHIBIT 28-1

IMX MEDICAL SURVEILLANCE RECOMMENDATIONS

Preplacement Examination

- Complete history using DD Form 2807-1, Report of Medical History: a review of systems with emphasis on the eyes, gastrointestinal tract, skin, and the hematologic, reproductive, central nervous, cardiovascular, and respiratory systems.
- Medical examination should be recorded on DD Form 2808, Report of Medical Examination, and include vital signs, and a focused exam of the eyes, gastrointestinal tract, skin, and the hematologic, reproductive, central nervous, cardiovascular, and respiratory systems.
- Laboratory tests should include the complete blood count (CBC), compete metabolic panel (CMP), dipstick urinalysis, γ-glutamyltransferase (GGT), alkaline phosphatase (ALP), and glucose-6-phosphate dehydrogenase.

90-Day Assessment

- Repeat the history and physical elements of the preplacement examination with a focus on the male reproductive system and hematopoietic changes.
- Repeat CBC, CMP, GGT, ALP, and dipstick urinalysis.
- Abnormal labs require follow-up by the occupational health clinic provider or personal physician. If there are no health status changes, a 6-month evaluation cycle starts.

Semiannual Examination

- Repeat the history and physical elements of the preplacement examination with a focus on the male reproductive system and hematopoietic changes.
- Repeat CBC, CMP, GGT, ALP, and dipstick urinalysis, and add a haptoglobin (Hp) and serum lactic acid dehydrogenase (LDH). The occupational health provider should consider adding a peripheral blood smear, a reticulocyte count, and other testing as indicated.

Termination Examination

- Perform the examination within 30 days of the end of employment.
- The termination exam contains the same evaluations as the semiannual evaluation.

Temporary Removal From Work

- The healthcare provider should consider medical removal when lab test abnormalities exist compared to the baseline or periodic laboratory exam, AND one confirmatory lab finding is abnormal.
- Primary lab test abnormalities include a fall in hemoglobin of 2.0 g/dL or more from the initial or periodic test, and a level for a male below 14.0 g/dL or for a female below 12.0 g/dL.
- Confirmatory lab abnormalities include a decreased Hp, increased reticulocyte count, increased LDH, or abnormal peripheral blood smear.
- The worker's supervisor must be notified of the recommendation for medical removal, including the duration of the removal and the indicators for return to work that will be tracked.

Return to Work

- Any worker who is medically removed should be examined by a medical provider and cleared to work after follow-up lab testing confirms a return to baseline primary or confirmatory lab values.
- The employee may be tested at the occupational health clinic, or they may see their own provider for testing.
- Once testing is completed, the employee should be cleared by the occupational health clinic provider to return to work.

Data source: Monks WS, Mirza RA. Medical surveillance examinations for workers exposed to IMX-101 and its components. *Army Med Dep J.* In press.

established because the only observed health effects with IMX-101 are attributed to DNAN (hematopoietic effects) and NTO (reproductive effects in males).[100]

At the same time, the Occupational Alliance for Risk Science produced workplace environmental exposure levels (WEELs) for DNAN, NTO, and nitroguanidine. The WEELs for DNAN (8-h TWA: 0.1 mg/m^3) and NTO (8-h TWA: 2 mg/m^3) were published in 2014,[101,103] and the WEEL for NQ (8-h TWA: 7 mg/m^3) was published in 2016.[104]

THE INITIATING EXPLOSIVES

The initiating explosives, which are used in combination with more powerful explosive charges, are a heterogeneous group of chemicals that are prepared and used in very small quantities (thus limiting their potential for exposure). The most frequently used initiating explosives are lead azide and lead styphnate. A less common initiator is diazodinitrophenol (DDNP), an ingredient in primers and commercial blasting caps.

Lead Azide

Lead azide, first prepared in 1890, is produced when lead nitrate reacts with sodium azide; sodium nitrate is a byproduct.[27] Because it is quite stable, lead azide is one of the best initiators for sensitive explosives such as tetryl and RDX. Lead azide is usually used in combination with lead styphnate and DDNP. In the civilian sector, it is used in cartridge primers, primer cords, and blasting caps.

Lead azide is composed of 70% lead by weight, and it releases poisonous lead and nitrogen oxide fumes when heated. However, due to safety constraints, there is little opportunity for exposure to lead azide itself. During its manufacture, lead azide is screened in barricaded rooms to avoid continuously exposing the workers. Workers can be exposed intermittently while entering the screening rooms, but they should only do so when wearing respiratory protective equipment. Some exposure can occur while primers are loaded, but this can be prevented by local exhaust ventilation.

The acute effects of exposure include vasodilation and headache, and the chronic effects are those of lead intoxication. Due to these health effects, silver azide has been investigated as a substitute for lead azide. Regulations and medical surveillance associated with exposure to lead azide should be based on the lead content. These specific requirements are dictated by 29 CFR, Part 1910.1025.[105]

Lead Styphnate

Lead styphnate was first prepared in 1914 by von Hertz in Germany, and it was used as an explosive by Russia in World War I. Although lead styphnate is easily ignited, it is a relatively poor initiator, and thus is often used in combination with other primary explosives. Manufactured from 2,4,6-trinitroresorcinol, magnesium oxide, and lead nitrate, lead styphnate may be used as a covering charge (ie, the booster) for lead azide, as an ingredient of priming compositions, as a component in blasting caps, and as a component in small-arms primers (eg, M16 primer uses 4 mg of lead styphnate).

The effects on human health have not been well studied, but acute effects appear to be limited to dermatitis and yellow staining of the hair and skin.[20] Chronic exposure may result in lead toxicity, and the lead content of this explosive should form the basis of monitoring and medical surveillance for exposure.

COMPOSITE PROPELLANTS AND EXPLOSIVES

Composite propellants are solid rocket fuels that are being used in an increasing number of applications. As with all explosives and propellants, they consist of an oxygen donor—the oxidizer—and a hydrocarbon fuel. The oxidizer is usually an inorganic salt, and the fuel is a polymeric binder (essentially a plastic). The composites have a wide range of performance characteristics, are tremendously stable, and are inexpensive. However, they are so reactive that they corrode the metal in gun barrels.

The vast number of alternatives available for use as oxidizers and binders preclude discussion of them all. Information about the toxicity of the inorganic salts is widely available in the toxicology and occupational medicine literature. Therefore, this discussion focuses on ammonium perchlorate, the most widely used oxidizer in composite propellants due probably to its cost, stability, ease of manufacture, and versatility. Ammonium perchlorate is used in the Multiple Launch Rocket System and in rocket-assisted howitzer projectiles. Workers can be exposed via the dermal and inhalational routes during all stages of propellant production.

Before it can be used in munitions, an oxidizer must be ground and screened by particle size to ensure it will burn uniformly. Both grinding and screening raise

significant levels of dust, some of which is respirable and must be controlled. The process of mixing the oxidizer with the binder can also be quite dusty.

Numerous polymeric binders are currently in use. After the binder is mixed with the oxidizer, the resultant propellant can either be cast or pressed into a mold. Cast materials are melted, then poured as a liquid into a mold, while pressed materials are kept in their solid state and shaped by simply molding or extruding. A high-temperature curing process then effects polymerization, a process that releases toxic vapors, to which the workers can be exposed. The propellant core is then removed from the mold and machined or trimmed as needed. Workers can be exposed to dust during these operations.[106]

Plastic-bonded explosives are similar in concept to the composite propellants, but are designed to function as high explosives rather than as propellants. Several major groups are the PBX, PBXN, and LX-10 series. These explosives represent a variety of mixtures combining high mechanical strength, excellent stability, and a wide range of explosive properties. They contain a high percentage of basic explosive (RDX, HMX, hexanitrostilbene, or penta-erythritol-tetranitrate), which is mixed with a polymeric binder (polyester, polyurethane, nylon, polystyrene, rubbers, nitrocellulose, or Teflon [DuPont, Wilmington, DE]); plasticizer (dioctylphthalate or butyldinitrophenylamine); and metallic fuel (powdered aluminum or iron). A major advantage of using plastic-bonded explosives is that the final product can be injection- or press-loaded at ambient temperatures, or even loaded in the field. The binders are thermally degradable, so that in demilitarization operations the ingredients can be completely recovered.[5]

Specific medical information regarding composite propellants and explosives is difficult to provide. For all practical purposes, the polymers are medically inert. The other components, which are heterogeneous and from different chemical families, have vastly different effects, many of which are not yet characterized.

LIQUID PROPELLANTS

The two types of liquid propellants are liquid rocket propellants and liquid gun propellants. Both the National Aeronautics and Space Administration and the US Air Force use liquid rocket propellants in high-performance missile systems. The armed services have developed liquid gun propellants for use in large-caliber weapons such as the 120-mm main tank cannon, 105-mm howitzer, 155-mm howitzer, and 8-in. howitzer.

Rocket Propellants

Many chemicals have been used as components of liquid rocket propellants**.** Most of them have only limited military use and therefore will not be discussed in this chapter. The liquid rocket propellants that do have military applications include (*a*) hydrazine, (*b*) nitrogen tetroxide, and (*c*) boranes.

Hydrazine is widely used in the chemical industry, where most of the studies of its effects on human health have been conducted. Studies on humans and animals have demonstrated deleterious health effects. The effects on humans have been limited to irritation of the skin and mucosa and hepatic disorders, but the effects found in animal studies have been more severe. Mice have developed hepatomas after being fed hydrazine, rats exposed to hydrazine vapor have developed nasal tumors, and hamsters have developed lung adenomas. Urinary levels of hydrazine have shown some utility in monitoring exposure. At a minimum, medical surveillance should periodically assess erythrocyte indices, hypoglycemia, kidney and liver disease, hemorrhagic diathesis, and allergies to phenylhydrazine and isoniazid.[107]

Nitrogen tetroxide has also been used widely in the space program, with potential health effects. The vapors can cause immediate or delayed swelling and blistering of the adnexa oculi and severe burns of the dermis. When nitrogen tetroxide is inhaled, it can react with moisture in lung tissue to form nitric acid and cause delayed pulmonary edema.[5]

During the past 60 years, the fuel boron hydride and its derivatives, also known as boranes, have become widely used in rocketry as rubber vulcanizers, corrosion inhibitors, and components in other chemical processes. The reactivity of the boranes has led to a proliferation of uses, but has also contributed to their significant toxicity. Regardless of their use, boranes are toxic to the respiratory system, cardiovascular system, CNS, skin, kidneys, and liver.

Carboranes—boranes that contain carbon in addition to boron and hydrogen—have been developed and investigated for use in solid-fuel systems. The carboranes are skin irritants, but they do not sensitize. They appear to have relatively low acute toxicity. Subchronic inhalation exposure in dogs resulted in interstitial pneumonitis and early emphysematous changes, but no developmental effects were noted.[108]

Gun Propellants

Liquid gun propellants have several advantages over solid propellants for use in self-propelled howitzers and naval vessels: they are less expensive to produce and transport, less vulnerable to secondary ignition, and easier to store in combat vehicles; they can also be demilitarized more safely and easily than solid propellants.[109] However, more workers can be exposed to the chemical components during the manufacture, transport, and use of liquid propellants compared to solid propellants.[110]

Liquid gun propellants consist of aqueous solutions of hydroxyl ammonium nitrate (HAN) mixed with either trimethanol ammonium nitrate or triethanol ammonium nitrate. No studies on the effects on human health have been reported on either of the mixtures or the individual components. However, the aqueous solutions and pure HAN have been evaluated for mammalian toxicity.[111–116] The mixtures were found to be moderately toxic to both rats and rabbits: for male rats, the oral LD_{50} was 822 mg/kg, and for female rats, 520 mg/kg; for rabbits, the oral LD_{50} was 101 mg/kg.[113] Oral exposure to the mixtures induces cyanosis, respiratory distress, and, at high doses, death.[111] A single intragastric dose of 400 mg/kg produced no ECG changes in dogs. Treatment with methylene blue rapidly reversed the acute toxic effects. The mixtures were also found to be ocular irritants, but were not corrosive to the cornea.[110] However, exposure to mixtures induced hematological changes: methemoglobinemia occurred; oxygen tension decreased; free nitrites, Heinz bodies, and crenated erythrocytes formed; and, at lower doses, serum potassium decreased.[111]

The rabbit studies also found that HAN applied to the dermis caused chronic and ulcerative dermatitis, and at higher doses, hemolytic anemia in addition to the systemic effects described previously for exposure to the mixture. However, no blood chemistry changes were noted.[112] When administered orally to three groups of rabbits (1, 5, and 25 mg/kg/d) for 21 days, HAN induced splenic congestion and hyperplasia of the reticuloendothelial system at all doses.[113] At 25 mg/kg/day, HAN caused anemia and myeloid hyperplasia of the bone marrow.[113] Inhalation of aerosolized HAN has been found to induce Heinz-body formation and upper respiratory irritation.[114] Several other liquid gun propellants have also been investigated as aerosols, and the effects they elicited were qualitatively similar to those of HAN.[115]

The Occupational Medicine Division of the USAPHC has established preliminary guidelines for medical surveillance, and a provisional military exposure guideline of 3 mg/m^3 has been proposed for liquid gun propellants.[116,117] Testing for methemoglobinemia or examining the peripheral blood for Heinz bodies should be considered part of the medical monitoring for exposed employees. Reasonable occupational precautions include restricting employees from eating, drinking, and smoking in areas where these chemicals are handled or stored; ensuring adequate ventilation; preventing spills and splashes; and using PPE such as splash goggles and gloves.

SUMMARY

In defending the United States, military and civilian personnel must necessarily produce, store, and handle a variety of munitions. In the Army, these operations occur around the country at various arsenals, proving grounds, depots, and ammunition plants, which together employ more than 100,000 workers. Despite incomplete laboratory studies and imperfect data, information has been gathered during the last 50 years on the effects of workplace exposures to these chemicals, much of it recorded during wartime while large quantities were being produced.

The chemical families represented among energetic materials (explosives, propellants, and pyrotechnics) include aliphatic nitrate esters (such as nitroglycerin), nitroaromatics (such as TNT), and nitramines (such as RDX). Considering the properties of the energetic materials—explosives, propellants, and pyrotechnics—it was inevitable that they would be utilized in military weapons. Explosives create a shock wave that progresses rapidly, while propellants release large amounts of hot gas in a more controlled manner. Pyrotechnics burn slowly, emitting tremendous heat or light. Most modern weapons utilize energetic compounds in combination, capitalizing on their individual properties.

As these energetic materials are synthesized and assembled into munitions, workers can be exposed to the raw materials, the finished product, or any number of chemical intermediates along the way. These chemicals are usually absorbed via the dermal, inhalational, and, less importantly, the ingestional routes; as a class they can produce dermatitis, methemoglobinemia, vasodilation, and cancer. The standard industrial hygiene principles of engineering and administrative controls and PPE can minimize exposures. Obviously, the explosive properties of these chemicals necessitate strict compliance with safety guidelines. Preplacement screening and periodic surveillance must be tailored to

the specific hazards in each industrial operation and at each site. Generalized medical guidance regarding these mixtures has little practical significance.

Individuals exposed to mixtures of chemicals such as TNT and IMX must be enrolled in medical surveillance programs for each chemical. Where the laboratory tests overlap, redundant labs should be eliminated. The effects of exposure to multiple chemicals cannot be predicted with certainty because the response may be additive or synergistic, or the exposure may have no effect at all. Thus, a thorough baseline medical examination done prior to exposure is important; the provider should review of the occupational history and capture previous exposures and work-related injuries and illnesses. Depending on the exposure, an endocrinology consult may help in developing medical surveillance recommendations for these individuals.

The above approach should also be followed for individuals in other unique populations, such as those who work in research and development of chemical munitions; those with hormone abnormalities; those undergoing active chemotherapy or biologic therapy; and those with blood disorders. A thorough medical evaluation of these individuals and a conversation with their providers may be necessary for a coordinated care approach to ensuring worker safety.

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